Geriatrics 2

Digestive System · Endocrine System
Kidney and Urogenital System
Haematological System · Respiratory System
Rehabilitation · Nutrition · Drug Treatment

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The Upper Gastrointestinal Tract

Esophagus, Stomach, Small Bowel, and Exocrine Pancreas

A. M. Gelb and B. Straus

A. Manifestations of Gastrointestinal Disease in the Aged

While there may be debate as to whether gastrointestinal (GI) disease in the elderly is fundamentally different from that occurring in younger individuals, there are clearly enough differences in frequencies and sites of origin to make a separate consideration of geriatric GI disease worthwhile (Schuster 1978a). The elderly patient is subject to particular socioenvironmental stresses, such as retirement, loss of income, loneliness, lack of sexual outlet, fear of ill health, cancerphobia, and death, which color his or her illness. The situation may be further complicated by attempts to compensate which may result in overcompensation by way of excessive use of alcohol and medications such as aspirin. Also there are errors of omission and commission in taking medication resulting in either lack of response or toxic symptoms.

In the aged there may be problems in history taking because of forgetfulness (Straus 1979). Relatives and friends must be depended upon for details. Pain is sometimes inappropriately minimal, perhaps due to cerebral disease. It may be exaggerated in an attempt to gain attention. Anxiety and depression may be reported as pain. The common symptom of weakness may be due to serious organic illness, such as carcinoma, to psychological factors, or to less serious organic disease, such as mild to moderate osteoarthropathy. Constipation is so common in the aged, that the change in bowel habits signaling a carcinoma of the colon may be overlooked.

Physical signs may be atypical. Serious infection may present with little or no fever. An abdominal mass may be impacted feces, or distended bladder.

The gastrointestinal system is the most common cause of distress in the elderly patient. While the separation of functional and organic illness is artificial, varying proportions of both existing at any one time in any individual, the majority of GI problems are functional. In one study of 300 patients over 65 years of age, 56% had functional disease (Sklar 1978). The mortality from GI disease is about one-third of that due to cardiovascular disease.

Patients of all ages, but especially the elderly, may not be able to accurately perceive or articulate psychological problems and seek appropriate help. They often "somatosize" their feelings in order to gain admission to a physician when they do not know where else to turn. Understanding by the physician of the patient's affective state behind the presenting gastrointestinal symptom is necessary for successful therapy. Otherwise the physician will be frustrated in attempting to relieve the symptom, or one symptom will be replaced by another. Sometimes just support

by the primary physician is sufficient, sometimes psychotropic drugs and/or psychiatric consultation and/or therapy is necessary.

While death in the aged is never due to a simple wearing out of digestive organs, aging produces rather profound changes in the morphology and physiology of these organs, which affect the manifestations of both functional and organic disease. A general decline in cellular reproduction and survival has been reported, as well as degeneration of the collagen and elastic supporting tissues. While this subject will be discussed more fully under specific organs, changes such as loss of teeth and alterations of taste must also be mentioned. Inadequacies of diet and even malnutrition because of these factors, produce and alter symptoms. In the aged, the gastrointestinal tract is also affected by vascular disease. The correlation between age-related morphologic and physiologic changes, and the appearance and character of symptoms is poorly defined.

B. Esophagus

I. The Aging Esophagus

Anatomic changes in the aging esophagus have not been described. Abnormalities in motility caused by aging, referred to as presbyesophagus, have been studied to some extent, although not extensively (Hollis and Castell 1974). Based on a manometric study of patients in their nineties, presbyesophagus was first described as consisting of a high incidence of absent peristalsis after swallowing, and frequent nonperistaltic, repetitive contractions. Many of the patients, however, had neurologic disease and/or diabetes mellitus. Another study of patients in their seventies and eighties, who were well, revealed decreased amplitude of peristaltic waves. This occurred more often in the 80-year-old group, than in the 70-year-old group. It was noted both in the basal state and post edrophonium. These findings suggest a weakening of smooth muscle. The nerve pathways appeared intact, since the speed and duration of contraction were unchanged compared to younger controls, as was the onset of contraction after swallowing.

II. Symptoms

1. Dysphagia

The symptoms of esophageal disease in the aged are not unlike those in younger patients (Pope 1978 a). One of the most important is dysphagia, which always must be taken seriously and investigated. As a guideline, the dysphagia of organic disease tends to be constant, progressive and, at least in the early stages, more for solids than liquids. The dysphagia due to a motor disorder tends to be intermittent, produced both by solids and liquids, and not necessarily progressive. The ability to localize the site of obstruction is usually good, the lesion being at the level of the perceived dysphagia. The exception is that lesions in the region of the gastroesophageal junction may produce symptoms referred to the suprasternal notch region.

2. Pain

Severe pain, often colicky in nature, is felt substernally, and may radiate directly through to the back, or to the neck, jaw, and arms, or both. Motor disorders marked by increased amplitude of contraction, and/or simultaneous contractions through the body of the esophagus are the manometric accompanyment. In patients with angina-like pain, and with normal coronary arteriograms, esophageal disorders are frequently responsible for the symptom. Response to medications usually used for angina, such as nitroglycerine, cannot be used to differentiate, since the pseudoangina of esophageal origin may also respond to these medications.

3. Heartburn

Heartburn is a word loosely used. Patients must be questioned as to what they precisely mean by the term. Usually it is used to describe substernal burning which radiates to the neck. It is associated with acid or alkali reflux from the stomach. Occasional heartburn is universal and of no serious consequence. Frequent and persistent heartburn, sometimes accompanied by painful swallowing (odynophagia) and/or regurgitation of fluid into the mouth (water brash), suggests reflux esophagitis.

4. Bleeding

Bleeding from esophageal disease may occur, and occasionally be profuse. Aspiration into the lungs with a variety of pulmonary complications may result.

5. Impaction

Impaction of food in the esophagus, especially at the lower end, may occur, especially in patients who develop rings in the region of the gastroesophageal junction, or who develop inflammatory strictures or neoplasms. Pain due to spasm may ensue, as the esophagus contracts in an effort to push the bolus through. Elderly patients who have problems with chewing, and who may swallow a large bolus, are prone to this problem.

III. Diagnostic Modalities

The diagnostic modalities available for the study of esophageal disease have increased in recent years. Some are primarily for research purposes, and are not widely used. They are applicable to patients of all ages.

1. Radiography

The value of conventional X-ray can be increased by a radiologist interested in the esophagus if he or she carefully observes peristalsis under the fluoroscope, with the patient in a variety of positions. The frequency of hiatus hernia, and reflux, is re-

lated to the amount of pressure on the abdomen the radiologist uses to demonstrate their presence. Cineradiography may be used to study motor disorders, giving a dynamic view of the coordination of motor events. This may be especially valuable for swallowing problems in the pharynx and upper esophagus.

2. Esophagoscopy

Esophagoscopy is particularly useful for the study of organic lesions, and appears to be as safe in the elderly as in other patients (JACOBSOHN and LEVY 1977). Its value is enhanced by the ability to obtain biopsy specimens and material for cytologic study through the instrument. In the study of reflux esophagitis, esophagoscopic biopsy may be too superficial to demonstrate early changes adequately. Suction biopsy, which allows one to obtain a larger specimen, permits study of the deeper layers, where the earliest changes of esophagitis may be found.

3. Manometry

Manometry has proved to be a valuable tool, both in the delineation of motor disorders in general, and in the study of individual patients (HIGHTOWER 1974). It has also given insight into the physiology of the lower esophageal sphincter and the problem of reflux. Manometric instruments and technics continue to be refined, so that new understanding of esophageal motor disorders may be expected. Not all patients with a motor disorder need manometry; frequently the diagnosis can be made clinically and with other methods. In the confusing case, however, it may be of great value.

4. Acid Drip Test

The acid drip (Bernstein) test is of value when it is unclear whether or not the symptoms are coming from the esophagus. The reproduction of symptoms when 0.1 *N* HCl is dripped into the esophagus, and the absence or diminution of symptoms when saline is dripped is a positive test. It does not necessarily mean that reflux esophagitis is present, although it is frequently positive in its presence. It may be negative when reflux esophagitis is present, and positive in its absence. A positive test only indicates that the esophagus is the probable origin of the symptoms.

5. Tests of Reflux, pH Probe, and Radioisotopic Scintigrams

Methods for the demonstration of reflux at the esophageal gastric junction include the use of a miniature pH probe which is inserted into the distal esophagus. While a marked fall in pH, indicating acid reflux, will occur occasionally in everybody, frequent falls in pH, which are not rapidly restored to normal, are abnormal and consistent with reflux esophagitis. Reflux can also be demonstrated by radioisotopic scintigrams with ^{99m} Technetium sulfur colloid. Normally, no radioactivity is detected in the esophagus. If no spontaneous reflux is visualized, an abdominal binder with gradual pressure may be used to provoke it.

IV. Diseases of the Esophagus

1. Motility Disturbances of the Oropharynx and Upper Esophagus

In the aged, chronic or intermittent dysphagia involving the oropharynx and upper esophagus is frequently caused by neurologic disorders, particularly cerebrovascular disease and the neuropathy of diabetes mellitus (Pitcher 1973). Hypertrophic cervical vertebrae may also impinge sufficiently to be responsible. At any age, a variety of neurologic diseases, such as myasthenia gravis, Parkinson's disease, and multiple sclerosis may cause dysphagia. Diseases of muscle, such as dermatomyositis, may produce symptoms, also at any age.

In recent years, there has been interest in abnormal motility of the cricopharyngeal sphincter at the upper end of the esophagus, which may occur at any age (Pope 1978 b). Hypertonicity of this sphincter has been described, and may be responsible for most of what was formerly diagnosed as globus hystericus. Failure of the upper sphincter to relax on swallowing, referred to as cricopharyngeal achalasia, has also been described as a cause of symptoms. Premature closure of the sphincter after initial relaxation, but before swallowing is complete, may be responsible for the development of a Zenker's diverticulum. Through the fibers of the cricopharyngeus muscle, the diverticulum itself may not appear until the patient is elderly, although the motility disorder may occur at any age. When the diverticulum is large, symptoms may include regurgitation, foul breath, gurgling, aspiration, and a neck mass. Not all investigators have been able to confirm the presence and nature of motility disorders of the upper sphincter, and its relationship to symptoms. Clarification will require more study and improved technology.

2. Motility Disorders of the Middle and Lower Esophagus

a) Achalasia

Achalasia usually appears in the middle years, but continues to produce symptoms, especially dysphagia, throughout life. The manometric abnormalities are hypertension and failure of relaxation on swallowing of the lower esophageal sphincter, and absence of coordinated peristalsis in the body of the esophagus. Exaggerated responsiveness to cholinergic drugs is present. Progressive dilatation of the body of the esophagus occurs because of the functional obstruction at the lower end. Pathologic examination reveals diminished numbers of ganglion cells in Auerbach's plexuses in the body of the esophagus. Changes in the vagus nerve, and in its dorsal motor nucleus in the brain have been described, and raise the question of whether the disease is primarily in the esophagus, or in the brain and/or vagus nerve.

The initial treatment is usually forceful dilatation of the lower esophageal sphincter, either by mechanical or pneumatic means. If this fails, surgical therapy with a Heller myotomy frequently succeeds. Long-standing achalasia predisposes to carcinoma, which has been reported in from 2%–7% of patients, due to chronic stasis and inflammation.

b) Diffuse Spasm

Diffuse spasm is a less common and less well-defined entity than achalasia, but more likely to be present in the elderly. When its presence is clear cut, its major

symptom is substernal colic. On X-ray examination, tertiary contractions (curling, corkscrew esophagus) are seen with the barium swallow. On manometry there are frequent simultaneous, high amplitude contractions in the lower two-thirds of the esophagus. However, often the entire symptom and sign complex is not present, and one or two parts of the triad of symptoms, X-ray findings, and manometric abnormalities may be absent. Patients frequently respond to anticholinergic medication. Forceful dilatation and/or a long myotomy has been required by an occasional patient. At least some instances of esophageal diverticula appear to be related to the presence of diffuse spasm. A variant syndrome, sometimes referred to as vigorous achalasia, has the typical manometric abnormalities of achalasia in the lower sphincter, but simultaneous high amplitude contractions, characteristic of diffuse spasm in the body of the esophagus are seen. Transition from one to the other has been described. For these reasons, there has been speculation that achalasia and diffuse spasm are not separate entities, but part of a spectrum of disease.

c) Collagen Vascular Disease

Collagen vascular disease, particularly scleroderma, may affect the esophagus, and may sometimes present initially in the aged. The lower esophageal sphincter is incompetent and there is absent peristalsis in the lower body of the esophagus. Replacement of muscle by fibrous tissue is thought to be the initiating pathologic lesion. Reflux of gastric contents results in, and causes inflammation and stricture in the lower esophagus. Measures to prevent reflux may prevent some of the damage.

d) Diabetes Mellitus

Diabetes mellitus is more common in aged patients. On manometric study in diabetics, a variety of abnormalities have been reported. These include diminished amplitude of contraction, nonperistaltic contractions, absent peristalsis after swallowing, and diminished lower esophageal sphincter pressure. Despite the abnormal manometry, the patient is frequently without symptoms.

3. Reflux Esophagitis, Hiatus Hernia, and Barrett's Epithelium

Reflux esophagitis is perhaps the most common cause of esophageal symptoms in the aged. Although the disease may start at a much younger age, incidence increases with advancing age, perhaps due to diminution in cellular replication and changes in the supporting tissues. Heartburn is the most frequent symptom, although in advanced disease with stricture formation, dysphagia may be present. The decrease in the intrinsic pressure of the lower esophageal sphincter and decreased competency when faced with increased gastric pressure (yield pressure) are thought to be the most important factors in the pathogenesis (POPE 1978 c). Defects in esophageal motility that result in a decreased ability to clear regurgitated gastric contents from the esophagus, may be an important contributing factor. Everybody regurgitates gastric contents from time to time, but the material is usually cleared from the esophagus within a few seconds. Patients with reflux esophagitis have frequent regurgitation, and the material remains in contact with the esophageal mucosa for a longer time. The role of the diaphragm, phrenicoesophageal liga-

ment, mucosal rosette, and intact angle between the esophagus and stomach are thought to be of little or no importance. The composition of the refluxed material may be important. Usually it is acid combined with pepsin. More rarely it is alkaline from reflux of duodenal contents.

The role of hiatus hernia in the pathogenesis of reflux is controversial. The frequency of direct hiatus hernias increases with age to 60% in patients over age 60 (Katz and Pitchumoni 1973). In practice, their frequency is somewhat related to the diligence with which they are sought. The argument against their having a role in reflux esophagitis is that the disease can occur in the absence of a hernia. Also the lower esophageal sphincter pressure is the same whether the sphincter is at the diaphragm or above. Lastly, most patients with hiatus hernias are asymptomatic and do not require treatment. The role of the intraabdominal esophagus, which serves as a pinchcock mechanism, and which is absent in the presence of a hiatus hernia, has been stressed by some observers, who think that the success of surgical procedures is related to the restoration of this segment. Whether there is an increased incidence of hiatus hernia in patients with reflux esophagitis compared to those without it, is not settled.

The therapy of reflux esophagitis involves avoiding factors that contribute to reflux, such as overeating and improper position after eating. Factors that lower sphincter pressure, such as alcohol, smoking, and chocolate, should be avoided. Elevating the head of the bed at night to overcome the effects of gravity is often worthwhile. Antacids should be given on a regular basis. Cholinergic medication is used; anticholinergics are to be avoided. Metoclopramide has been reported to be of value. The majority of patients will respond to medical therapy, although response may take weeks to months. Those patients who continue to have symptoms that recur frequently, do better in the long term with surgery than with persistence of medical treatment. Patients with stricturing in the lower esophagus require endoscopic dilation, or rarely esophageal resection.

Barrett's epithelium is a complication of reflux esophagitis, the normal squamous epithelium being replaced by columnar epithelium. It is considered a premalignant lesion, with an incidence of malignancy of perhaps about 10%. It may also predispose to deep ulcerations of the esophagus.

4. Paraesophageal Hiatus Hernia

Paraesophageal hiatus hernias occur much less frequently than direct hernias. However, since they often give rise to acute surgical problems, such as incarceration, obstruction, gangrene, perforation, and hemorrhage, surgical intervention has been recommended by some investigators (Weinstein and Kohn 1976).

5. Lower Esophageal Rings

Lower esophageal rings (Schatzki rings) may cause intermittent dysphagia. If food becomes impacted, colic may occur. They appear in middle or later life, and their etiology is uncertain. Two types of rings have been described, a mucosal ring at the squamocolumnar junction, and a muscular ring at the upper border of the lower sphincter (Spiro 1977a). Endoscopic bougienage is usually sufficient therapy; rarely is surgery necessary.

6. Infection of the Esophagus

Infection of the esophagus is rare except in debilitated patients, especially those compromised immunologically due to chemotherapy of malignancy or as a result of primary immunologic disease. Painful swallowing (odynophagia), dysphagia, and bleeding may occur. Monilia and herpes simplex virus are the most common organisms, but others have been reported.

7. Tumors of the Esophagus

Tumors of the esophagus are a very important problem in the aged (POPE 1978 d). Predisposing causes include lye stricture, achalasia, and Barrett's epithelium as a result of reflux esophagitis (HASS and SCHOTTENFELD 1978 a). Smoking and alcohol, particularly together, are important etiologic factors. The common denominator appears to be chronic irritation. Squamous cell carcinoma is by far the most common. Adenocarcinoma rarely occurs, and when in the lower third, the possibility of an upward extension from a gastric adenocarcinoma is raised. The geographic incidence varies markedly. It is almost four times more common in men than women. Progressive dysphagia is the most common symptom, one which should never be ignored. It must be promptly investigated. Bleeding may occur but is not common.

The majority of cases of esophageal carcinoma have spread to contiguous lymph nodes when first encountered. This accounts for the poor survival rate. Surgery and radiation, alone and together, have been used with varying success. Often the surgery is performed in stages. Operative mortality for esophageal surgery in the aged has been reported not to be increased, and advanced age should not be a reason for withholding surgery (MOHANSINGH 1976). Even if the tumor cannot be resected, sometimes palliation can be achieved either by radiation, insertion of an indwelling tube through the tumor, or by surgical bypass. Chemotherapy has been generally disappointing.

C. Stomach and Duodenum

I. Anatomy and Physiology of the Aging Stomach

Atrophic gastritis, varying from mild to severe and ultimately to atrophy, occurs in aged patients. With advancing years, it appears with increasing frequency. The incidence varies in different series. A 50% incidence of gastric atrophy in asymptomatic people over age 60 was reported by one group (BRYK and ELGUEZABAL 1975). In another study, 23 and 24 people over age 64 had some degree of atrophic gastritis (ANDREWS et al. 1967). These changes may occur despite the absence of any symptoms.

The histologic changes of atrophic gastritis involve the full thickness of the mucosa and muscularis mucosa (VILARDELL 1974). Specialized gland cells are replaced by nonspecific or mucus secreting glands, or by intestinal type glands, resulting in thinning of the mucosa. In the lamina propria, there is edema, and infiltration by inflammatory cells, mostly plasma cells. The fibers of the muscularis mucosa are

split by fibrous tissue and inflammatory cells. In gastric atrophy, there is a lack of inflammatory infiltration, and more intestinal metaplasia.

The radiologic manifestation of the atrophic stomach is usually an absence or diminution of mucosal folds (BRYK and ELGUEZABAL 1975). Gastric retention after an overnight fast or after ingestion of an oral cholecystographic medium has been reported in the absence of true obstruction. Narrowing of the antrum, simulating scirrhous carcinoma, may also be a problem. These changes are thought to be due to disordered motility.

On gastroscopic examination, atrophic gastritis, and gastric atrophy have a characteristic appearance (BELBER 1978). The mucosa has a gray color and the folds are less numerous and disappear quickly when air is introduced. In the advanced stages, the submucosal vessels are easily seen through the transparent mucosa.

Acid secretion decreases with increasing severity in atrophic gastritis, paralleling the reduction in parietal cells. The incidence of complete achlorhydria after stimulation increases with advancing age. Intrinsic factor secretion is also diminished although it may still be present when acid secretion is absent. In many patients with atrophic gastritis, parietal cell antibodies are found in the peripheral blood. The more advanced the gastritis, the more frequent is the presence of antibody. In gastric atrophy, their presence is very common.

II. Diagnostic Modalities

1. Radiography

The conventional GI X-ray series remains an important means of examination of the stomach. There has been interest in discerning very small lesions by the use of the double contrast technique, in which the stomach is distended with air after being coated with a small amount of thick barium which adheres to the surface.

2. Endoscopy

Endoscopy has become an increasingly important diagnostic tool. Together with biopsy and cytologic brushing its effectiveness is enhanced. It is especially useful for upper GI bleeding, in which it is the primary diagnostic modality. Problems regarding questionable abnormalities on X-ray can be resolved. From biopsy through the endoscope, only superficial tissue can be obtained. Deeper lesions may be missed. If diffuse, tissue from deeper lesions may be obtained by biopsy with a suction capsule. Cytologic brushing can be very valuable for the diagnosis of malignancy, if properly performed and interpreted. Sonography and computerized axial tomography have little use in the diagnosis of intragastric lesions. Arteriography may be useful in the diagnosis of the source of GI bleeding when the bleeding point cannot be seen through the endoscope.

3. Gastric Analysis

Gastric analysis is performed using histamine, histalog, or pentagastrin as a stimulant. The latter has become increasingly more popular since few side effects occur.

Maximum stimulation is used. Results are expressed differently in various laboratories, usually as maximum acid output (MAO) or peak acid output (PAO). The role of gastric analysis is limited. It is of value in excluding adult pernicious anemia. In peptic ulcer disease, in which there is a large overlap between normal and abnormal, it may be useful in a patient with atypical findings by history, X-ray, or endoscopy, provided the results are very high or low, outside the normal range. In gastric ulcer, when there is a question of malignancy, it is of value only when there is achlorhydria. Hypochlorhydria is of no value in distinguishing between benign or malignant ulcer. In patients having gastric surgery for ulcer, it is of value to know acid output before and after the surgery to assess the effectiveness of surgery. If symptoms recur after surgery, gastric analysis may be helpful in the diagnosis of recurrent ulcer. In patients who have had vagotomy as part of their gastric surgery, and have recurrent symptoms, gastric analysis with insulin stimulation is used to determine the adequacy of vagotomy.

4. Serum Gastrin

Serum gastrin is elevated in gastric atrophy and in gastrin secreting tumors (Zollinger-Ellison syndrome). These are easily distinguished, since the former is accompanied by low or absent gastric acid, and the latter by hypersecretion of acid. In antral G-cell hyperplasia, serum gastrin is also elevated as is gastric acid secretion. This condition, the gastrin-secreting tumor, and some cases of duodenal ulcer, may not be distinguishable on the basis of serum gastrin level and acid secretion. They can, however, be distinguished by differential response to secretin administration, calcium infusion, and to a test meal (McGuigan 1978).

III. Diseases of the Stomach and Duodenum

1. Functional Disease

Functional disease of the stomach, although very common, is not well understood. In this area, the artificiality of the distinction between functional and organic may be particularly relevant. The role of psychological factors in chronic peptic ulcer has been long considered, and remains unsettled. The same is true for acute erosive gastritis and stress ulcers. In addition, patients are encountered who have typical ulcer symptoms, but negative X-ray and endoscopy. Are they part of the peptic ulcer spectrum or different? Many patients complain of nonspecific "dyspeptic" symptoms, and no anatomic abnormality is found. Do they have symptoms due to adaptive changes, or do they have "irritable bowel" syndrome, which in most patients causes colonic symptoms, but may also involve the upper tract? Because of upper tract involvement, the term irritable "gut" syndrome is preferred by some. Whether there are abnormalities in the basic electric rhythm of the upper tract in irritable gut syndrome, as has been demonstrated in the colon, is unknown. The participation of the stomach in adaptive behavior has been shown (Almy 1978). Anger, hostility, and resentment are associated with hypermotility and hypersecretion. Depression is associated with hypofunction. It is not clear whether older

patients have more functional complaints, but many clinicians have that impression. In older patients, the possible relation of symptoms to the presence of atrophic gastritis should be considered.

2. Peptic Ulcer

The prevalence rate for peptic ulcer in the elderly is substantial and is either equal or greater than in younger age groups (NARAYANAN and STEINHEBER 1976). In recent years, the epidemiology of peptic ulcer is changing so that it is now occurring in an older age group. Among patients hospitalized for peptic ulcer, the trend is for a larger percentage to be elderly compared to prior years. While ulcers in the elderly may have their onset many years before, in one study 58% had their initial symptoms after the age of 60 (LEVRAT et al. 1966). Serious complications, however, and deaths are more common in the elderly (NARAYANAN and STEINHEBER 1976). In fact, a major complication is more likely to be the first indication of the presence of an ulcer than in the younger patient. Mortality from peptic ulcer is more closely related to age than to any other factor.

The clinical course is more likely to be atypical: the typical ulcer pain pattern is frequently not present. Complications may lead to symptoms from other organ systems such as cardiac symptoms from blood loss, which may divert attention from the existence of an ulcer.

In general, acid secretion decreases with age. Duodenal ulcer appears to occur in the elderly at lower acid levels than in younger patients. Gastric ulcer can occur with minimal acid output. The relative frequency of gastric ulcers to duodenal ulcers increases with age, so that in some series, but not the majority, gastric ulcers are more common. Gastric ulcers, however, account for the majority of deaths.

The problem of malignancy is raised in relation to gastric ulcers. Considered opinion is that benign gastric ulcers are virtually never transformed into malignant ones, or at least it is so rare that it is not a significant problem. The real problem is distinguishing a benign ulcer from a malignant ulcer. By the use of diagnostic modalities including endoscopic biopsy and brush cytology, the risk of confusion is reduced. A trial of therapy is also helpful. A benign ulcer should heal completely after 1–6 weeks of treatment, while a malignant ulcer will, with rare exception, persist, although it may change size. Using all criteria including response to therapy, the error should be less than 1%.

The therapy of peptic ulcer in the elderly is based on suppression of acid secretion as in younger patients, with some modifications (STURDEVANT and WALSH 1978). Anticholinergic agents are avoided in the elderly by many physicians because of urinary, ocular and cardiovascular side effects. The initial approach is to use antacids for 4–6 weeks. Liquid preparations are better than tablets, and are taken 1 and 3 h after meals and at bedtime. Cimetidine may be added if initial therapy with antacids does not produce satisfactory results. Cimetidine may sometimes cause confusion in patients whose mental status is borderline. Controlled studies have not demonstrated any benefit from a bland diet. A regular diet can be prescribed. Bedtime snacks, alcohol, and foods causing distress in individual patients are best avoided. Cigarette smoking, aspirin, and other antiinflammatory agents should also be avoided. Sucralfate is probably as effective as cimetidine.

Gastric irradiation is a modality to be considered in aged patients who do not respond to the usual measures, and especially in those who are poor surgical risks. Either achlorhydria or significant reduction in acid secretion can be obtained in almost all patients without significant side effects and will persist in many for several years.

3. Gastritis and Duodenitis

The increasing incidence of atrophic gastritis and gastric atrophy occurring in the aging stomach has been mentioned above. The majority of patients remain asymptomatic (VILARDELL 1974). Some have nonspecific symptoms such as intolerance of fatty and spicy food, discomfort or pain after eating, distention, and belching. Patients with gastric atrophy may develop pernicious anemia. Vitamin B_{12} reverses the hematologic and neurologic component of the disease, but gastric atrophy remains. In some patients with pernicious anemia, corticosteroids will cause regeneration of parietal cells, although this is not the treatment of choice. Atrophic gastritis and gastric atrophy are premalignant lesions. Both benign polyps and carcinoma occur. The risk of carcinoma may be increased 20-fold over age-matched controls.

Acute erosive gastritis may be diffuse, localized, or patchy (JEFFRIES 1978). The terms acute or stress ulcer are frequently used for the localized or patchy form. This condition occurs particularly in patients with trauma, sepsis, or shock, and at any age, not particularly the aged. Although the etiology is not well understood, there has been some progress. For various reasons there is a break in the normally tight mucosal barrier, and back diffusion of acid ensues. Vascular changes seem also to be involved. Bleeding is the most important manifestation. Because of associated diseases in the elderly, they are less able to withstand the effects of bleeding, and have a significant mortality, despite a variety of medical and surgical therapeutic approaches.

Duodenitis is not a well-understood entity. It may be part of the spectrum of peptic ulcer disease.

4. Bezoars

Bezoars occur in elderly people, particularly in patients with prior gastric surgery (RAFFIN 1978). Most often they are phytobezoars, composed of plant matter. A food bolus may occur, consisting of undigested pits, seeds, citrus pith, and poorly chewed food. Epigastric pain or fullness is common. Gastric outlet obstruction may occur. Endoscopic fragmentation and enzymatic digestion is sometimes sufficient therapy. At other times surgery is necessary for their removal.

5. Tumors

Tumors of the stomach are a major problem in elderly patients. Malignant tumors are the most common by far. Adenocarcinoma makes up 97% or more of malignancies. The remainder are sarcomas. The incidence of adenocarcinoma varies

geographically, being highest in Japan, Chile, and Iceland (PALMER 1974). Changing incidences with migrant populations suggest that environmental factors are of prime importance in etiology (HASS and SCHOTTENFELD 1978 b). Genetic factors, however, probably do have some role. Families have been described with an unusually high occurrence. There is also a weak association with the presence of blood group A. It is more common in low socioeconomic groups, and in those with diets high in starch and low in fresh fruit and vegetables. The incidence has decreased in the United States over the past few decades, the death rate declining from 28 per 100,000 in 1930, to 10 per 100,000 in 1967. The reason for this is unknown. Certain lesions are considered premalignant. They include pernicious anemia, atrophic gastritis, and adenomatous polyps.

Males predominate. In the United States the male to female ratio is 2 to 1. The peak incidence is in the 6th decade. About half are in the pyloric area, and a quarter are along the lesser curvature. They may be polypoid, ulcerating, or scirrhous in nature.

The most common symptoms of gastric malignancy are weight loss and pain (BRANDBORG 1978 a). Anorexia, nausea, and vomiting are frequently present. Symptoms, however, may be quite mild and nonspecific. Upper gastrointestinal symptoms in an elderly patient should be investigated at least with conventional X-ray. Certain malignancy-associated conditions may be the initial manifestation of gastric adenocarcinoma, although they are found with other internal malignancies as well. These include dermatomyositis, neuromyopathy, acanthosis nigricans, and thrombophlebitis (CURTH 1971). A palpable mass will be found in about half the cases of advanced disease. Metastatic disease may be detected in a hard nodular liver, in lymph nodes draining the stomach (left supraclavicular or axillary), umbilical mass, in the ovary (Krukenberg tumor), and in the anterior rectal wall (Blumer's shelf). An elevated carcinoembryonic antigen (CEA) level may sometimes be found in the presence of metastatic disease.

An uncommon but important type is superficial spreading carcinoma. Its importance is that the survival rate after surgery is good, over 90% at 5 years. It is not clear whether superficial spreading carcinomas are merely those detected early, or a different type of malignancy. The 5-year survival rates for the remaining carcinomas are usually under 10%.

Surgery is the treatment of choice in most instances. Subtotal gastrectomy is usually performed, but sometimes total gastrectomy is necessary. If the adenocarcinoma is not curable by surgery, palliation is usually best accomplished with local resection to prevent bleeding or obstruction. The role of adjuvant radiotherapy and/or chemotherapy has not been fully evaluated. Combinations of chemotherapeutic agents in advanced and metastatic disease produce palliation in about 15%–20% of patients. 5-Fluorouracil is used together with a nitrosourea derivative, mitomycin C, cytosine arabinoside, or adriamycin. Sometimes more than two drugs are used together.

Of the remaining 1%–3% of malignancies, the majority are lymphomas followed in frequency by leiomyosarcomas. When limited to the stomach, lymphoma is treated by resection followed by radiation. When disseminated, radiotherapy, perhaps with chemotherapy, is used. Resection is usually effective for leiomyosarcomas, which frequently bleed from central ulceration and cause pain.

Among benign tumors, leiomyomas are the most common. If large enough they may produce symptoms identical to leiomyosarcomas, from which they cannot be distinguished on clinical grounds, but only on pathologic examination. When symptomatic, they should be resected.

Benign gastric polyps are infrequent lesions. Most are hyperplastic. Adenomas account for fewer than 10% of all polypoid tumors. The adenomas are considered to have a low potential for malignant transformation. They are often associated with gastric atrophy in the remainder of the stomach and achlorhydria. Polyps can frequently be removed via the fiberoptic endoscope.

D. Small Intestine

I. The Aging Small Intestine

Almost nothing is known of the effect of aging on the structure of the small intestine in humans. There is evidence for a decrease in weight of the entire small bowel after age 40 (SCHUSTER 1978 b). The villi are shorter and broader in the elderly (WEBSTER 1978 a).

In animals, there is atrophy of all three layers of bowel, and an increase in fibrous tissue. There is a general reduction in cellularity. The generation time for crypt cells is prolonged, and transit time of cells from crypt to villous tip is increased.

Evidence exists for a decreased absorption of some substances by the aging small intestine of humans. These include galactose and d-xylose (MONTGOMERY et al. 1978). In animals, the transport of essential amino acids is decreased. Fat absorption, calcium, and iron transport are decreased with aging in animal studies (WEBSTER 1978 b). Whether these decreases are due to changes intrinsic to the small intestinal mucosa or to other factors, such as pancreatic changes, is not clear. In general, there has not been very much study of the subject.

II. Diagnostic Modalities

1. X-ray

Radiology of the small intestine is a valuable diagnostic tool when performed and interpreted properly by an experienced radiologist. The major indications are unexplained abdominal pain, diarrhea and steatorrhea, bleeding when other sources have been excluded, and suspected small intestinal obstruction (GOLDBERG 1978). Judgements are made on the basis of caliber of the lumen, contour, fold pattern, and transit time. The radiologist has advanced beyond the time when only a nonspecific diagnosis of "malabsorption syndrome" was forthcoming. In many instances, the recognition of subtleties permits a more precise diagnosis. Although a coarsening of fold pattern in the aged has been reported, it is not conspicuous and usually does not enter the radiologic differential diagnosis.

2. Tests of Malassimilation

Malassimilation can be divided into disorders of digestion (maldigestion) where the defect occurs in the intraluminal handling of food, and abnormalities in intestinal transport (malabsorption) where the defect is in the intestinal wall. Some authors subdivide the latter and refer to defects in the removal or delivery of nutrients after absorption by the intestinal cell (GRAY 1978a).

A number of serum tests help in the diagnosis of malassimilation. The serum albumin and cholesterol are usually low. The serum carotene is a good screening test. A low value is compatible with either poor nutrient intake or malassimilation. A normal value suggests that neither condition is present. A vitamin A serum level and vitamin A tolerance test are also of use.

A deficiency of intestinal enzymes for the final stage of sugar digestion can be diagnosed by tolerance tests. Under normal circumstances, the digested disaccharide will lead to an increase in serum glucose, giving values not unlike those of a normal glucose tolerance test. In the presence of enzyme deficiency the glucose levels do not rise.

Some substances that are absorbed are then excreted in the urine. Malassimilation of the substances leads to reduced urinary excretion. A reduced d-xylose urinary excretion, after a test dose is ingested, indicates malabsorption and an abnormality in the intestinal wall. This test is interfered with in patients with renal disease or who have poor urine flow as a result of dehydration. Serum d-xylose levels during the test eliminates these false positives. Under normal circumstances, there is a decrease in the amount excreted by the aged, but usually not to the degree seen in disease.

B_{12} absorption is complex. The vitamin combines with intrinsic factor from the stomach, and is then actively absorbed in the distal ileum. In the Schilling test, in which a dose of radioactive-labeled B_{12} is administered orally, a low urinary excretion is found, even when intrinsic factor is given together with the test dose of B_{12}, when the ileum is diseased or absent.

Fecal fat is valuable for the diagnosis of steatorrhea. A qualatative test in which a smear of suspected stool is stained with a fat stain is useful as a rough screening test. For quantatation, a 72-h stool collection, while the patient ingests a diet reasonably normal in fat content, is performed. Fat excretion of more than 6 grams/day is abnormal.

Breath tests are a recent innovation that may prove valuable to clinicians. Developed first to study the enterohepatic circulation of bile acids, the test substance is marked with radioactive ^{14}C. If absorbed, the substance is metabolized, $^{14}CO_2$ is formed, and is measured in the breath. ^{13}C stable isotopes, measured by mass spectrophotometry, can also be used as markers. The absorption of other substances besides bile acids can be studied by breath tests. ^{14}C-labeled fats and fatty acids, if proven reliable, may eliminate the need for stool collections. Breath tests for impaired disaccharide digestion have been developed. The undigested material enters the colon where bacterial fermentation occurs. Hydrogen is produced, absorbed, and then measured in the breath by chromatography.

Small intestinal biopsy has been of great value in developing concepts of small intestinal disease and in their diagnosis. Suction biopsy is necessary in order to ac-

quire a specimen adequate in size to study the villous architecture. Certain abnormalities are pathognomonic, while others may be compatible with several diseases. Still others are patchy and diagnostic material cannot consistently be obtained.

Hormones and hormone-like agents may produce secretory diarrhea. Some of these substances are produced by tumors. Serum and resected tumor tissue can be assayed for these substances, which include VIP, GIP, serotonin, glucagon, prostaglandins, and others. Some of these assays are not readily available, only being performed in specialized laboratories.

III. Diarrhea

Diarrhea may be due to disorders involving small intestine, large intestine, or both. The role of the small intestine is being increasingly appreciated. Diarrhea is best defined in terms of stool volume and not frequency of bowel movement (KREJS and FORDTRAN 1978). Above 200 ml/day is abnormal. In small bowel diarrhea, however, the stool volume is usually large, much over the above minimal figure, and usually not bloody. There are four basic mechanisms for diarrhea, although in any one patient several mechanisms may be operative. Osmotic diarrhea is due to large amounts of poorly absorbable osmotically active substances in the lumen. Secretory diarrhea is due either to active ion secretion into the lumen by the mucosal cell or to increased hydrostatic and tissue pressure. Abnormal motility may also cause or contribute to diarrhea. Loss or diminution of normal active ion absorption is another mechanism that may contribute to diarrhea.

Bacteria are responsible for many if not most instances of acute self-limiting diarrhea (BRANDBORG 1978 b). Since the symptoms subside quickly, a precise diagnosis is usually not made. Bacterial toxins have been shown to mediate the diarrhea in many instances. In cholera, the organism produces a toxin which activates adenyl cyclase and increases cyclic AMP, which in turn increases ion secretion into the lumen. Toxogenic *E. coli*, responsible for the majority of instances of "traveler's diarrhea," produces two toxins, one of which increases adenyl cyclase. Other bacteria, including *Shigella*, staphylococci, and *Clostridium perfringens*, produce a toxin which is cytotoxic. In many instances, the mechanism of the diarrhea is unknown, and a toxin may not be involved. There may be direct penetration of the epithelium by the bacteria. In some instances a combination of mechanisms may be involved.

New bacteria capable of producing diarrhea have been identified in recent years. *Yersinia* may produce an ulcerative enteritis. The symptoms of nonbloody diarrhea and abdominal pain may be brief, or last for weeks or months. They may simulate acute appendicitis or nonspecific regional enteritis (Crohn's disease). Campylobacter may also infect the small bowel, producing an acute enteritis that may last for several weeks (SKIRROW 1977). In some epidemics, this organism has been cultured from the stool in a significant number of patients.

Viral agents have been identified as the cause of diarrhea in several epidemics, the agent frequently being named for the location of the outbreak (BRANDBORG 1978 b). The disease is usually short and self-limiting. In adults, parvovirus-like agents have been identified.

Parasitic agents usually produce chronic diarrhea. Their incidence appears to be increasing, perhaps because of increased travel in recent years. Also, anal–oral venereal transmission may have increased the endemic incidence, particularly in promiscuous male homosexuals (Mildvan et al. 1977). While amebae usually invade the colon, at least initially, *Giardia lamblia* is primarily an upper small intestinal parasite which produces diarrhea and steatorrhea. The parasite may not be found in the stool. Small intestinal aspiration or biopsy may be required to demonstrate the organism.

IV. Diseases of the Small Bowel

1. Regional Granulomatous Enteritis

Regional granulomatous enteritis (Crohn's disease) appears to be increasing in incidence (Kirsner 1978). While most commonly making its appearance in early adulthood, it may first appear in the aged. Since it is chronic and the majority of patients live with it for many years, it presents management problems in the older patient no matter at what age it initially manifests itself. Its cause is unknown. Infectious agents, particularly viruses, have been suspected, especially in the light of evidence for a transmissible agent. Altered immune mechanisms may also play a role. Since in many patients there are overlapping features with ulcerative colitis, it has not been established whether these are separate diseases, or different manifestations of the same disease.

The clinical features and course, extremely variable from patient to patient, are characterized by remissions and exacerbations, but often also by gradual progression of the disease (Bockus 1976). Nonbloody diarrhea, abdominal pain, fever, malaise, and weight loss dominate the clinical picture. Systemic manifestations such as arthritis, iritis, and erythema nodosum may also be present. Fistulas and other complications in the perineal area frequently occur. Obstruction may supervene.

Therapy with sulfasalazine and steroids is superior to a placebo in controlled trials. The role of immunosuppressive agents is uncertain. Surgery is reserved either for complications or intractable disease because of the high rate of recurrence. Advanced age, per se, is not a contraindication to surgery including ileostomy. Despite recurrence, most patients are improved by operation, either because of a long disease-free interval, or an amelioration of the symptoms and course.

2. Vascular Diseases

Vascular problems of the small intestine are of particular concern among elderly patients, because of the high incidence of arteriosclerosis (Kairaluoma et al. 1977). The clinical situation will be determined by which vessels are involved, the extent of involvement in terms of how much, if any, blood flow is still occurring, and how rapidly the vascular obstruction occurs. The vascular syndromes can be divided into acute and chronic.

Acute vascular occlusion usually leads to intestinal infarction. The most common etiology is arterial thrombosis due to atherosclerosis, which usually occurs in the most proximal segment of the artery near its take off from the aorta. Arterial

embolism is another common cause. Bowel infarction without major vessel occlusion occurs frequently, probably due to low flow to the intestine secondary to shock and/or congestive heart failure. Digitalis may also reduce mesenteric vascular flow. Dissecting aneurysm of the aorta and venous occlusion secondary to blood dyscrasia or tumor also may result in infarction. Occasionally, arteritis may present as acute intestinal infarction. The clinical picture is dominated by severe abdominal pain. Especially in the early phase, there may be a paucity of abnormal physical findings in relation to the severity of the pain. Intestinal infarction should be suspected in elderly patients with symptoms of an acute abdomen, especially in cardiac patients. Early diagnosis, rapid support, and aggressive surgical treatment are important management principles.

Chronic intestinal ischemia sometimes occurs, producing a syndrome of abdominal angina (SPIRO 1977 b). Usually more than one of the three major splanchnic vessels are involved in this syndrome. The patient experiences pain, usually 15 to 30 min after eating. The pain may last several hours. Patients may develop a fear of eating and lose a great deal of weight. Mild to moderate malabsorption may occur. Angiography shows narrowing of more than 50% in at least two vessels. Surgery frequently results in relief of both symptoms and malabsorption.

3. Maldigestion due to Gastric Surgery

Maldigestion secondary to gastric surgery is important in elderly patients. The causes include accelerated gastric emptying, incoordination between gastric emptying and biliary and pancreatic secretion, reduced pancreatic stimulation, diminished luminal bile salt concentration, altered intestinal transit time, and impaired gastric dispersion of solid food. There may also be bacterial overgrowth in an afferent loop. Despite all these factors, diminished food intake is still the most important cause of weight loss after gastric surgery.

4. Disaccharidase Deficiencies

Disaccharidase deficiencies are due to defects at the brush border cell surface of enzymes necessary for the complete digestion of carbohydrates (DONALDSON 1978 a). The most common is acquired lactase deficiency, which may be either primary or secondary. The primary variety usually makes its appearance in early adulthood and persists throughout life. The secondary type may complicate a wide variety of other intestinal diseases. These patients cannot tolerate milk, although the severity of the deficiency and resulting milk intolerance may vary. The undigested lactose passes into the colon where bacterial fermentation occurs. Cramps and diarrhea result. Therapy involves avoiding milk products, although a commercial preparation of lactase is available for the treatment of milk prior to ingestion. Of the other disaccharidase deficiencies, which are all uncommon, sucrase deficiency is the most frequently encountered.

5. Gluten-Sensitive Enteropathy

Gluten-sensitive enteropathy, also known as nontropical sprue, is identical to celiac disease in childhood (TRIER 1978 a). Sometimes, however, it may be diag-

nosed for the first time in elderly patients. The disease is caused by the interaction of peptides from wheat, rye, barley, and sometimes oats with the intestinal mucosa. Experimental data from animals, the increase in plasma cells in the lamina propria, and the association with HLA-B8 and HLA-DW3, all suggest that an immunologic mechanism is operative. In addition to the clinical and laboratory evidence for malabsorption, the typical, but not specific, findings of villous atrophy, elongated crypts, and increased plasma cells in the lamina propria are found on small bowel biopsy. Removal of gluten from the diet is sufficient therapy for most patients. A few are refractory to this, but may respond to steroids, while occasional patients are encountered who are refractory to all therapy. There is an increased incidence of small intestinal lymphoma and carcinoma in these patients.

6. Bacterial Overgrowth Syndromes

Bacterial overgrowth syndrome may occur following abdominal surgery, with structural abnormalities of the intestine, and with small intestinal motor abnormalities. In the elderly, it may occur without an anatomic cause (Roberts et al. 1977). The common denominator for bacterial overgrowth in areas of the bowel where there are usually very few organisms is stasis or recirculation of intestinal contents. The pathophysiology is not completely understood. Steatorrhea is produced through the effect of bacteria on bile salts which are deconjugated and dehydroxylated (Donaldson 1978 b). Whether the defect is loss of normal bile salts which are necessary for micelle formation, or the toxic effect of altered bile salts is not clear. B-12 absorption is decreased because the bacteria take it up, making it unavailable to the host. Tests useful in diagnosis, in addition to the usual tests of malabsorption, include an abnormal Schilling test not corrected by intrinsic factor, an abnormal bile acid breath test, and an abnormal bacterial colony count in fluid aspirated from the small intestine. Therapy with a variety of broad spectrum antibiotics is usually successful. Surgical resection of stagnant areas may be necessary.

7. Systemic Diseases Involving the Small Intestine

In certain systemic diseases involving the small bowel, particularly scleroderma, diabetes, and amyloidosis, in which there are motor abnormalities, bacterial overgrowth occurs in many instances (Gray 1978 b). Broad spectrum antibiotic therapy has been found to improve the malabsorption not infrequently. Other factors, however, many of which have not been elucidated, may be operative in these diseases. Other systemic diseases which may sometimes have malabsorption as a feature and in which the mechanism is not completely clear, include collagen vascular diseases other than scleroderma, congestive heart failure, and severe malnutrition from any cause.

8. Malabsorption due to Drug Ingestion

Drug ingestion may produce malabsorption (Gray 1978 c). Incriminated agents include ethanol and antibiotics, particularly oral neomycin. Diphenylhydantoin in-

terferes with folate absorption. Cathartic-induced rapid transit may also cause malabsorption.

9. Immunologic Deficiency Associated with Malabsorption

Immunologic deficiency syndromes may sometimes be associated with malabsorption, villous atrophy, and abnormal small bowel X-rays (MARSHAK 1975). The exact relationship is not clear. Giardiasis has been found to be present in many of these patients. The absence of plasma cells in the lamina propria is pathognomonic of this condition.

10. Whipple's Disease

Whipple's disease is of interest because it appears to be a malabsorptive disease produced by bacteria (TRIER 1978 b). The periodic-acid-Schiff-positive material in macrophages has been shown to be destroyed bacteria. This formerly uniformly fatal disease responds to antibiotic treatment.

11. Short Bowel Syndrome

Short bowel syndrome after intestinal resection is an important cause of malabsorption in the elderly beause of the incidence of mesenteric infarction discussed above. The morbidity is related to the site and extent of resection (WESER 1976). Jejunal resection is tolerated better than ileal resection because the ileum has the capacity to adapt and is the site of bile acid absorption. As much as a 50% resection of the proximal jejunum and midbowel is fairly well tolerated. An intact ileocecal valve is important. The morbidity and mortality rise markedly if it is resected. The duodenum is also essential. If the patient survives the acute episode, hyperplasia of the remaining bowel results in adaptive changes.

12. Tumors

Tumors of the small intestine account for 5% or less of all bowel tumors (O'BRIEN 1978). Why this region is relatively resistant to neoplasm is unclear. The majority are discovered in patients over the age of 50.

a) Adenocarcinoma

Among malignant tumors, adenocarcinoma is the most frequent. Most of them occur in the upper small intestine within 25 cm of the ligament of Treitz. Abdominal pain and bleeding are the most common symptoms. An abdominal mass may be present. Partial or complete obstruction may occur. Because of the relative rarity of the lesion, there is frequently delay from onset of symptoms to diagnosis. Radiology both with barium and angiography are helpful in diagnosis. Fiberoptic examination of the small bowel is still not practical except for the first portion of the duodenum. The prognosis is usually poor although a twenty percent 5-year survival has been reported with surgery.

b) Lymphoma

Primary lymphoma is the next most frequent malignancy (Trier 1978c). A single lesion is found most often, but in about 20%–25%, multiple lesions occur. Sometimes a large segment of bowel is involved, and malabsorption is produced. They occur mostly in ileum and jejunum. Usually the duodenum is spared. Sometimes the bowel is involved secondarily when lymphoma is disseminated. The peak age of occurrence is about a decade earlier than adenocarcinoma. The symptoms, however, are similar. Therapy depends on the extent of intestinal involvement, and whether or not there is extraintestinal involvement. Surgical resection produces the best results when the disease is localized, with a 5-year cure rate of 50%–75%. If disease involves adjacent tissue, postoperative radiotherapy or chemotherapy is used. Some physicians advise postoperative therapy with all lymphomas. With diffuse or disseminated disease the prognosis is much poorer. Radiotherapy and/or chemotherapy, with and without surgery are used. Hodgkin's lymphoma of the small intestine is much less common than non-Hodgkin's lymphoma. It is more likely to produce obstructive symptoms because of its greater tendency to produce a desmoplastic reaction.

c) Leiomyosarcoma

Leiomyosarcomas are next in frequency after adenocarcinomas and lymphomas (O'Brien 1978). They occur more in the distal small intestine than the proximal. As in other malignancies, they produce pain and bleeding, but are more likely to produce a palpable mass. Therapy is surgical, and 5-year survivals approaching 50% are reported. Rarely other histologic elements of the small intestine may give rise to malignancy.

d) Premalignant Lesions

Premalignant lesions of the small intestine have been identified. In regional enteritis, especially where bypassed segments are present, there is an increased incidence of adenocarcinoma. The Peutz-Jeghers syndrome has also been reported to show an increased incidence of both adenocarcinoma and lymphoma. In Middle Eastern countries particularly, but also in other places, Alpha Chain disease is accompanied by an increase in diffuse intestinal lymphoma.

e) Carcinoid Tumors

Carcinoid tumors are intermediate between benign and malignant. They arise in the area of the embryologic midgut, from midduodenum to midtransverse colon, the appendix being the most common location. In the absence of metastases and the carcinoid syndrome, most are silent, and are discovered incidently at surgery. The larger the tumor, the more likely it is to metastasize. The carcinoid syndrome is associated with tumors that have metastasized, especially to the liver. A variety of chemical substances have been isolated from the tumor, which are responsible for the symptoms, which can often be managed by a variety of drugs. The metastatic tumor itself is often indolent in its course, and may sometimes respond to chemotherapy.

f) Benign Tumors

Benign tumors are often asymptomatic, and are discovered incidently at surgery or on autopsy. Adenomas, leiomyomas, and lipomas are the most common. Fibromas and angiomas are less common, and others are rare. Symptoms, when present, are usually related to gross structure and location in the bowel. Bleeding may occur. They are least common in the duodenum, and increase in frequency toward the ileum. Those beyond the ligament of Treitz may produce intussusception.

g) Telangiectasia and Angiodysplasia

Telangiectasia of the small intestine are not tumors, but vascular malformations which may be single or multiple, hereditary or nonhereditary. Their importance is that they may sometimes be a source of massive and repeated hemorrhage. They can sometimes be identified by angiography during the bleeding episode. Although angiodysplastic lesions occur mostly in the ileum and ascending colon, they may possibly occur in the small intestine. The spectrum of vascular malformations of the bowel, and the separation of acquired from congenital lesions, both of which may cause bleeding, are unsettled matters.

E. Exocrine Pancreas

I. The Aging Pancreas

There has been little study of age changes in the pancreas. Change in size with old age in humans has not been noted, although the pancreas may be at a lower position, sometimes descending so that the papilla of Vater is below the level of L-3 vertebra (WEBSTER 1978 b). Duct hyperplasia has been reported. The proliferating duct cells extend both into the lumen and between pancreatic lobules. This causes duct obstruction and alveolar degeneration. Locules may be formed. Adipose tissue invasion was also seen. In aged patients and at postmortem, retrograde pancreatography reveals dilated ducts and small cysts without evidence of obstruction.

In elderly people, a reduction in lipase in the duodenal juice has been reported (WEBSTER 1978 b). Amylase, trypsin, total volume, and bicarbonate were not altered. Response to stimulation of the pancreas by injections of pancreozymin and secretin in terms of volume was not affected by age, but response to repeated stimulation was diminished in the elderly.

II. Diagnostic Modalities

1. Radiography

Conventional radiography of the pancreas may sometimes be helpful. A flat plate may show calcifications in the pancreas. Barium studies may show extrinsic pressure on the duodenum or stomach. Extrinsic pressure on the duodenum can be brought out more clearly with the use of hypotonic duodenography. For identify-

ing small masses, sonography, and computerized axial tomography have been major advances. Sonography is valuable for the differential diagnosis of extrahepatic jaundice which, in the elderly, is often due to carcinoma of the pancreas. Computerized axial tomography is valuable for detecting tumors of the body and tail of the pancreas in the nonjaundiced patient. The procedure can be used to guide a needle into the pancreatic tumor and obtain an aspiration biopsy. Angiography is useful for detecting islet cell tumors, which are frequently highly vascular. It is also of use to determine if a pancreatic carcinoma has invaded blood vessels, and is, therefore, unresectable for cure.

2. Endoscopic Retrograde Pancreatography

Endoscopic retrograde pancreatography may be done alone or in conjunction with cholangiography. A cannula is inserted through the endoscope and is positioned opposite the ampulla of Vater, and into the opening of the duct. Dye is injected, the cannula is removed, and X-rays are obtained. The procedure is contraindicated in acute pancreatitis, but may be very helpful in the diagnosis of chronic pancreatitis, pseudocysts, and tumors.

3. Function Tests

Function tests of the pancreas are performed by insertion of a double lumen tube, so that pure duodenal juice is collected through one lumen. After stimulation of the pancreas by injection of secretin, pancreozymin, or both, the juice is collected, volume measured, and bicarbonate and enzyme concentration measured. In tumor, volume is frequently diminished, while in chronic pancreatitis, bicarbonate, and enzyme concentrations are diminished. Cytologic study of material obtained at time of this test or at endoscopic retrograde pancreatography may be helpful in the diagnosis of malignancy.

Attempts have been made to develop tubeless function tests, which would be simpler to perform and of less discomfort to the patient. A test using *N*-benzoyl-L-tyrosyl-*P*-aminobenzoic acid, which is split by chymotrypsin, has been developed (IMAMURA et al. 1978). If sufficient chymotrypsin is present, *P*-aminobenzoic acid is split off, and absorbed. It is then excreted in the urine, where it is measured.

Stool measurements of pancreatic enzymes are not helpful in adults. Since pancreatic insufficiency produces steatorrhea, qualitative and quantitative measurement of fecal fat is of value. Breath tests using C^{14}-labeled fat and fatty acid can be used. Pancreatic insufficiency causes intolerance to fat, but fatty acids can be absorbed. In small bowel steatorrhea, both fat and fatty acids are not tolerated. This differential can be used both in stool analysis and in breath tests.

Blood and urine levels of amylase and lipase are valuable in the diagnosis of acute pancreatitis. Since blood amylase is elevated in other conditions, attempts have been made to find a more specific measurement. The ratio of urinary amylase clearance to creatinine clearance appears to be more specific, although not absolutely so. The ratio may be elevated in several other conditions.

III. Diseases

1. Acute Pancreatitis

Acute pancreatitis may occur at any age, and is associated with a variety of etiologic factors. In elderly patients, the association with biliary tract disease is more frequent than in younger patients (WEBSTER 1978 b). Postoperative pancreatitis is also more common in the elderly. Other associations such as alcoholism, hyperparathyroidism, and idiopathy seem not to be age related. Since elderly patients are frequently on medication, drug-associated pancreatitis may occur. Incriminated substances that are important in elderly patients include corticosteroids, thiazide diuretics, furosemide, isoniazid, azathioprine, and anticoagulants.

The clinical presentation in the elderly may be different. Silent attacks are more common, the diagnosis being made at postmortem. Alterations of consciousness are common. As in younger people, pain, nausea, and vomiting are common. When hypotension occurs, cardiac and cerebral complications may occur in the aged. This contributes to the increased mortality in the elderly.

Acute edematous pancreatitis can usually be managed medically by analgesics and by maintaining the patient with intravenous fluid replacement and nothing by mouth. Nasogastric intubation and antibiotics are not of value in the mild to moderate case. In acute hemorrhagic pancreatitis, there is a high mortality with medical therapy, even when antibiotics and intubation are used. Peritoneal lavage, surgical drainage and perhaps pancreatic resection may be of value. Surgery is important if a pancreatic abscess develops. It is also important for management of a pseudocyst or pancreatic ascites.

2. Chronic Pancreatitis

Chronic pancreatitis may be of the relapsing kind, in which there are repeated acute attacks; it may present with chronic pain, or it may occur with little or no early symptoms, so that the initial manifestations are related to the maldigestion of pancreatic enzyme insufficiency (REBER 1978). Since pancreatic insufficiency probably takes many years to develop, it is seen in older, rather than younger patients. As with acute pancreatitis, chronic pancreatitis is most often associated with alcoholism and cholelithiasis. Trauma, malnutrition, and hyperparathyroidism are less common causes. Calcification of the pancreas is seen in about 30% of patients.

Pancreatic insufficiency does not occur until 90% of the secretory capacity is lost. Steatorrhea is the most prominent manifestation. Weight loss occurs in most patients. Both steatorrhea and weight loss are controlled by oral administration of pancreatic extracts containing the missing enzymes. Frequency of administration and potency of preparation used may be important to achieve optimal response. Concomitant use of antacids and/or cimetidine to suppress acid secretion can be important, since pancreatic enzymes are pH-dependent and most active in a slightly alkaline medium.

Complications of acute and chronic pancreatitis include pseudocyst formation, due to tissue necrosis and ductal obstruction. Since they may rupture, bleed, or become infected, it is suggested that if they do not resolve spontaneously in 4–6 weeks, surgery is indicated.

Jaundice may occur in acute and chronic pancreatitis. Usually it is mild and subsides spontaneously. Less commonly, the edematous, inflammed head of the pancreas may compress the distal common bile duct. Occasionally surgery is necessary to decompress the duct.

Pancreatic ascites is sometimes seen, the result of a persistent leak of pancreatic juice from a pseudocyst or torn duct. The ascites is usually massive. If the ascites does not subside with parenteral alimentation, surgery is necessary.

Diabetes is seen in many patients with chronic pancreatitis, especially in the presence of pancreatic insufficiency. The diabetes is usually mild and not associated with the complications of diabetes but occasionally may be severe.

3. Tumors

a) Adenocarcinoma

Adenocarcinomas arising from duct cells are the most common malignant tumor of the pancreas, and present a major problem in aged patients (Melnyk 1978). Their incidence is clearly rising. The reasons for the rise are unknown. Some suspected causes are cigarette smoking, dietary habits, and chemical carcinogens. Whether chronic pancreatitis and diabetes are precursors is still not settled, although some evidence links these diseases. It is slightly more common in men than women. The incidence of other malignant tumors of the pancreas is less than 4%.

The symptoms depend on the location of the tumor whether in the head of the pancreas or body and tail. In the latter site, pain and weight loss predominate; in the former site jaundice is also present. Sometimes unusual clinical syndromes are encountered. These include acute cholecystitis and pancreatitis, peptic ulcer syndrome, neuropsychiatric disturbances, pulmonary manifestations, arthritis, skin nodules, and diabetes. Since the pancreas is retroperitoneal, a mass may not be palpated until late in the course. This may delay the diagnosis, especially of body and tail lesions. It is hoped that the newer diagnostic technics of computerized axial tomography and sonography will detect pancreatic masses earlier than before.

The course of pancreatic carcinoma is usually brief, rapidly progressive, and downhill. At surgery, only about 14% are resectable and only about 2% survive 5 years. In many series there are no 5-year survivors. Palliative surgery has a role. Jaundice can be relieved by an anastomosis of the gall bladder or common duct to the intestine. Gastroenterostomy will palliate the duodenal obstruction which may be encountered toward the end. The nonoperative treatment involves the control of pain with analgesics and nerve blocks. Roentgen therapy and chemotherapy are used in an attempt to control tumor growth. Although recognized as among the least responsive tumors to chemotherapy, a few patients may respond to combined 5-fluorouracil and nitrosourea compounds.

b) Islet Cell Tumors

Pancreatic islet cell tumors have been of increasing interest in recent years. They occur in all age groups and are not common. They are thought to be from cells having their origin in the embryonic neural crest (Haubrich and Berk 1976). With other progeny of embryonic neural crest cells, they have the capacity to concentrate

and decarboxylate precursors of certain biogenic amines. They are referred to as APUD (amine precursor uptake and decarboxylation) cells. Whether benign or malignant, cytologically and histologically they appear similar. Their hormonal activity is more life threatening than the tumor bulk. Diagnosis and treatment depend largely on delineating and controlling this hormonal activity. Insulinomas, the most common, were the first to be clinically recognized. They may occur as an isolated entity or as part of the multiple endocrine adenomatosis syndromes (MEA). Gastrinomas produce the Zollinger-Ellison syndrome, which has both ulcerogenic and diarrheagenic features. The ulcerogenic potential, which in the short run is more life threatening than the slow growing tumor, was in the past treated by total gastrectomy. More recently it has been controlled by the combined use of cimetidine, an H_2 antihistamine, and anticholinergic drugs. Both insulinomas and gastrinomas sometimes respond temporarily to chemotherapy. Streptozotocin alone and in combination with 5-fluorouracil has been used. Tumors producing vasoactive intestinal polypeptide (VIP) result in a large volume watery diarrhea. Glucagonomas, a rare tumor, produce both diabetes and a necrolytic migratory cutaneous erythema resembling pemphigus. Single islet cell tumors may elaborate multiple hormones, some of which are inappropriate to the pancreas but consistent with the concept of islet cells being derived from multipotential cells.

c) Benign Tumors

Benign tumors of the pancreas are uncommon. They may be solid or cystic. Often discovered incidentally at surgery, they may sometimes grow large enough to be palpable and cause symptoms. Surgical removal is usually curative.

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The Large Intestine

A. M. Gelb and B. Straus

A. The Anatomy and Physiology of the Aging Large Intestine

There has been little study of the effects of aging on the colon. Reasoning that constipation is a common problem in the elderly, it has been supposed that the aging colon is atonic and atrophic (Schuster 1978 a). Autopsy study shows aging changes consisting of mucosal atrophy, cellular infiltration of the lamina propria, hypertrophy of the muscularis mucosa, atrophy of the muscularis propria, increased connective tissue, and arteriolar sclerosis (Brocklehurst 1978 a). Arteriosclerosis develops in the mesenteric vessels and the celiac axis.

Study of the effects of aging on colonic motility has been minimal. Part of the problem is methodological, i.e., measuring pressures in an open-ended cylinder. Balloons and open-ended tubes have been used, as well as movement of radiopaque markers. How to express the findings has been a problem. Clear-cut change in pressures with aging has not been described. Since propulsion occurs mostly in physically active people, the lack of physical activity in the aged may contribute to constipation (Brocklehurst 1978 b). Also, an increase with age in the amount of rectal distention required to produce discomfort has been noted. The rectums of constipated subjects were even less sensitive than others.

The appendix shows histologic changes, the lumen closing from the tip inward, so that by age 50 it has been obliterated in half the population (Schuster 1978 b). The occurrence of diverticula increases with aging, starting at about age 40.

B. Diagnostic Modalities

I. Radiography

The barium enema remains a very important diagnostic modality. In the aged, good preparation prior to the examination is of the utmost importance since residual fecal material may prevent a lesion from being detected, or be mistaken for one. Good preparation may be difficult to achieve in the elderly, but is essential, nevertheless. The preparation and barium enema may have to be repeated until a good study is obtained. The acceptance of poor studies, which occurs only too frequently, leads to missed lesions. The right colon should be filled with sufficient barium so that the appendix or terminal ileum is visualized. Otherwise, an obstructing lesion of the ascending colon may simulate the appearance of the cecum, and the lesion will have been missed.

The air-barium double contrast technique for barium enemas is favored by some radiologists. It allows study of mucosal detail, being especially valuable for the detection of small polyps, and early inflammatory disease.

Because of the convolutions of the colon, which result in overlapping on the X-ray film, the barium enema can be a very difficult examination for the radiologist. If the clinician has a strong suspicion of colonic disease, the examination should be repeated, or endoscopy performed, despite an initial negative study.

II. Endoscopy

Endoscopy with the rigid sigmoidoscope still remains an important examination for the study of the rectum and lower sigmoid, despite the fact that in a significant number of patients the scope cannot be fully inserted due to spasm and/or tortuosity of the lumen. Flexible colonoscopy with the fiberoptic colonoscope, however, has been a revolutionary development. Not only does it allow the entire colon to be visualized in the majority of instances, depending on the skill of the examiner, but it allows biopsy, cytologic brushing, and in the case of many polyps, complete removal. The complication rate is low, and the procedure is well tolerated in the elderly. Colonoscopy should not be regarded as a replacement for barium enema, but rather as a complementary procedure. A lesion is sometimes missed by one technique only to be discovered by the other.

Fiberoptic sigmoidoscopes have been developed. Their role has not yet been delineated. The symptomatic patient needing endoscopy should have a complete colonoscopy. Perhaps the flexible sigmoidoscope will be of value for the screening of asymptomatic people.

III. Fecal Examination

Fecal examination can provide a great deal of important information. Occult blood testing of the stool using a commercially available impregnated guaiac slide test is of value for screening asymptomatic populations for neoplasia (Winawer 1980). The procedure must be done in a prescribed way to be reliable. Even a single positive slide must be investigated with barium enema and/or colonoscopy. Positives will be found in 1%–2% of people, of whom about 50% will have significant neoplasia.

In patients with diarrhea, the volume of stool, normally 100–200 ml/day, may be important to measure. To define diarrhea in terms of stool volume is probably more accurate than in terms of frequency of stool, which can be very variable. The consistency is affected by diet, which may also alter the color.

Microscopic examination of the stool can be very helpful. Staining for fat gives a clue to steatorrhea. The presence of leukocytes suggests inflammatory disease.

Bacterial culture of the stool, and examination for parasites and ova are important for the diagnosis of diarrheal states. Three-day stool collections for fat measurement are still important for the precise measurement of steatorrhea. Perhaps in the future they will be replaced by breath tests using labeled fats and fatty acids. Electrolyte content and osmolality of the stool may sometimes be of value in the diagnosis of large volume diarrhea of obscure etiology.

C. Diseases of the Large Intestine

I. Functional Bowel Disorders

1. Irritable Bowel Syndrome

The irritable bowel syndrome involves a variety of disorders of bowel function, chronic, and recurrent, often associated with stress and emotional tension (ALMY 1978). Other terms include spastic colon and spastic colitis. The latter is a poor term since it is a noninflammatory disorder. Most emphasis has been on the colon, but the upper bowel can be involved. It affects people of all ages, not particularly the aged. In fact, it usually presents in childhood or early adulthood, and since it does not shorten life, persists into old age. To varying degrees, it may involve as much as 10% of the entire population, and 30–50% of all digestive disorders seen by the physician.

Although there is variation, three patterns are discernible: constipation and lower abdominal pain; painless diarrhea marked by numerous small stools; and alternating constipation and diarrhea.

Motility studies in the irritable bowel syndrome have been largely limited to the distal colon. Segmental, nonpropulsive contractions are increased in the constipated pain pattern, and decreased in the diarrhea pattern. Recent studies of myoelectric activity of the distal colon show an increased prevalence of low-frequency three-cycles-per-minute basic electric rhythm. The abnormality is present even during periods of remission. It may be responsible for the increased reactivity of the musculature to food and certain hormones and drugs that has been observed.

The association between the emotional state and disordered colonic function in patients with the irritable bowel syndrome is clear, although the interrelationship is not. It may be that the observed symptoms are normal bodily manifestations of emotional tension, which in people with the syndrome represent the upper end of a distribution curve. Perhaps they occupy the end of the curve because of the observed abnormality in basic electric rhythm, although this is hypothetical.

An important part of the diagnosis involves ruling out other conditions which may mimic the irritable bowel syndrome. Unfortunately the list of other conditions to be ruled out is large. The therapy has undergone changes recently. There is interest in a high-roughage, fiber-containing diet, often with added bran. This may help many patients, but not all. Stool-bulking agents, stool softeners, and anticholinergics to relieve spasm are useful. Tranquilizers may help. Support from an interested physician, who does not make the patient feel that he or she is responsible for the symptoms, and that a character weakness is at work that the patient should control, can be of great benefit. Reassurance that the condition is not serious is often helpful.

2. Constipation

Constipation among the aged is one of the most frequent complaints, having different meanings to different people. It may mean to some a hard stool while to others it refers to infrequent stool. Most people have from two bowel movements

a day to two a week. In at least one study, there was no difference in frequency in people over 60 compared to those under 60 (BROCKLEHURST 1978 c). The experience of most physicians, however, is that older patients are more often constipated than the general population. For the constipated older patient, laxatives and enemas are often required.

Constipation occurs in many diseases (DEVROEDE 1978). Many systemic disorders, metabolic and endocrine, which occur in the aged may be responsible. Medications used in the elderly may cause it. Neurogenic diseases, to which the elderly are prone, may be accompanied by constipation. A large number of gastrointestinal diseases may have constipation as a feature, and include both organic and functional disorders. When constipation is of recent origin, it is particularly important to rule out a malignancy. In the aged, in addition to the atrophy of aging, lack of physical exercise, being bedridden, dietary factors (lack of fiber), chronic use of laxatives, and enemas are all contributing factors.

A high-residue diet, added bran, fluids, and exercise may be helpful in preventing constipation in patients with a recurring problem. A variety of stool softeners and laxatives are available. Mineral oil can be helpful. Judicious use of enemas and suppositories may be necessary. There is some doubt as to whether aged patients with constipation can ever be retrained with regard to bowel habits. It often comes down to trial and error to find the best program for the individual. In some centers, surgical disruption of the sphincter has been used.

Megacolon and megarectum may occasionally occur in elderly patients due to constipation, diabetic autonomic neuropathy, and parkinsonism. The possibility of a primary muscular disorder or neurogenic degeneration, perhaps secondary to chronic laxative abuse, has been raised.

3. Incontinence

Fecal incontinence occurs in aged patients from three main causes. It may occur because of local disease involving the colon, rectum, and anus. It may occur secondary to fecal impaction in which there is seepage of liquid stool around the impaction. Thirdly, it may occur due to neurogenic changes. There is evidence to suggest that in some incontinent elderly patients, distention of the rectum is followed by rectal contractions, and inhibition of anal contractions. Therapy involves excluding local disease and eliminating impaction, should that be responsible. Neurogenic incontinence is treated by inducing constipation with medication, followed by periodic induced evacuation. Electric stimulation of the sphincters, and operant conditioning involving biofeedback techniques have also been used.

II. Diverticular Disease

Diverticular disease is a common problem in the elderly, with the risk of developing diverticula nearly 50% (ALMY and HOWELL 1980). The incidence varies in different geographic areas and ethnic groups. It is found most often in developed western nations. Epidemiologic evidence suggests that environmental causes predominate in its etiology. Attention has been focused on a low-fiber diet as being responsible for its increased incidence in recent decades.

The majority of patients with diverticula never have symptoms, the diverticula being discovered incidently. Among the rest, symptoms may vary from episodes of mild recurrent lower abdominal pain to severe inflammation, sometimes with abscess and/or fistula formation of perforation.

The pathogenesis of diverticula, which are really pseudodiverticula, is not entirely clear. It is assumed that it involves both a pressure gradient from the lumen outward, and areas of relative weakness of the colonic wall. Motility studies had suggested that the high pressures that develop in occluded short segments of bowel due to muscular spasm cause the herniation in the place where the blood vessels penetrate the muscular layer, a point of weakness. The irritable bowel syndrome was thought to be a precursor. Hypertrophy of the muscular layer has been described. More recent studies in asymptomatic people with diverticula have revealed a majority with normal motility patterns, casting doubt on the older hypothesis. It is pain, with or without diverticula, that appears to be related to hypermotility.

Therapy depends on the stage of the pathologic process and the severity of symptoms. Patients with pain and disordered bowel movements can often be managed with high-fiber diets, sometimes with added bran, antispasmodics, and analgesics. Antibiotics are used when diverticulitis is suspected. If inflammation does not respond to antibiotics, or if abscess, perforation, fistula, or obstruction develops, surgery is indicated.

Hemorrhage may occur from uninflamed diverticula. Intramural arterial branches run in close proximity to the neck and dome of the outpouching. Intimal thickening and eccentric rupture of these branches on the side of the vessel facing the bowel lumen have been described. The bleeding usually stops spontaneously, although volume loss may be large before bleeding is appreciated because of the capacity of the colon to contain a large amount of blood. With persistent bleeding, intraarterial infusion of vasopressin has been used. Occasionally, surgery is necessary for persistent bleeding. Prior to surgery, the site of bleeding should be localized by selective abdominal angiography. The right colon is more commonly the site of bleeding than the left colon. Whether hemicolectomy or subtotal colectomy is to be done depends on the clinical situation and judgement of the surgeon. The extent and distribution of diverticulosis enters into the decision. If bleeding does stop spontaneously, the incidence of rebleeding is low enough that elective surgery is not indicated after the first bleeding episode. Depending on the clinical situation, elective surgery should be considered after the second or third episode. Bleeding from a diverticulum should be differentiated from bleeding from angiodysplasia of the cecum or right colon since the latter usually requires a more limited resection.

III. Appendicitis

Appendicitis in the elderly is not common, although it may be increasing in incidence (OWENS and HAMIT 1978). It is, however, a more serious disease with a much higher morbidity and mortality than in younger people. The presenting signs and symptoms are more variable in the aged. There are other explanations for the increased risk. There are other causes of intraabdominal inflammation in older people. Concomitant chronic disorders are more common. Older people may be more likely to bear pain without complaining, which may lead to delay in seeking medi-

cal attention. Defense against inflammation is diminished, which causes rapid progression. The latter two factors may be particularly important since the incidence of gangrene and rupture at surgery is much more common in elderly patients.

Anatomic changes in the aging appendix have been described. The lumen is narrowed or obliterated, the mucosa is thin, and there is fibrosis and fatty infiltration of the muscular wall. Arteriosclerosis is present. Since rapid progression to gangrene and rupture occurs, a high index of suspicion and early surgery is important. It has been stated that if all patients over age 50 admitted for possible appendicitis had surgery almost immediately, mortality would be reduced since the death rate from missed appendicitis and delayed surgery is greater than from unnecessary appendectomy (HOWIE 1970).

IV. Vascular Insufficiency

Vascular insufficiency of the colon, manifesting itself as ischemic colitis, is an important problem in elderly patients. The extent of disease depends on the location and extent of the vascular compromise, and on other systemic conditions (OCKNER 1978). Nonthrombotic infarction may occur,as well as interruption of the circulation by thrombus and embolism. Less commonly, vasculitis, hypercoagulable states, amyloid, and carcinoma may be responsible and may follow vascular surgery in the abdomen. The region of the splenic flexure is particularly vulnerable because it is the area where branches of the superior mesenteric and inferior mesenteric arteries anastomose. Other segments of the bowel, including recto-sigmoid, can be involved. The involved colon usually lies between two adjacent arterial supplies.

Ischemic colitis may be quite variable in its presentation, and in its prognosis. It may present in catastrophic form with abrupt onset of abdominal pain and rectal bleeding. With bowel infarction, an acute surgical abdomen quickly develops, and surgery is required if the patient is to survive. At the other end of the spectrum the presentation may be more benign, and the patient and bowel may recover without surgery. Sometimes the healing occurs with stricture formation, which may require surgery at a later date.

An important clinical clue to the presence of ischemic colitis and other vascular syndromes is that, at least initially, the severe pain which begins suddenly is usually out of proportion to the physical findings. Only after some hours do the signs of the peritonitis resulting from infarction appear. Angiography may sometimes be helpful, but frequently will be normal. Moreover, since vascular narrowing is so common in elderly patients, its presence does not prove the diagnosis of ischemic vascular disease. If the patient's clinical condition permits, barium enema can be performed. A characteristic thumbprinting due to submucosal hemorrhage is often present. On endoscopy, the same submucosal hemorrhage can be identified as blue-black nodular lesions.

Initial treatment is supportive. If, during frequent observation, the patient's condition deteriorates, then surgery is indicated. The early administration of drugs that inhibit vascular spasm, such as intravenous papaverine, may improve the prognosis, and possibly make surgery unnecessary in some patients.

V. Vascular Ectasia

Vascular ectasia (angiodysplasia) of the large bowel may be a more common cause of lower intestinal bleeding than previously suspected (BALINT et al. 1977). How common is not clear since its establishment as an entity is recent. Formerly, if no other cause of bleeding could be identified, diverticular disease was held responsible. Now, vascular ectasias can be identified by angiography and colonoscopy even in the absence of bleeding (WOLFF et al. 1977). These lesions are thought to be degenerative lesions associated with aging, rather than malformations. The dilated, tortuous submucosal veins may be due to repeated, partial, intermittent, low grade venous obstruction over a period of years at the place where the veins pierce the muscular layers of the colon. They are usually multiple, and are located in the right colon but may occur elsewhere in the bowel. They are common, being found in as many as one-quarter of elderly patients without any bleeding. In those who bleed, hemorrhage may stop spontaneously or may respond to vasopressin infusion. Only a few require surgery for persistent bleeding. Hemorrhage tends to be recurrent. Because of this, surgery has been recommended even if the bleeding ceases. This is in contrast to bleeding from diverticular disease, in which bleeding is seldom recurrent, and in which surgery is not indicated unless bleeding continues or recurs.

Vascular ectasias have been reported to occur in the small bowel. Their relationship to telangiectasias, vascular malformations which may be hereditary or spontaneous, is not clear. Whether these lesions are part of a spectrum or separate is not settled. Vascular ectasias have been associated with aortic stenosis, although the cause and effect relationship is unknown.

VI. Infectious Disease

Infectious disease of the bowel occurs in all age groups. Because of complicating conditions, it is more serious in older patients. Also, it may be more of a problem to the extent that the aged are institutionalized since transmission is facilitated.

1. Bacteria

Bacteria account for many infections. They have been shown to produce their effects either by a toxin, by direct invasion, or by a combination of both (BRANDBORG 1978). *Shigella* prefers the colon, producing bacillary dysentery, characterized by fever, cramps, tenesmus, and bloody diarrhea. Since this is a virulent organism, an innoculum of very few bacteria is needed to produce disease. In mild cases, the patient may improve spontaneously in several days. In more severe disease, treatment with ampicillin may shorten the illness. *Salmonella* mainly involve the small bowel, but may also involve the colon. *Campylobacter* may cause acute colitis as well as enteritis (SKIRROW 1977). Its identification requires special culture techniques. In some situations, it may account for 10%–15% of acute enterocolitis. Erythromycin is the preferred treatment.

Pseudomembranous enterocolitis may develop during or after antibiotic therapy (BARTLETT et al. 1980). Although associated with clindamycin in the past, a wide variety of antibiotics may be responsible. The responsible agent is toxin-producing

Clostridium difficile, which proliferates when other colonic bacteria are repressed. The whitish membranes seen on endoscopy of the colon are quite characteristic. The diagnosis usually has to be made on clinical grounds, since most laboratories are not set up to isolate the organism or demonstrate the toxin. This disease, which was formerly fatal in the majority of instances, has been shown to respond to oral vancomycin. Since the pathogenesis of pseudomembranous colitis has been elucidated, it has been shown that many, if not most, cases of postantibiotic diarrhea in which there is minimal to moderate inflammation of the colon are due to the toxin of *Clostridium difficile*.

2. Parasites

Parasites involve the colon not infrequently. Because of increased travel, they are an increasing clinical problem. Amebiasis may run the gamut from an asymptomatic carrier state to fulminant colitis, which may be difficult to distinguish from nonspecific ulcerative colitis. If endoscopy reveals discrete ulcers separated by seemingly normal mucosa, this favors amebiasis. Before treatment of ulcerative colitis with steroids, it is important that amebiasis be excluded since steroid treatment will greatly aggravate amebiasis. Besides stool examination and mucosal biopsy, serologic tests are useful. Several different treatment programs for amebic colitis are available.

Tuberculosis of the bowel as an isolated event is rare. When it does occur, the ileocecal region is most often involved, although any part of the bowel can be involved.

Schistosomiasis is an important problem on a world-wide basis. During the acute stage, colitis may develop. In the chronic stage, which involves the liver, the organisms can still be found in the stool and on rectal biopsy.

VII. Inflammatory Bowel Disease

Inflammatory bowel disease may either appear de novo in the aged, or, more commonly, appear earlier but persist for many years extending into old age. Whether nonspecific ulcerative colitis and Crohn's Disease are different diseases or part of a spectrum is not clear, and may not be clear until their precise etiologies are established (KIRSNER 1978). There are enough clinical differences, however, to consider them separately. In both diseases a bimodal age incidence has been reported, with the second peak around the age of 70. With granulomatous disease, the peak in the elderly mainly involves the colon. That this second peak in the elderly really represents ischemic colitis, which mimics inflammatory bowel disease, has been suggested (EISENBERG et al. 1979).

1. Ulcerative Colitis

Ulcerative colitis is of unknown etiology. Theories concerning cause involve primarily infectious and immunologic factors. Genetic and psychosomatic factors al-

so play a role. Inflammation is confined to the mucosa and adjacent submucosa, and is continuous without skip areas. Frequently the entire colon is involved although the disease may be segmental. The clinical course runs the gamut from mild to fulminant. Remissions and exacerbations are common. Less often the course is continuous. There is nothing that is absolutely specific for the diagnosis. Colitis of known etiology, such as bacterial, parasitic, or ischemic, must be excluded by appropriate tests. Extraintestinal manifestations occur in the elderly as they do in younger patients.

Therapy involves, besides general support, the use of corticosteroids and ACTH, and sulfasalazine. When and if the acute episode is brought under control, maintenance therapy with sulfasalazine may prevent recurrance. The indications for surgery, which usually involves total colectomy, are intractable disease and complications, such as toxic megacolon, severe hemorrhage, perforation, and extensive perianal disease.

Surgery in the elderly patient with ulcerative colitis is a problem. It has been suggested that for acutely ill patients, earlier operative intervention should be considered (Windle and Street 1979). Elderly patients accept and manage an ileostomy as well as younger patients (Abrams et al. 1975). The eventual outcome in older patients is complicated by a failure to correctly diagnose the disease at the onset and differentiate it from other colonic disease of the aged, and by a high incidence of associated disease of other organ systems.

Carcinoma of the colon occurs in patients with ulcerative colitis with an increased incidence related to the duration of colitis and to the extent of colonic involvement. With less than a decade of disease, the carcinoma risk is small, rising steeply to a cumulative incidence of 25%–40% at 25 years. The cancer tends to be flat and infiltrative rather than polypoid. Not uncommonly, it is multicentric. The clinical course is virulent, although the cure rate in older patients is better than in younger ones. Attempts are being made to identify patients with ulcerative colitis at risk for carcinoma. Patients with ulcerative colitis of more than 8–10 years duration should have yearly proctosigmoidoscopy, and colonoscopy every 2–3 years, at which time multiple biopsies should be obtained. Moderate to severe mucosal dysplasia on multiple endoscopic biopsies may be an indication for colectomy (Nugent et al. 1979).

2. Crohn's Colitis

Crohn's colitis may occur with only colonic involvement or may occur as ileocolitis. As with ulcerative colitis, the etiology is unknown, and infectious, immunologic, genetic, and psychomatic factors have received consideration. Successful transmission experiments in animals have focused attention on a possible viral agent, although this is by no means certain. While the incidence of ulcerative colitis seems to be steady, Crohn's disease is increasing in incidence for unknown reasons.

Pathologically, advanced Crohn's disease is characterized by transmural inflammation. The bowel is thickened, stenotic, with deep linear ulcerations, which give a cobblestone appearance. The lymphatics in the bowel wall and the mesenteric nodes are involved. Granuloma formation is found in most specimens but is absent in many. The early lesion has been identified as a aphthous-like ulcer, which

can be identified on double contrast barium enema and on endoscopy, as well as in the gross specimen. The anatomic distribution of colonic disease is characteristically segmental with the right side predominating. The majority of patients have ileal and colonic involvement, although the colon may be diseased alone. Skip areas are common. Usually, but not always, the rectum is spared, although biopsy of a seemingly normal rectum may show granulomata.

The clinical course is marked by remissions and exacerbations. It is more likely than ulcerative colitis to have perianal complications, abscess formation, and fistulas. Rectal bleeding is less likely. As with ulcerative colitis, extraenteric complications are frequent. The incidence of carcinoma is increased compared to normals, but not of the magnitude as in ulcerative colitis. The two diseases can be differentiated also on the basis of radiographic and endoscopic findings.

When Crohn's disease involves the sigmoid colon in an elderly patient with diverticulosis, there may be confusion with diverticulitis. In an occasional patient diverticulitis may coexist with Crohn's colitis. If a patient with supposed diverticulitis has atypical features and fares poorly, especially after surgery, inflammatory bowel disease should be suspected. As with ulcerative colitis, bacterial, parasitic, and ischemic colitis must also be considered.

The therapy of Crohn's disease is similar to that of ulcerative colitis, the major modalities being corticosteroids and sulfasalazine. Whether azathioprine and 6-mercaptopurine have a role is not clear. A major difference between the two diseases is that ulcerative colitis is cured by total colectomy, while Crohn's disease may not be. The recurrence rates and reoperation rates are high. In Crohn's disease, one buys time with surgery, which may be especially important in the elderly. The most common indication for surgery in patients with colonic involvement is intractability. If the disease is segmental, segmental resection may suffice.

VIII. Colorectal Cancer

Colorectal cancer is the most common gastrointestinal cancer. When the incidence in both sexes is combined, it is the most common of all cancers, and thus a major problem in the aged. More than 94% are adenocarcinomas (SCHOTTENFELD and HAAS 1978). The age-specific incidence rates rise steadily until age 85, after which a slight drop off is noted, perhaps due to incomplete case findings in the very old. Colon cancer involves both sexes at similar rates, while rectal cancer is more common in men. Geographic variations in incidence are quite striking, being highest in the developed countries of the West and lowest in the developing nations of the East. Migration studies, in which after one generation the incidence in migrants from the East approaches that of the West, suggest that environmental factors play the major role in etiology. Genetic influences are of lesser importance. Race, social class, and occupation may also have a role, although not a major one.

Certain diseases are considered premalignant. These include ulcerative colitis and to a lesser extent, Crohn's colitis. Familial polyposis and its variations are closely related to the subsequent development of malignancy. Certain families have been noted to be cancer prone, even without the occurrence of polyposis. The vast majority of adenocarcinomas, if not all, are considered to arise in adenomatous tis-

sue (LANE et al. 1978). De novo carcinoma is rare if it occurs at all. As the carcinoma grows, the adenoma from which it arose is destroyed. Since there are many more adenomas than carcinomas, only a fraction of adenomas give rise to malignancy. The transition from adenoma to focal carcinoma to invasive carcinoma is slow, probably extending over many years.

There has been a great deal of attention given to the role of diet in the etiology of colorectal cancer. Increased beef and decreased fiber in the diet of people in developed countries has been held responsible. Alterations in the bacterial flora by diet, which may affect bile acid metabolism in the bowel lumen, have been postulated as the mechanism.

Most adenocarcinomas occur in the rectum and sigmoid colon. There is a suggestion that in recent years the incidence in the more distal bowel is decreasing, while the incidence more proximally is increasing. Multiple carcinomas, either synchronous or metachronous are common, as are coexisting adenomas. Colorectal carcinomas may spread either by direct extension to adjacent structures, or by invasion of lymphatics and blood vessels.

Symptoms may be absent or minimal in the early stages. As the malignancy grows, pain, change in bowel habits, hematochezia, anemia, and obstruction may occur (HAUBRICH and BERK 1976a). Obstruction is more common with left-sided lesions due to the narrower caliber of the lumen. Right-sided lesions may grow to be quite large without significant symptoms. Sometimes right-sided lesions present with anemia and anemia-associated symptoms. Sometimes the initial symptoms are from metastatic disease. After the regional lymph nodes, the liver, peritoneum, lung, and distant nodes are the most common sites for metastases. Seemingly unrelated symptoms may accompany the disease. Acanthosis nigricans, dermatomyositis, neuropathy, and endocrine abnormalities have been associated. A palpable abdominal mass is frequently present especially in right colon lesions since the tumor can grow to significant size without producing symptoms. Rectal examination is still a valuable part of the physical examination since the majority of rectal carcinomas can be thus detected.

The major techniques for diagnosis are radiography and colonoscopy. Patients over the age of 40 who have change of bowel habits that persist more than a few weeks, and/or the onset of rectal bleeding, should have one or both tests. How to screen asymptomatic people has received consideration. It has been suggested that yearly stool examination for occult blood with the hemoccult test and proctosigmoidoscopy every 2–3 years in the most effective way. Even a single positive hemoccult slide should be followed by either X-ray or colonoscopy. Whether proctosigmoidoscopy with the conventional rigid scope or with the newer flexible fiberscope is more "cost effective" for screening has not been settled. Also unsettled is how to screen people of higher than average risk. They include people with a history of prior colorectal carcinoma or polyps, members of families with hereditary polyposis or cancer family syndrome, and perhaps women with breast or genital carcinoma.

Tumor-specific antigens that would be useful for screening have been sought. Carcinoembryonic antigen (CEA) levels in the serum reflect the tumor bulk and spread. Useful for detection of recurrence after surgery or metastatic disease, they have not proved useful in screening.

Surgery is the treatment of choice in the vast majority of instances. Even far-advanced tumor usually requires surgical palliation. In elderly patients, more than 70 years, the resectability rates are lower, and the surgical mortality higher than in younger patients (KRAGELUND et al. 1974). With intensive preoperative preparation, the mortality can be reduced. Carcinoma of the lower rectum presents a special problem since abdominal perineal resection and colostomy is the conventional operation. Various sphincter-saving procedures have been tried in order to maintain continence.

Radiation therapy has been used before and after surgery in an attempt to improve results. It is of occasional benefit as palliation when surgery is not possible. Chemotherapy, particularly with 5-fluorouracil alone or in combination with other agents will produce remission in some patients with recurrent or metastatic disease. Whether chemotherapy during and after surgery improves survival is not certain.

Prognosis depends on multiple factors. The degree of penetration of the bowel wall, the involvement of regional nodes, and the histologic grade are all important. Classifications have been developed to standardize these elements in order to predict outcome more accurately and compare results. The original Dukes' classification is: (A) not beyond the muscularis propria; (B) into the pericolic tissues in continuity and no lymph node involvement; (C) regional lymph nodes; and (D) distant metastasis. Modifications of the original Dukes' classification have been used, in which (A) is confined to the mucosa, (B) extends into but not through the muscularis propria, (B-2) involves the serosa and pericolonic tissues and (C) and (D) are as in the original Dukes. Broders' classification, less commonly used, has to do with the percentage of well-differentiated cells. Lesions that are detected by screening in asymptomatic people are likely to be early, confined to the bowel wall, and have a 5-year survival of well over 80%. The overall survival is somewhere about 50%, the colon cancer patients doing better than the rectal cancer patients. Patients surviving colorectal cancer must be followed since new cancers appear with a frequency greater than in the general population. Whether dietary manipulation involving less-saturated fat and more fiber will decrease the incidence of colorectal carcinoma is speculative.

Malignant tumors, other than adenocarcinoma, are uncommon. They include sarcomas and melanomas. Squamous cell carcinoma may occur at the anorectal junction. Cloacogenic carcinoma, derived from transitional cells, also occurs at the anorectal junction.

IX. Benign Tumors

Benign tumors of the colorectal area are an important problem for elderly people. Referred to imprecisely as polyps, this term refers to any outgrowth on the luminal surface (HAUBRICK and BERK 1976b). Benign tumors can be either neoplastic or nonneoplastic. The latter are either hyperplastic, inflammatory, or hamartomas. They have little or no potential for malignant transformation and rarely present a clinical problem except in the differentiation from true neoplasm. It is the benign neoplasm that is important because of its potential for the development of malignancy.

The important benign neoplasms are those of epithelial origin. Based on morphology, they can be divided into tubular adenomas, villous adenoma, and mixed villotubular adenomas, the latter being a mixture of the first two. Their frequency increases with age, being present eventually in about 10%–15% of older people. Their etiology is not understood. Environmental influences such as diet which are operative in colorectal carcinoma may also operate for adenomas. There are probably also genetic influences in sporadic adenomas. The genetic influence in the multiple polyposis syndromes is clear.

While it may be true that all carcinomas arise from preexisting adenomas, it appears that only a small percentage of adenomas become malignant. A spectrum of malignant changes is noted from cellular atypia to "carcinoma-in-situ" to invasive carcinoma. "Carcinoma-in-situ" indicates that the malignancy is superficial in the adenoma and has not penetrated the muscularis mucosa. The transformation to invasive carcinoma, when it does occur, is thought to be slow, perhaps taking 10–15 years. The etiology of malignant transformation is not understood at all. It is much more common, however, in villous adenomas, which tend to be sessile, than in tubular adenomas, which are likely to have a well-defined pedicle. The larger the adenoma the more likely it is to contain malignancy. In those less than 1 cm in diameter, malignancy is a rare finding.

Occasionally a benign neoplasm will cause rectal bleeding, but the majority are asymptomatic, being detected by screening examination as is performed for detection of colorectal cancer. Colonoscopy has been a major advance in detection. Many polyps can be detected by single contrast barium enema examination. Double contrast barium enema examination appears to be especially valuable for the detection of small lesions. Techniques for the examination of the proximal colon have made it apparent that the preponderance of lesions in the rectum and sigmoid is not as great as formerly thought. Adenomas may be found in any part of the colon. Also multiple polyps, from two to five in number, are common. Multiple sporadic polyps should be distinguished from the genetic multiple polyposis syndromes, in which there are usually more than 100 lesions, and in which eventually malignancy will occur in all patients.

Colonoscopy has been a major advance in the treatment of adenomas. Pedunculated lesions can usually be removed in one piece by use of a wire snare, and the application of electrocautery. Many sessile lesions can be removed in similar fashion, although it may have to be done in sections. Surgery may be required for large, sessile lesions. If malignancy is found in the removed specimen, the need for surgery will depend on the invasion of the carcinoma through the muscularis mucosa, into lymphatic and vascular channels, the histologic degree of differentiation, and whether adequate uninvolved margin is present. Follow-up colonoscopy in about 3–6 months is necessary in patients who have a sessile adenoma removed since there may be recurrence. It is also necessary in those in whom a pedunculated lesion is completely removed since such patients are at increased risk for the development of new adenomas. In this group initial follow-up should be in about 1 year, and subsequent follow-up about every 2–3 years.

Lipomas occur in the colon, particularly in the region of the ileocecal valve. These soft rubbery tumors usually require no treatment, and must be differentiated from other tumors.

Carcinoids occur in the colon occasionally and often involve the appendix. They usually do not cause carcinoid syndrome. Small lesions, less than 1 cm, can sometimes be removed through the colonoscope. Larger lesions should have more radical surgical resection since they may metastasize.

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The Liver and Biliary System

D. E. HYAMS

A. Liver

I. Physiological Aging

1. Anatomical Changes

The liver loses weight from 50 years onwards (BEAN 1926; RÖSSLE and ROULET 1932; BOYD 1933; MEYER et al. 1964; THOMPSON and WILLIAMS 1965). Racial and environmental differences occur in this age-related loss of liver weight (TAUCHI and SATO 1975). Liver weight correlates with total body weight (THOMPSON and WILLIAMS 1965).

Liver volume (measured by ultrasound) decreases with age in adults and correlates with total body weight, lean body mass and body surface area (RASMUSSEN 1978).

In extreme old age, the liver may be particularly small (550–1,400 g) (HOWELL 1978; ISHII and STERNBY 1978).

Eventration of the right lobe of the liver increases with age, especially in elderly women (OKUDA et al. 1979).

Hepatic blood flow decreases with aging (VESTAL et al. 1978). Drugs with high hepatic extraction may show altered pharmacokinetics in old age (VESTAL et al. 1978).

Microscopic studies in aging human liver have shown fewer but larger hepatocytes, with more binuclearity (TAUCHI and SATO 1978) and enlarged nuclei with cytoplasmic inclusions (ANDREW 1971). Mitochondria decrease in number and increase in size; their cristae show increased density. These changes appear earlier but progress more slowly in whites in the United States than in native Japanese; nutritional as well as racial factors are involved (TAUCHI and SATO 1978). Lipofuscin granules increase and lysosomes enlarge (LINDNER et al. 1977).

Increased collagen deposition occurs in aging human liver (BARROWS et al. 1980). Portal fibrosis is common without evidence of liver disease (WANLESS and SEGER 1980).

2. Functional Changes

a) Biochemical Changes

Age changes in chemical composition of the liver include: increased lipid, decreased glycogen and ascorbic acid (FINDOR et al. 1973).

b) Enzymatic Changes

There is indirect evidence of decreased enzyme activities and decreased enzyme induction in the elderly (SALEM et al. 1978) (see next section).

c) Hepatic Drug Metabolism in Old Age

The influence of age-related reduction in hepatic blood flow on the hepatic metabolism of some drugs has been mentioned above. The intrinsic hepatic clearance of drugs may also change with age due to reduced activity of liver microsomal drug-metabolizing enzymes and alterations in microsomal enzyme induction.

Direct evidence of reduction in microsomal drug metabolism is lacking in elderly human subjects, but indirect evidence suggests that such changes do occur (O'MALLEY et al. 1971, 1978; TRIGGS and NATION 1975; CROOKS et al. 1976; KLOTZ and WILKINSON 1978; VESTAL et al. 1978; SCHMUCKER 1979). However, no consistent pattern has emerged from the published studies (KLOTZ and WILKINSON 1978).

Cigarette smoking may induce drug-metabolizing enzymes in young adults, but the elderly are resistant to this effect (VESTAL et al. 1978). Reduced induction of drug metabolism has been reported in geriatric patients (SALEM et al. 1978).

Drug interactions are more likely in elderly patients, who often receive multiple drugs (MACLENNAN 1974; HYAMS 1981). In view of the multiple pathology characteristic of illness in old age, such interactions may escape recognition.

d) Changes in Liver Function Tests

In general, biochemical tests of liver function show little or no change with advancing years (THOMPSON and WILLIAMS 1965).

Serum alkaline phosphatase (SAP) levels in old age remain a controversial subject, some authors finding an age-related increase (CLARK et al. 1951; HOBSON and JORDAN 1959; KLAASSEN 1966; SHARLAND 1972; LEASK et al. 1973) and some finding no increase (THOMPSON and WILLIAMS 1965; CANAPA-ANSON and ROWE 1970; HODKINSON and MCPHERSON 1972; KAMPMANN et al. 1975). An age-related increase may be seen in women only (ROBERTS 1967; KEATING et al. 1969; CHEN and MILLARD 1972; REED et al. 1972). A slight increase may remain within the normal range (HEINO and JOKIPII 1962). Enzyme-inducing drugs may increase SAP (FLANAGAN et al. 1977); otherwise an increase may result from skeletal changes despite lack of clinical features (WOLF 1978). Occult osteomalacia is common in the elderly (EXTON-SMITH 1978). Low plasma 25-OH vitamin D_3 levels are common in old age (STAMP and ROUND 1974) and low 1, 25$(OH)_2$-D_3 levels have been reported in postmenopausal women (GALLAGHER et al. 1976). However, SHARLAND (1972) reported that the increased serum 5′-nucleotidase levels seen in 15 of 70 "healthy" non-hospitalized old persons were due to the liver isoenzyme in most instances.

Serum bilirubin shows no age-related trend (THOMPSON and WILLIAMS 1965; SHARLAND 1972; LEASK et al. 1973; KAMPMANN et al. 1975; FLANAGAN et al. 1977), nor do serum aminotransferases (THOMPSON and WILLIAMS 1965; KAMPMANN et al. 1975).

Serum albumin is often low in the elderly (BOCK 1948; CHEN and MILLARD 1972; REED et al. 1972; WEEKE and KRASILNIKOFF 1972), especially in ill old people in hospital (HODKINSON 1973; FLANAGAN et al. 1977; MACLENNAN et al. 1977).

Prothrombin time is normal in the elderly unless vitamin K deficiency exists (HAZELL and BALOCH 1970).

Many authors have reported increased bromsulphthalein (BSP) retention in old age (THOMPSON 1977; SKAUNIC et al. 1978), due to selective reduction in the uptake and relative storage capacity (S) of BSP by the liver without any age-related change in the maximum secretory rate (T_m) for BSP. BURKE (1974) stressed that these results are not reflecting hepatic excretory function.

Of all these age-related changes in liver function, those of major practical importance for geriatric medicine relate to the handling of drugs and to the synthesis of proteins which bind not only drugs but also hormones and ions.

e) Bile Formation and Composition

In an evaluation of the intravenous sodium glycocholate test in subjects without evidence of liver disease, BECKETT et al. (1980) found that the clearance of the bile salt was inversely correlated with age.

VALDIVIESO et al. (1978) found increased biliary cholesterol and lithogenic index in elderly Chilean women. This accords with BERTOLINI's (1969) statement that the bile of the elderly is richer in cholesterol than that of younger subjects; he also described smaller volume, greater viscosity and decreased inorganic constituents. Biliary lecithin may be decreased after middle age (FUJIYAMA et al. 1979).

II. Diseases of the Liver in Old Age

1. Clinical Evaluation

A careful history (including a detailed drug history) and clinical examination are mandatory.

a) Biochemical Investigation

1. *Urine and stool tests* should be employed as for younger patients.
2. *Liver function tests* fall into three main groups:
   (i) *Excretion* (bilirubin, BSP, bile salt tests)
   (ii) *Liver cell integrity* (enzymes and flocculation tests)
   (iii) *Synthesis* (proteins)

The standard tests often performed are serum bilirubin, alkaline phosphatase and aminotransferases (ASAT and/or ALAT). Serum alkaline phosphatase (SAP) has been considered above, in relation to aging. For clinical purposes it falls into groups (i) and (iii). In view of the controversy over normal values in old age, the standard normal range should be used (21–93 units/litre, or 3–13 King-Armstrong units/100 ml). SAP is increased in jaundice; in obstructive jaundice it will usually exceed 210 units/litre (30 K-A units/100 ml) – but this is not invariable (STERN et al. 1973). Since SAP may be derived from bone or gut as well as liver, the source of any excess may be clarified by measuring other enzymes known to be increased in cholestasis (5′-nucleotidase or leucine aminopeptidase) or by electrophoresis;

but it has been shown that after a fracture the increased SAP (which may persist elevated for several months) is not always due to the bone isoenzyme, and in some cases may be due entirely to the liver isoenzyme (SHARLAND and OVERSTALL 1978). This may be related to events connected with operation (e.g. anaesthesia) or to poor health in the patients. Increased SAP may be artefactual (e.g. storage of serum in a refrigerator for 12–24 h – MASSION and FRANKENFELD 1972), or physiological (e.g. normal adults of blood groups B or 0 who are secretors have increased SAP (derived from small intestine) after a fatty meal – WOLF 1978).

For all these reasons, the diagnostic value of elevated SAP concentrations in evaluating liver disease may be lessened; nevertheless it is frequently a valuable adjunct in laboratory investigation. Serial tests may be helpful in diagnosis and prognosis.

Serum aminotransferases increase due to hepatocellular damage – and to muscle damage. The highest levels occur in acute hepatic necrosis – except that they may fall again in fulminating cases when most hepatocytes have been destroyed. Modest increases occur in acute alcoholic hepatitis; an ASAT/ALAT ratio greater than 2.0 is said to be strongly suggestive of alcoholic liver disease (COHEN and KAPLAN 1979).

Serum gammaglutamyl transpeptidase (GGPT) is increased in cholestasis (intra- or extrahepatic), hepatitis, cirrhosis, and infiltrations of the liver. It is a sensitive indicator of alcohol-induced liver damage (although glutamate dehydrogenase is more reliable – VAN WAES and LIEBER 1977). GGPT is also increased by hepatic enzyme induction due to drugs (ROSALKI et al. 1971; FLANAGAN et al. 1977; ALLAM 1979). This test is now widely available. The enzyme is not confined to the liver and may be mildly elevated in patients with lobar pneumonia or inflammatory bowel disease (BMJ 1977a).

Serum albumin and total protein, and prothrombin time (after vitamin K treatment) are not sensitive indices of mild liver disease but are useful in more severe cases for assessment and prognosis. Occasionally these tests are abnormal in patients with cirrhosis who have normal standard liver function tests. Electrophoresis of protein may show a markedly increased gammaglobulin band in chronic active hepatitis.

Other specific proteins may aid in diagnosis of liver disease.

Increased alpha-fetoprotein concentrations may be found in primary hepatocellular carcinoma (KEW 1975), especially those developing in cirrhotic patients (JOHNSON et al. 1978b). Alpha-1-antitrypsin deficiency may be associated with primary hepatoma and cryptogenic cirrhosis in later life (BRUNT 1975).

Lipoprotein X (an abnormal low density lipoprotein) occurs in the serum of patients with cholestasis (SALMON 1976). Concentrations tend to be higher in extrahepatic cases, but differentiation from intrahepatic cholestasis is not absolute (MAGNANI and ALAUPOVIC 1976).

Bile salt tests (HEATON 1979) are of value in selected cases. Serum bile acid tests provide the most sensitive test of liver function and are valuable in following progress of liver damage, detecting early relapse or identifying resolution (SOLOWAY 1977; BOUCHIER and PENNINGTON 1978; GILMORE and HOFFMAN 1980).

Serum amylase may be raised in acute cholecystitis, but levels above 1,850 units/litre (1,000 Somogyi units/100 ml) strongly suggest acute pancreatitis.

b) Immunological Tests

Markers of hepatitis B infection are discussed later, under that disease.

Auto-antibodies to smooth muscle, nuclei or mitochondria increase with age (DONIACH 1972; MACKAY 1972; BURNET 1974; CHENEY and WALFORD 1974; FIXA et al. 1975). Increasing or high titres are found in auto-immune liver disease such as active chronic hepatitis or primary biliary cirrhosis.

c) Haematology

Anaemia is common in liver disease, mainly due to liver dysfunction and blood loss (especially in cirrhosis), but malnutrition, haemolysis, and hypersplenism may contribute. The severity of the anaemia is not related to the severity of the liver lesion.

In alcoholic liver disease, the alcohol may exert toxic effects on the bone marrow (SULLIVAN and HERBERT 1964; WU et al. 1974). Excess of bile salts in blood causes abnormalities in size, shape, and fragility of erythrocytes. Haematological effects of folate deficiency appear more readily in liver disease. Vitamin B_{12} stores decrease in the liver, but B_{12} and iron levels may increase in the blood due to liver cell necrosis. A haemostatic defect may occur (ALEDORT 1976; CANOSO et al. 1979).

d) Radiology of the Hepatobiliary System

A plain X-ray of the abdomen may provide valuable information. Liver and spleen size and shape may be noted; calcification may be seen in tumours (primary or metastatic), infections (e.g. hydatid cysts, tuberculosis) and simple cysts. The gallbladder may be seen as a soft-tissue shadow if distended, usually due to malignant obstruction; or its walls may be calcified. Radio-opaque bile may occur in chronic cholecystitis. Gallstones, very common in the elderly, may be seen if opaque, but may be incidental.

Gas in the liver or bile ducts may follow surgery on the biliary tree, or be due to a biliary fistula or to regurgitation through an incompetent sphincter of Oddi.

Oral cholecystography is often unhelpful in old people; it should be avoided if jaundice is present.

Intravenous cholangiography is used if oral cholecystography has failed, or if symptoms recur after cholecystectomy. If serum bilirubin is elevated, high-dose infusion techniques and body-section radiography may be used, but are unlikely to succeed if serum bilirubin exceeds 34–51 μmol/litre (2–3 mg/100 ml). Infusion tomography has been found useful in diagnosis of acute cholecystitis (MONCADA et al. 1977).

Endoscopic retrograde cholangiopancreatography (ERCP) is of great value in the differential diagnosis of causes of jaundice and for evaluation of biliary tract disease without jaundice (ANACKER et al. 1977; SALMON 1978). In elderly patients, this technique offers the advantages of brevity, the need for minimal sedation, visualization of the pancreatic duct (but age-related changes in the calibre of that duct may mislead – see ANACKER et al. 1977), the possibility of endoscopic examination of stomach and duodenum and of obtaining biopsy and cytology material as well as pure bile; and it can be combined with sphincterotomy where indicated

(see Sect. B.II.2). Good tolerance and safety of ERCP in the elderly has been reported (WONG and SCHUMAN 1976) and a diagnostic laparotomy may be avoided in patients with jaundice or with upper abdominal pain or mass suspected of being related to biliary tract or pancreas. Complications (LANCET 1976a; BENNETT 1979) occur in up to 3% of patients; mortality is 0.1% and is usually due to sepsis.

Percutaneous transhepatic cholangiography has become easier and safer using the "skinny" needle (LANCET 1978; OKUDA 1980) but is not without risk (BENNETT 1979; HADAS et al. 1979; ZILLY et al. 1980) and surgical intervention may be required the same day if extrahepatic obstruction is present. It has less application in the elderly, and ERCP should be performed first. Full patient cooperation is essential. There is evidence that ultrasonic tests may be equally accurate in the differential diagnosis of jaundice (GOLDSTEIN et al. 1977).

Selective angiography (coeliac and superior mesenteric) is preferable to percutaneous trans-splenic portal venography in investigation of portal hypertension in the elderly and may be especially valuable in hepatoma (OKUDA et al. 1977).

Barium studies may reveal the presence of oesophageal varices, peptic ulceration, duodenal loop deformity and other relevant abnormalities. Double-contrast barium examination has proved valuable in recent years and rivals endoscopy in the investigation of upper gastro-intestinal bleeding (LAUFER 1979), although it is less accurate (STEVENSON et al. 1976) and may best be regarded as a complementary investigation (MONTAGNE et al. 1978).

e) Endoscopy

Flexible fiberoscopy has revolutionized the investigation of gastro-intestinal problems (COTTON 1976), and some therapeutic applications add to its value. The usefulness, safety and reasonable tolerance of endoscopy in the elderly have been shown by STANLEY and COCKING (1978), who compared the results of oesophagogastroduodenoscopy and radiology in 100 consecutive elderly patients aged 70 and above.

Laparoscopy is useful when accurate diagnosis defies other available investigative procedures (BARRY et al. 1978; BMJ 1978a). It allows inspection and, if necessary, guided biopsy of the liver or brush cytology of the liver or peritoneum, and greatly increases diagnostic accuracy. It is relatively simple and safe, and its use may save an unnecessary laparotomy. Experience in 165 geriatric patients has been reported (MÜLLER et al. 1978).

f) Liver Biopsy

The diagnostic accuracy of liver biopsy has been reviewed by THEODOSSI et al. (1980). It is a relatively safe procedure (PERRAULT et al. 1978; BENNETT 1979), but the risk is greater in certain types of liver disease (e.g. cholangitis, obstructive jaundice, secondary carcinoma), which are common in old age. The risks may be increased further in the elderly because of decreased liver size and less effective patient cooperation. Nevertheless, MUNZER (1966) and EASTWOOD (1971) state that liver biopsy may be valuable in old age; guided liver biopsy at laparoscopy may be needed.

g) Liver Imaging

α) Radioisotope Scanning. This non-invasive technique is a simple and sensitive method for assessing the hepatobiliary system. It has been reviewed by SPENCER (1978) and WENZEL (1979). The agent most used is ^{99m}Tc sulphur colloid, which is taken up by the Kupffer cells. Newer agents labelled with ^{99m}Tc are taken up by the hepatocytes (e.g. ^{99m}TC PG, ^{99m}Tc HIDA) (WISTOW et al. 1977) and have improved the diagnostic accuracy of isotope scanning (JENNER et al. 1978a, b; WENZEL 1979; SILBERSTEIN 1980). Lesions which do not take up the isotope (e.g. cysts, abscesses, secondary carcinoma) show as "cold areas," but false results are common (ROSENTHAL 1976). "Hot areas" are due to increased vascularity (JOHNSON and DE FORD 1978), but when ^{67}Ga citrate is used as the imaging agent it is taken up by growing lesions (e.g. abscesses, neoplasms), which then appear as "hot areas" (HAUSER and ALDERSON 1978).

Diagnostic accuracy may be increased by combining isotope scanning with ultrasound (SULLIVAN et al. 1978).

β) Ultrasound. Ultrasound displays soft tissues. Grey-scale ultrasound has improved resolution from 2 cm down to 3 mm, for gallstones at least, so that this technique now equals oral cholecystography in diagnostic success (FERRUCCI 1979). Some workers have found ultrasound to be superior to oral cholecystography, and recommend that ultrasound should be the first technique in evaluating patients with suspected gallbladder disease (COOPERBERG and BURHENNE 1980). However, it is not suited to the detection of small common bile duct stones, for which intravenous cholangiography should be used if serum bilirubin is less than 51 μmol/litre (3 mg/dl) (TAYLOR and ROSENFIELD 1978).

It will be realized that this technique will often have advantages over others in ill elderly patients, especially if jaundice is present. Accuracy is considerably less in diffuse parenchymal liver disease (LOMONACO et al. 1975; GOSINK et al. 1979), although it remains useful as a non-invasive procedure.

Real-time ultrasound is useful for studying gallbladder kinetics (size, mobility, response to cholecystokinin) (PALFRAMAN 1979) and for the early detection of small hepatomas (OHTO et al. 1980).

γ) Computed Axial Tomography. This non-invasive technique has become widely popular, although it is not available everywhere on grounds of expense. It is very valuable in the differential diagnosis of jaundice and for the detection of masses. It can also detect infiltrations with fat or iron, but is less useful in diagnosis of non-fibrotic parenchymal liver disease (KREEL 1980). It can be useful in biliary disease but less expensive procedures (e.g. ultrasound or cholecystography) are more usually sufficient for this purpose.

δ) Perspective on Imaging Techniques. Isotope scans are useful screening procedures in liver disease, but may require further evaluation by ultrasound or CAT scans. Ultrasound is particularly useful in biliary tract disorders and to show intrahepatic bile duct dilatation. It will also show abnormal masses, but CAT can provide more specific information and is useful for identification and quantification of hepatic infiltrations (see also Sect. A.II.2).

These non-invasive techniques are of great benefit in geriatric practice. Comparative reviews include those of MACCARTY et al. (1979); PETASNICK et al. (1979); SODEE and VERDON (1979); WEISSMANN et al. (1979); and KREEL (1980).

ε) *Laparotomy*. The need for diagnostic laparotomy has receded with the introduction of sophisticated investigative techniques such as those described above – provided the condition of the patient allows for the time required to complete the tests desired. Obscure abdominal pain or pyrexia of unknown origin may ultimately require a diagnostic laparotomy (BMJ 1977 b) and the risks of undue procrastination in cases of jaundice of unknown aetiology have been stressed (BOURKE et al. 1967), especially in the elderly (HAZELL 1967).

2. Jaundice in Old Age

a) Unconjugated (Prehepatic) Hyperbilirubinaemia

Not commonly seen in the elderly (in whom haemolytic anaemias are rare), the most usual cause is pulmonary infarction in a patient with congestive cardiac failure.

b) Conjugated (Hepatic or Posthepatic) Hyperbilirubinaemia

Intrahepatic cholestasis (READ 1979) may be due to drugs, hepatitis, cirrhosis (macronodular or primary biliary), hepatic infiltrations, and associated diseases, (e.g. ulcerative colitis, non-metastatic prostatic carcinoma). Cardiac failure is another hepatic cause of hyperbilirubinaemia; both conjugated and unconjugated bilirubin levels may increase in the blood (WARE 1978).

Extrahepatic cholestasis (posthepatic) is mainly due to gallstones or carcinoma in the ampullary region.

Obstructive jaundice may have intra- and/or extrahepatic causes. Several surveys of jaundice in the elderly have shown that obstructive jaundice predominates (HUETE-ARMIJO and EXTON-SMITH 1962; ELMSLIE 1966; EASTWOOD 1971; SPELLBERG and GARAU 1972), although this was not the case in the reports of NASO and THOMPSON (1967) and O'BRIEN and TAN (1970). Various factors operate to produce selection in such series, but HAZELL's (1967) view is a practical working guide: in elderly patients jaundice is often due to drugs, gallstones, or malignant obstruction. Nevertheless, cirrhosis and hepatitis occur in the elderly sufficiently often to be included in the differential diagnosis (EASTWOOD 1971), and hepatitis in particular may mislead and even lead to unwarranted laparotomy in elderly patients (HUETE-ARMIJO and EXTON-SMITH 1962; FENSTER 1965).

Malignant obstruction is usually due to carcinoma of the head of the pancreas or to metastases in the liver or the porta hepatis. Other primary sites include the ampulla of Vater, the bile ducts and the gallbladder. Primary hepatic carcinoma is much less common.

Calculous obstruction is due to a gallstone in the common bile duct; the elderly may not complain of pain and the diagnosis may be difficult.

Differential diagnosis may be difficult if pain is absent in calculous disease (as may be the case in old age) or present in malignant cases; similarly, fluctuation in jaundice – classically suggesting a calculous aetiology – may occur in malignant obstruction.

3. Circulatory Disturbances

a) Acute (Heart Failure, Shock)

Hepatomegaly, often tender and possibly progressive, is accompanied by impaired liver function. Histologically, centrilobular congestion, haemorrhage, and necrosis may occur with litle inflammatory response. The reticulin framework remains intact.

b) Chronic Heart Failure

A large firm liver may change to a shrunken fibrotic one if cardiac cirrhosis develops.

α) Pathological Changes. At postmortem, the cut surface shows a "nutmeg" appearance due to centrilobular congestion and haemorrhage surrounded by fatty change. The hepatic veins are distended. The centrilobular parenchymal cells degenerate, accumulate lipofuscin, and atrophy, and the stroma condenses. Proliferation of collagen may lead to periportal fibrosis ("reversed lobulation").

For fuller details of the liver in congestive heart failure, see DUNN et al. (1973). Note also that left heart failure, whether alone or in association with right-sided failure, may present with prominent hepatic signs (COHEN and KAPLAN 1978). In the elderly presenting with acute or chronic liver disease, it is wise to exclude left heart failure (WARE 1978).

β) Clinical Features. Pain or discomfort is common over the liver, which may be enlarged, firm, smooth, and tender. Hepatic pulsation occurs if there is tricuspid incompetence (unless cardiac cirrhosis has supervened). Splenomegaly is surprisingly common.

Jaundice may appear, usually when pulmonary infarction has occurred. Hepatojugular reflux may be found. Ascites may be present, especially if the serum proteins are low.

Hepatic failure is rare.

γ) Biochemical Changes. Liver function tests are abnormal. Mild prolongation of the prothrombin time is common. Serum aminotransferases are commonly increased, though not very greatly. Rarely, acute liver disturbance is associated with very high serum aminotransferase levels and jaundice: such patients may be considered mistakenly to have acute viral hepatitis.

The place of laboratory tests in the diagnosis of chronic hepatic congestion due to cardiac failure is discussed by CASSAN et al. (1976).

Drug disposition may be altered and conjugation by glucuronidation is decreased (FARLEIGH et al. 1980).

c) Hepatic Vein Occlusion

Though rare, this may be suspected if a patient with polycythaemia vera or malignant disease in or near the liver develops a large tender liver and gross ascites. Liver scans may be characteristic (MEINDOK and LANGER 1976), but congestive cardiac failure and cirrhosis must be excluded.

4. Toxic Liver Injury (ZIMMERMAN 1978)

Drugs, chemicals, irradiation, plants, and fungi may produce hepatotoxicity, but do so in different ways.

a) Hepatic Necrosis

Halogenated hydrocarbons, heavy metals, and cytotoxic drugs are directly hepatotoxic in a predictable dose-dependent manner. Other such agents include paraquat, DDT, benzene derivatives, tannic acid, *Amanita* mushrooms, irradiation, and hyperpyrexia. Hepatic necrosis has followed intravenous tetracycline; ferrous sulphate or paracetamol overdose; and dantrolene administration.

b) Fatty Liver

Common in alcoholics, this subject is reviewed by BRUNT (1971) and LEEVY et al. (1975). Various chemicals, drugs, and physical agents may produce fatty liver, and to some extent it may develop in severe anaemia, diabetes mellitus, and ulcerative colitis. Focal fatty changes may cause diagnostic confusion (BRAWER et al. 1980).

c) Hepatitis-like Reaction

Some drugs may produce liver changes identical to those of infective hepatitis; hypersensitivity may play a role. Mortality exceeds that of hepatitis; however, jaundice may develop well after the drug has been stopped.

The main groups of drugs implicated are: antidepressants (including especially monoamine oxidase inhibitors), anticonvulsants, antituberculous drugs, antirheumatic drugs, and certain anaesthetic agents, notably halothane (KLATSKIN and SMITH 1975; SIMPSON et al. 1975). Methyldopa and dantrolene have also been implicated.

d) Intrahepatic Cholestasis

Women are affected more often than men.

α) Hypersensitivity Cholestasis. The classic example is phenothiazine jaundice, seen particularly with chlorpromazine (ISSELBACHER and LESSER 1975). It occurs in less than 0.5% of patients on chlorpromazine and is unrelated to dose or duration of therapy.

Other drugs implicated include antidepressants, benzodiazepines, oral hypoglycaemic agents, thiazide diuretics, antithyroid drugs, and phenylbutazone. Some reactions to chemotherapeutic agents are of this type (e.g. sulphonamides, *p*-aminosalicylate).

Jaundice may be preceded by malaise, anorexia, and pruritus. A leucopenia is common but eosinophilia may develop, and sometimes a rash. Serum alkaline phosphatase often rises above 210 units/litre (30 K-A units/100 ml); aminotransferases are moderately raised.

Recovery usually takes a few weeks; less often jaundice persists and rarely a picture resembling primary biliary cirrhosis develops (although the immunofluorescent test is negative).

Chronic cholestatic jaundice may mimic extrahepatic biliary obstruction (see obstructive jaundice, above).

Treatment is symptomatic. Corticosteroids may reduce the serum bilirubin but do not shorten the course of the illness.

β) Non-sensitivity Cholestasis. This is related to dose and duration of therapy. The cholestasis is unaccompanied by inflammatory or necrotic changes. Various steroid sex hormones and anabolic steroids have been implicated (methyltestosterone but not testosterone propionate; methandienone and norethandrolone but not nandrolone); all patients on the drugs involved will have abnormal BSP tests.

Mixed pictures may be seen with some drugs (e.g. sulphonamides, erythromycin estolate, methyldopa, oral antidiabetic agents, antituberculous agents). Hepatic granulomata are sometimes seen (e.g. after allopurinol or clofibrate). Nitrofurantoin has been reported to cause chronic active hepatitis.

5. Inflammatory Diseases

a) Viral Hepatitis

The three major types of human viral hepatitis are now known as A, B, and "non-A, non-B" (ZUCKERMAN 1978; LANCET 1979a).

Hepatitis A was formerly known as infective hepatitis or catarrhal jaundice. It is a faecal-oral infection, with an incubation period of 3–5 weeks. It is relatively uncommon in the elderly, in whom it takes a more severe course; jaundice may be prolonged and death may result, especially during epidemics (BINDER et al. 1965). FENSTER (1965) reported 23 elderly patients with "viral hepatitis" – these would now be classified as hepatitis A. About half had prodromal symptoms, and one-quarter had pruritus. Twenty patients presented with jaundice, one with ascites and one with a confusional state with rapid development of jaundice and stupor. Mental changes, as might be expected, were common, and so was weight loss. Investigations were performed as for younger patients, but the diagnostic accuracy was only 52%: the commonest mistaken diagnosis was neoplasm, because of the patient's age, weight loss, and jaundice with some obstructive features. Ten patients had an acute or subacute course, and four others had a prolonged or progressive illness. There were six deaths (i.e. a mortality of 26%). Late diagnosis (and, in two cases, unnecessary laparotomy) undoubtedly contributed to this high mortality.

Hepatitis B was formerly known as serum hepatitis or homologous serum jaundice. It is usually a parenterally transmitted infection, although non-parenteral routes of spread may also occur. The incubation period varies from 14 to 180 days. The onset is more insidious and the mortality higher than hepatitis A, since it tends to affect older and more debilitated patients. Underlying malignancy or pre-existing liver disease predisposes to increased morbidity and mortality (ROBINSON and GREENBERG 1977).

After infection, numerous antigen and antibody markers appear in the serum at various times. These include: surface antigen (HBsAg) and its antibody; core antigen (HBcAg) and its antibody; a third antigen (e antigen) may appear (it cor-

relates with infectivity) and if present in addition to the persistence of HBsAg the patient usually has serious chronic liver disease (TREPO et al. 1976). The e antigen is less often found in asymptomatic carriers as age advances. In contrast, antibody to e (anti-e) increases with age (OHBAYASHI et al. 1976). This may relate to lesser infectivity of older subjects.

Most patients develop sufficient anti-HBs response to clear the infection; a small percentage cannot do so and become chronic HBsAg carriers; these patients are at risk of chronic active liver disease, cirrhosis, and hepatoma (DUDLEY et al. 1972; WOOLF and WILLIAMS 1976) and an increased susceptibility to alcoholic liver disease (LANCET 1979a). The liver damage is mediated by auto-immune mechanisms (DIENSTAG 1978).

Spread of infection is especially related to blood, but may be by various body fluids – hence the possibility of spread by intimate personal or sexual contact. Bed bugs and other blood-sucking insects may be vectors (BMJ 1979a).

Non-A, non-B Hepatitis is a milder parenteral infection than hepatitis B, which it otherwise resembles. It is the commonest post-transfusion hepatitis in the United States, but is much less frequent in other countries. It may lead to chronic liver disease (KNODELL et al. 1977; RAKELA and REDEKER 1979).

Recent trends in therapy of viral hepatitis have been discussed by MURRAY-LYON and REYNOLDS (1976). Some promise has been shown in acute HBsAg-positive hepatitis by a flavonoid drug, (+)-cyanidanol-3 (BLUM et al. 1977), but it is generally still held that in acute hepatitis no treatment has proved superior to conventional supportive management (LANCET 1979a). Corticosteroids are contraindicated in uncomplicated acute viral hepatitis but may help if there is prolonged cholestasis (TANNER and POWELL 1979). Active immunization against hepatitis B is now a reality (BMJ 1980). Its major importance may be not so much the prevention of acute hepatitis as protection against chronic liver disease and hepatoma.

Other viruses causing liver damage include cytomegalovirus, Epstein-Barr virus, infectious mononucleosis, yellow fever, herpes simplex, herpes zoster/varicella and Coxsackie virus.

Infectious mononucleosis is rare in old age, but will often go unrecognized because it is mainly a disease of young people, and because its clinical features are often atypical and misleading (HORWITZ et al. 1976; PICKENS and MURDOCH 1979). Sore throat and malaise may occur, but significant myalgia and considerable liver dysfunction, with or without jaundice, are likely to be features of the illness. Lymphadenopathy and splenomegaly may be absent, and the Paul-Bunnell test may be persistently negative. The recognition of specific Epstein-Barr virus immunoglobulin (EBVIgM), using differential sucrose gradient centrifugation, confirms the diagnosis.

Chronic hepatitis may be relatively benign (persistent) or more subacute (chronic aggressive hepatitis). The latter may progress to cirrhosis and sometimes to primary hepatocellular carcinoma. There may be an association with other liver disease, especially the chronic HBsAg carrier state, haemochromatosis, or certain drugs (e.g. alcohol, methyldopa, nitrofurantoin, oxyphenisatin).

Chronic aggressive hepatitis, characteristically a disease of young women, has been reported in old age, when clinical and laboratory features may be atypical (WOOLF et al. 1974; WILLIAMS et al. 1976). The immunological disturbance is shown

by polyclonal hypergammaglobulinaemia and a high incidence of auto-antibodies (BMJ 1977c).

Treatment. Corticosteroids help in HBsAg-negative cases, and azathioprine may reduce the dose of steroid required (azathioprine alone is ineffective). In cases with HB virus markers, great caution is needed and response is much less likely (TANNER and POWELL 1979); such cases are often less aggressive, but if jaundiced, or if aminotransferases are considerably raised, similar treatment may be tried. Levamisole has been encouraging but the virus remains. Interferon can clear the virus markers but the clinical state is unchanged; adenine arabinoside is cheaper and more readily available (LANCET 1979a), and may lead to improvement in symptoms, liver function, and histology (SCULLARD et al. 1980).

Cholestatic hepatitis resembles drug-induced cholestasis (see above).

b) Cholangitis

Ascending cholangitis follows bile stasis, usually due to extrahepatic biliary obstruction. An obstructing gallstone may lead to "Charcot's intermittent biliary fever" with episodes of Gram-negative septicaemia. The latter may be particularly serious in the elderly, especially if shock occurs (KREGER et al. 1980).

Age over 70 years may predispose to bacterial infection in bile (KEIGHLEY et al. 1976).

Sclerosing cholangitis or pericholangitis may accompany chronic inflammatory bowel disease (BMJ 1979b).

c) Liver Abscess

α) Pyogenic. Despite antibiotic usage, there has been no reduction in the incidence of pyogenic liver abscesses. They may be multiple, associated with obvious acute infection such as cholangitis or bowel sepsis, and often with jaundice; or solitary and cryptogenic, with an insidious onset and long history (BUTLER and MCCARTHY 1969), often in elderly patients, with jaundice in 25%. A solitary abscess occurs most often in the right lobe of the liver.

Mortality is high (LANCET 1976b) but may be improved by early diagnosis and aggressive surgical and antibiotic treatment; however, even then patients over 60 years old have a higher mortality rate than younger patients (SATIANI and DAVIDSON 1978).

β) Other Abscesses. Amoebic abscesses are discussed by SATIANI and DAVIDSON (1978). Mortality is low if the abscesses are sterile but much higher if secondarily infected. Prognosis is worse in old age (MERIN et al. 1980).

d) Chronic Inflammations

Miliary tuberculosis may be clinically undramatic in the elderly (PROUDFOOT et al. 1969); it may present as anaemia and a raised erythrocyte sedimentation rate. Liver biopsy may be valuable in establishing the diagnosis (CUCIN et al. 1973); laparoscopy with or without guided liver biopsy may be needed.

Brucellosis may also involve the liver.

6. Cirrhosis

a) Classification

A variety of classifications has been used for some years (GALAMBOS 1975; ANTHONY et al. 1978).

Two complementary classifications are recommended: morphological (micronodular, macronodular, mixed) and aetiological (known – e.g. alcohol, virus, metabolic disorder – or unknown – cryptogenic). Functional staging has been described by BRUNT (1976).

b) Incidence and Mortality

The incidence of cirrhosis increases after middle life (MASSÉ et al. 1976). It is usually commoner in men than in women. Some countries show an increase after the age of 75 years (Japan, Denmark) but others report a decrease after that age (United States, France). In France, where there has been a rapid increase, especially in men, peak mortality is between 65 and 74 years in both sexes; but in the United States it has shifted from over 75 to the 55–64 decade.

c) Aetiology

α) Cryptogenic Cirrhosis. The commonest variety of cirrhosis in old age is latent, cryptogenic, and micronodular, without acites or portal hypertension (LUDWIG et al. 1970). Splenomegaly is common and may be found clinically or radiographically (KRAFT and FINBY 1970). The term "senile cirrhosis" is best avoided.

Drug therapy in the elderly cirrhotic needs particular care. Both aging and cirrhosis may lead to pharmacokinetic changes which alter distribution, clearance, detoxication, and elimination of various drugs (VESTAL et al. 1978; KLOTZ and WILKINSON 1978; BLASCHKE and RUBIN 1979; GEORGE 1979). Reduced dosage of many drugs commonly used in geriatric patients will be necessary – e.g. chlormethiazole (PENTIKÄINEN et al. 1978); benzodiazepines (KLOTZ et al. 1975) (oxazepam is the most useful if cirrhosis is present – SELLERS et al. 1979); beta-blockers (PESSAYRE et al. 1978; HOMEIDA et al. 1978). Frusemide commonly leads to adverse reactions in cirrhotic patients (NARANJO et al. 1979); in the management of ascites a potassium-sparing diuretic is often useful, alone or together with thiazide (YAMADA and REYNOLDS 1970). Well-documented associations have been established between cirrhosis and peptic ulcer (LIEBER 1952) and gallstones (BOUCHIER 1971).

β) Biliary Cirrhosis. Primary biliary cirrhosis (PBC) is a chronic non-suppurative destructive cholangitis of unknown cause, occurring mainly in females. Its onset is usually in middle age but may peak later (LUDWIG and BAGGENSTOSS 1970).

The classical clinical picture (pruritus, obstructive jaundice, skin pigmentation, xanthomata, steatorrhoea, bone rarefaction, and possibly bleeding and clubbing) represents advanced disease, with an average survival time of 6–11 years (ROLL et al. 1980). However, increasing numbers of asymptomatic patients are now being diagnosed by biochemical screening, liver biopsy, and immunological testing (FLEMING et al. 1978; JAMES et al. 1980). An appreciable proportion of asymptomatic patients have advanced histological lesions and may have had the disease for several years before being diagnosed.

Considerable immunological abnormalities occur in most cases, even if asymptomatic: serum IgM levels are commonly raised, and over 90% of cases have a positive immunofluorescent test for mitochondrial antibodies. PBC appears to be part of a multisystem disorder and may be associated with various auto-immune diseases such as rheumatoid arthritis, scleroderma, the sicca syndrome, and thyroid disease (THOMAS et al. 1977; CULP et al. 1980). The natural history of PBC has been reviewed by CHRISTENSEN et al. (1980), who found an unfavourable influence of older age on progression of the disease.

Treatment with D-penicillamine has shown some promise (FLEMING et al. 1978; EPSTEIN et al. 1979). Corticosteroids are usually contraindicated because they accelerate osteodystrophy, but have led to symptomatic improvement (TAAL and SCHALM 1980). Cyclosporin-A has led to some improvement in liver function tests (THOMAS et al. 1980) but is too toxic for general or long-term use. Azathiaprine has not been of help (CHRISTENSEN et al. 1980).

Osteodystrophy may be treated by 25-OH vitamin D (REED et al. 1980) or, in some patients, 1,25-$(OH)_2D_3$ (LONG et al. 1978). Pruritus may be relieved by oral cholestyramine, but this may prevent enterohepatic circulation of 25-OH-D and deplete already limited body stores of the vitamin (COMPSTON and THOMPSON 1977).

Secondary biliary cirrhosis occurs after long-standing extrahepatic biliary obstruction. Ascending cholangitis may produce the picture of "Charcot's intermittent biliary fever." The mitochondrial antibody test is negative.

γ) Haemochromatosis. Idiopathic haemochromatosis is a rare inherited disorder of iron metabolism found in middle and later life. Iron absorption is excessive despite a normal diet; this leads to progressive increase in tissue iron and widespread fibrosis develops in parenchymal organs.

Sex incidence is equal in the elderly; at younger ages males predominate since females lose iron during their reproductive years.

In addition to hepatic cirrhosis, late clinical features include diabetes mellitus, hypogonadism, arthropathy, skin pigmentation, and cardiac failure. In elderly patients a progressive polyarthritis with chondrocalcinosis is a common association, and abdominal pain and the development of primary hepatocellular carcinoma occur more commonly than at younger ages.

Diagnosis has been discussed by POWELL and HALLIDAY (1978), VALBERG et al. (1978), BOMFORD (1979), and BEAUMONT et al. (1980). In differentiating idiopathic haemochromatosis from hepatic cirrhosis with iron overload, the amount of iron in liver biopsy material is important, but lack of iron in reticuloendothelial cells is compatible with idiopathic haemochromatosis (VALBERG 1978). Iron absorption may be little raised when the patient presents initially, but increases markedly when venesection treatment is started.

Anaemia is rare unless there is folate or vitamin B_{12} deficiency. Sideroblastic anaemia may occur.

For further details of idiopathic haemochromatosis and its underlying genetic basis, see BOMFORD (1979).

Treatment includes removal of iron by regular venesections or (less effectively) by chelation therapy. Oral phosphates reduce iron absorption.

δ) Portal Hypertension. Old people tolerate gastro-intestinal bleeding less well than younger patients (AVERY JONES 1956; SCHILLER et al. 1970; WALLS et al. 1971; LOGAN and FINLAYSON 1976). This is especially true of bleeding oesophageal varices (WELLS 1973).

Fiberoptic endoscopy is well tolerated by the elderly (ANSELM et al. 1971; GIBBINS et al. 1974; STEVENSON et al. 1976) and its usefulness was stressed by STANLEY and COCKING (1978). Patients may have varices yet bleed from another site (MORRIS et al. 1975; BULL et al. 1979). The latter authors showed that if the spleen is impalpable, gastro-intestinal bleeding is probably *not* from varices.

Treatment in the acute stage of variceal bleeding may employ intravenous vasopressin and balloon tamponade, and various adjunctive procedures (MALT et al. 1979). Intra-arterial vasopressin was used by SHERMAN et al. (1979). Vasopressin may decrease oxygen availability (BERK et al. 1979). Intravenous somatostatin has been used successfully in a 67-year-old man (TYDÉN et al. 1978). Sclerotherapy has been reviewed recently by LANCET (1979 b) and LEWIS et al. (1980). Oesophageal transection using the SPTU gun has had good results in patients aged up to 80 years (JOHNSON 1978) and may save a desperate situation.

The prognosis of variceal bleeding is related to liver function and to age; hence it is poor in the elderly patient with alcoholic cirrhosis (SHIELDS 1979), in whom liver failure may ensue.

Portasystemic shunt operations are not generally favoured in the elderly (READ et al. 1961; HOURIGAN et al. 1971; SHIELDS 1979) but excellent results were reported recently by LIVINGSTONE et al. (1979) in 30 patients aged from 60 to 87 years who underwent an elective distal splenorenal shunt. Ascites is a bad prognostic feature in patients being considered for shunt operations (LANCET 1979 b).

7. Liver Failure

This term includes portal systemic encephalopathy (PSE). Chronic PSE may produce cerebellar and basal ganglion disturbances, possibly with parkinsonism and dementia (READ et al. 1967).

8. Infiltrations of the Liver

a) Malignant Disease (TERBLANCHE 1977)

α) Secondary Carcinoma. Hepatic metastases may occur from many primary sites.

Right-sided abdominal pain and tenderness plus a large irregular liver suggest the presence of hepatic metastases. Jaundice is often absent, but obstructive jaundice may be due to involvement of bile ducts in the porta hepatis.

Ascites may result from peritoneal involvement or direct spread of tumour to hepatic veins or inferior vena cava. The distended abdomen may contrast with generalized wasting.

It is always important to exclude primary carcinoma in the gastro-intestinal tract. Carcinoma of the body of the pancreas is often silent and difficult to diagnose; rectal carcinoma is easy to find yet often missed. Routine clinical examination of rectum, breasts, and thyroid is essential. Beware the tiny melanoma – or the melanoma long since removed.

Liver function tests are often unhelpful. Serum 5′-nucleotide phosphodiesterase isoenzyme V (5′NDP-V) appears in the serum of patients with liver metastases (MULLEN et al. 1976; POLLOCK et al. 1979). Liver biopsy is risky and should always be preceded by localization of metastases by X-ray and imaging procedures (as described above), since metastases may be friable and if punctured may bleed severely.

Treatment is difficult, especially in old age; but the prognosis is so poor in untreated cases that a fine judgment is needed in each individual patient. Cytotoxic therapy is rarely indicated since it may make the elderly patient more ill; but reasonable results have been reported in patients up to 75 years of age (FRIEDMAN et al. 1979). Partial hepatectomy for localized deposits (FORTNER et al. 1978) is rarely feasible. Palliative radiotherapy has helped patients with obstructive jaundice (MEYER et al. 1978).

β) Primary Carcinoma of the Liver. Hepatoma is a hepatocellular tumour; cholangioma is a (rarer) bile duct tumour.

Hepatocellular carcinoma may develop in patients with cirrhosis of the liver. In those areas where hepatitis B infection is endemic (Asia, Africa, Indonesia), this is the commonest antecedent, and hepatoma is seen in younger patients than elsewhere.

In the U.K., HBsAg-positive chronic active hepatitis carries a high risk of malignant change, especially in males over 50 years of age (JOHNSON et al. 1978a).

Alcoholic cirrhosis is a common antecedent in the United States (OMATA et al. 1979), Europe (NØRREDAM 1979; BASSENDINE et al. 1979), and Australia (MCCAUGHAN et al. 1979).

Haemochromatosis often ends in hepatocellular carcinoma, which is the commonest cause of death in elderly patients with primary haemochromatosis (DELAMORE 1972). A rare triad of haemochromatosis, hepatocellular carcinoma, and erythrocytosis occurs in elderly males; prognosis is poor (RAPHAEL et al. 1979).

Hepatoma is a rare complication of secondary iron overload, but has been reported recently in an elderly man with thalassaemia minor (PARFREY and SQUIER 1978).

Androgen-anabolic steroid therapy has been associated with development of hepatoma (RUDOLPH 1978).

The tumour may occur as a single mass or as multicentric nodules (BROCHERIOU et al. 1975).

Histological features have been reviewed by NØRREDAM (1979) and their prognostic significance discussed by LAI et al. (1979).

Clinical features include abdominal pain, a hard irregular abdominal mass and perhaps resistant ascites; if these develop in a patient with cirrhosis, hepatoma should be suspected. An arterial murmur may be heard over the enlarged liver.

Occasionally porphyria develops (BROCKLEHURST et al. 1965; EDDLESTON et al. 1971; KECZKES and BARKER 1976; STOUT and BIGGART 1978).

Other features relate to the cirrhosis and any local or general spread.

Liver function tests reflect the cirrhosis but other biochemical abnormalities have been described: dysproteinaemia, hypercalcaemia, hypoglycaemia. Serum alpha-1-fetoprotein (AFP) concentrations are raised in over 80% of patients with

hepatoma, but the increases are less marked in older patients than at younger ages (WEPSIC and KIRKPATRICK 1979). Serum ferritin may be increased (KEW et al. 1978).

Erythrocytosis and polymorphonuclear leucocytosis are common; eosinophilia and thrombocytosis may occur.

Investigative techniques such as ^{67}Ga scans, ultrasound, CAT scans, and selective angiography have been discussed earlier in this chapter. They have been compared with regard to the diagnostic evaluation of hepatoma by KUNSTLINGER et al. (1980) and – for early diagnosis of small hepatomas – by OHTO et al. (1980).

Cytopathological examination of tissue aspirated from the liver via a thin needle gave the diagnosis of primary hepatocellular carcinoma in three aged patients unfit for liver biopsy (GEBOES et al. 1978).

Surgical treatment is rarely feasible. Medical treatment employs doxorubicin (Adriamycin) (BERN et al. 1978; JOHNSON et al. 1978). High oral doses of urea have been claimed to be efficacious and non-toxic (DANAPOULOS and DANAPOULOU 1975).

Cholangiocarcinoma is reviewed by MURRAY-LYON 1979).

γ) Angiosarcoma of the Liver has been reviewed by LOCKER et al. (1979). It has been associated with chronic exposure to thorotrast, vinyl chloride, arsenic, radium, and possibly copper, and chronic idiopathic haemochromatosis. The long-term use of androgenic anabolic steroids, diethylstilboestrol, and phenelzine has also been implicated.

δ) Malignant Lymphoma has been discussed by KIM et al. (1976).

b) Amyloidosis

The liver may be involved in primary or secondary amyloidosis. Primary amyloidosis may be idiopathic or a complication in 10% of cases of multiple myeloma; secondary amyloidosis is an uncommon complication of diseases other than myeloma (BMJ 1979c). "Classical" causes of secondary amyloidosis are chronic suppurative conditions, caseous tuberculosis or tertiary syphilis; in modern geriatric practice commoner causes include rheumatoid arthritis, suppurative pyelonephritis, and decubitus ulceration complicating long-standing paraplegia, cancer (especially Hodgkin's disease and renal carcinoma), ulcerative colitis, and Crohn's disease.

An excellent up-to-date review of the nature of amyloid is given by GLENNER (1980).

Despite extensive hepatic infiltration with amyloid, clinical features are usually few. Hepatomegaly occurs in 50% of patients: the liver is smooth, firm, rubbery, and non-tender. The spleen is palpable in about one-third of cases. Serum alkaline phosphatase may be raised without other evidence of "obstructive" liver disease. Jaundice is unusual: it is due to intrahepatic cholestasis and is rarely severe (RUBINOW et al. 1978). Ascites is uncommon but may occur in advanced cases.

In diagnosis, dye tests have been superseded by rectal, liver, and perhaps renal biopsy; and liver scans may help.

Treatment is that of the underlying cause wherever possible.

Prognosis is poor if there is renal involvement, or severe jaundice and ascites.

9. The Liver in Systemic Disorders

a) Diabetes Mellitus

There is an association between chronic liver disease and diabetes. Impaired glucose tolerance is common in cirrhosis. Hepatomegaly and fatty change are common in untreated diabetics.

b) Chronic Bowel Inflammation

A wide range of hepatic disorders has been reported with chronic inflammatory intestinal disease, including fatty change, chronic active hepatitis, cirrhosis, granulomata, sclerosing cholangitis, pericholangitis, hepatic abscess, as well as amyloidosis (BMJ 1979b,c).

The bowel diseases most often associated with these conditions are ulcerative colitis and Crohn's disease. Lesser histological changes are quite common; serious liver disease is rare (less than 3%), but liver dysfunction may be detected in 8% of patients with inflammatory bowel disease (DEW et al. 1979).

These changes may be due to nutritional, toxic, and immunological factors.

c) Collagen Diseases

The association of liver disease with rheumatic disorders is well known. Biochemical abnormalities of liver function have been reported in up to 50% of patients with rheumatoid arthritis, and histological abnormalities on liver biopsy in 25%–50%; there was no relationship with age (FERNANDES et al. 1979). MILLS et al. (1980) reported that of 31 patients with rheumatoid arthritis and clinical and/or biochemical evidence of liver dysfunction, four (13%) had definite chronic liver disease, the remainder showing nonspecific reactive changes or normal histology. Immunological mechanisms may be responsible for the hepatic changes (FERNANDES et al. 1979).

The liver may also be involved in giant cell arteritis (MCCORMACK et al. 1978) and systemic lupus erythematosus (RUNYON et al. 1980).

The association between liver disease and immunological changes has been discussed by THOMAS (1977), SHERLOCK (1977), EDDLESTON and WILLIAMS (1978), and KANAGASUNDARAM and LEEVY (1979).

B. Biliary System

I. Physiological Aging

1. Anatomical Changes

The musculature of the gallbladder may hypertrophy, but decreased elasticity of the walls may lead to ptosis (IVY and GROSSMAN 1952). Changes in bile have been described earlier in this chapter.

2. Functional Changes

Delayed filling (SEYSS 1967) does not seem to be associated with impaired concentrating power or emptying time (IVY and GROSSMAN 1952).

II. Disease of the Biliary System

Disease of the biliary system is common and important in old age, gallstones and cholecystitis being the most frequent. Abdominal surgery in the aged is indicated for biliary tract disease more often than for other pathological conditions (STROHL et al. 1964).

1. Clinical Evaluation

Careful history and examination are essential. Biochemical tests are relevant mainly in jaundiced patients, as described previously. Pancreatic function tests may also be required.

X-rays and imaging techniques have been considered above, under liver diseases. Some further points will be made in connection with individual diseases later in this chapter.

2. Gallstones

The incidence of all types of gallstones increases with advancing age, especially in elderly males, although the overall incidence of cholesterol stones is commoner in females (BENNION and GRUNDY 1978; DOWLING 1979; FISHER 1979; POUPON et al. 1979).

There is a correlation with obesity and diet (BENNION and GRUNDY 1978) and, in women, with parity (FRIEDMAN et al. 1966; BERNSTEIN et al. 1973) and oestrogen administration – see above. In obese women the incidence per 100 women per decade is relatively constant, but the overall prevalence rate rises steadily after 20 years of age (BERNSTEIN et al. 1973). Autopsy studies or prevalence rates cannot be applied to the community as a whole, because hospital series are skewed towards an older age composition (BATESON and BOUCHIER 1975). There is in any case wide variation in reported figures; routine autopsy material has given 8%–25% prevalence (MCKEOWN 1965) but after 70 years of age this becomes 20%–50% or more (STROHL and DIEFFENBAUGH 1953; MCKEOWN 1975). There is wide variation between different parts of the world (BENNION and GRUNDY 1978; POUPON et al. 1979).

Mechanisms of gallstone formation and consideration of risk factors are discussed by BENNION and GRUNDY (1978) and DOWLING (1979).

a) Clinical Features and Associations

Gallstones are often symptomless, especially in the elderly, but complications leading to acute crises are four times as common after 60 years of age than at younger ages; and the outcome of such acute episodes is less favourable after 60 (POUPON et al. 1979).

Migration of gallstones into or through the common bile duct may or may not produce biliary colic. Common duct stones have been reported in 60% of 90-year-old patients (GAINES 1977). Obstructive jaundice may result, and may fluctuate. Ascending cholangitis may develop and may become purulent, with liver abscesses. Long-standing obstruction may produce sclerosing cholangitis and biliary cirrhosis.

Migration of gallstones to the neck of the gallbladder obstructs the cystic duct; stasis and infection lead to acute or chronic cholecystitis; rarely, empyema of the gallbladder occurs, and this may perforate. Internal biliary fistula (especially into the duodenum) or impaction of the stone in the ileum (producing gallstone ileus or perforation of the ileum) are other possible complications. A long-term sequel may be carcinoma of the gallbladder (*q.v.*).

Associations with other gastro-intestinal disorders, diabetes mellitus, and coronary artery disease are well known (KAYE and KERN 1971); as expected, the incidence of multiple associated illnesses is greater after 60 years than before this age (HAFF et al. 1971). An association with hiatus hernia has been established firmly only recently (CAPRON et al. 1978; BALDWIN 1978; CHOCTAW et al. 1978).

b) Silent Gallstones

The incidence of silent gallstones increases with age (SATO and MATSUSHIRO 1974), although it has been claimed that truly asymptomatic stones are rare (HORWITZ 1956). The incidence of complications certainly increases with age (STROHL et al. 1964; GLENN 1965; POUPON et al. 1979), and 40%–50% of patients with silent gallstones will develop significant symptoms within 5–20 years (COLCOCK et al. 1967; GAINES 1977), often severe and acute (SATO and MATSUSHIRO 1974; GAINES 1977), when the outlook deteriorates markedly (STROHL et al. 1964; SHELBY and LORHAN 1968; GRODSINSKY et al. 1972; ZIFFREN and HARTFORD 1972; POUPON et al. 1979).

The question of elective prophylactic cholecystectomy in elderly patients with silent gallstones is thus especially important; yet it remains controversial. The balance of risks is far from clear: the operative mortality in older patients has ranged from 1% or less (COLCOCK and PEREY 1963; WRIGHT et al. 1963; HERMANN and MARTIN 1969) to as much as 7.4% (AMBERG and ZBORALSKE 1965 – higher than in their unoperated cases). In non-operated cases aged over 65, LUND (1960) reported a mortality of 7.2%. Other factors need to be considered, e.g. postoperative morbidity is commoner in the elderly (BOLT 1960; HOERR 1963; WRIGHT et al. 1963; GRIFFITHS 1972; SZAUER and ZUKAUKAS 1975), whereas the risk of developing carcinoma of the gallbladder, after silent stones are discovered at age 65, has been calculated as only 0.44% (NEWMAN and NORTHUP 1964) – less than the operative mortality. This is offset by the possible hazards of infective complications and/or biliary obstruction and its sequelae.

BOUCHIER (1976) favours a conservative approach in truly silent stones; dissolution of gallstones may be tried (see below) but silent stones are usually calcified and do not respond to this treatment.

The current surgical philosophy appears to have shifted towards the opinion of GLENN and HAYES (1955) that *all* gallstone disease, whether silent or not, represents a potential hazard which warrants consideration of elective cholecystectomy. There is no doubt that geriatric patients, judiciously selected and well-managed perioperatively, can do very well after cholecystectomy (BRUCE and HARRISON 1967; DJOKOVIC and HEDLEY-WHITE 1979). Incidental cholecystectomy for gallstones discovered during unrelated major abdominal surgery in 44 elderly patients (average age 78 years) caused no significant change in the mortality or morbidity expected (SCHREIBER et al. 1978). The risk of leaving the gallbladder under such circumstances is illustrated by the frequency of postoperative acute cholecystitis

(GLENN 1977; SCHREIBER et al. 1978). This complication is more likely after the age of 50 years, and over half of such cases have gallstones. The mortality in these older patients is 7.6% (BELL and HOLUBITSKY 1969).

c) Medical Treatment of Gallstones (HOFMANN 1980)

Chenodeoxycholic acid (chenic acid), given orally, improves cholesterol solubilization in bile (THISTLE and SCHOENFIELD 1971; BELL et al. 1972) and cholesterol then redissolves from gallstones into the bile. This agent has now been used for 10 years and has been reviewed by its original investigators (THISTLE et al. 1978 b; HOFMANN et al. 1978) and by many others. Certain requirements are necessary for the success of this treatment: radiolucent stones, a functioning gallbladder, an adequate dose (not less than 15 mg/kg/day in most cases, more in obesity), small stones and an ability to wait 6–24 months for dissolution. Recurrence is possible, but may be slow. These criteria may obtain in some elderly patients (SUMMERFIELD 1979) in whom surgery is undesirable or rejected. The U.S. National Co-operative Gallstone Study, a prospective study of chenic acid therapy, recruited patients up to 79 years old (SCHOENFIELD 1978).

The commonest side effect is diarrhoea, which is usually mild and ceases spontaneously; it is dose related. Dyspeptic symptoms often decrease on chenic acid. Biliary colic does not appear to follow reduction in size of the stones. Serum aminotransferases are often raised transiently, but no notable change in liver histology has been observed (BELL et al. 1974; FROMM et al. 1975; PEDERSEN and BREMMELGAARD 1976; DOWLING et al. 1977; THISTLE et al. 1978 b; KOCH et al. 1980).

Ursodeoxycholic acid, the 7-β epimer of chenic acid, has advantages over chenic acid: smaller dosage, more rapid effect, and no diarrhoea or serum aminotransferase increase. With further experience, it may become the agent of first choice for gallstone dissolution (BMJ 1978 b; SUMMERFIELD 1979).

It is worth noting that ursodeoxycholic acid, unlike chenic acid, does not lower increased serum triglyceride concentrations (BATESON and IQBAL 1979).

Bile acids apart, there are two other compounds which have been shown to reduce cholesterol saturation in bile: *Zanchol*, a fluoranthene derivative (ZIMMON et al. 1976) and *Rowachol*, a choleretic consisting of six cyclic monoterpenes derived from plant essential oils (DORAN et al. 1979). The latter has been shown to dissolve gallstones (BELL and DORAN 1979).

d) Gallstones in the Common Bile Duct

These occur twice as often in the elderly as in younger patients (STROHL et al. 1964).

Treatment consists of medical treatment of biliary colic, if it occurs, and surgical measures (exploration of the common bile duct and removal of all stones, and cholecystectomy). Operative mortality and postoperative morbidity are higher than for elective cholecystectomy performed before the stones have migrated from the gallbladder (LUNDSTRÖM and HOLM 1979); this is especially true if acute obstructive cholangitis develops, when urgent decompression of the bile duct is needed (DOOLEY et al. 1979). With appropriate perioperative care, bile duct explorations need not be unduly hazardous for the elderly (SZAUER and ZUKAUKAS 1975;

MURRAY-LYON and REYNOLDS 1976; DJOKOVIC and HEDLEY-WHITE 1979). It is essential to locate and remove all the stones. Operative cholangiography is important (HERMANN and MARTIN 1969; MURRAY-LYON and REYNOLDS 1976; ASHBY 1978): if normal, the bile duct is not opened, but if abnormal, operative choledochoscopy may then be performed to aid retrieval of calculi, and to ensure that none remains in the common bile duct, the hepatic ducts and the papilla. This obviates the need for a T-tube drain, and simplifies and shortens the postoperative course (ASHBY 1978a). In patients in whom postexploratory operative choledochostomy is not used and a T-tube drain is inserted, postoperative cholangiography (SHERLOCK 1981) or choledochoscopy (ASHBY 1978b) should be carried out before removal of the T-tube.

Retained stones at the lower end of the common bile duct may be removed by endoscopic papillotomy (or sphincterotomy), which has been described as a major therapeutic advance in the management of elderly and high-risk patients with bile duct stones (COTTON 1980). COTTON's series included three patients aged 90–99 years and one aged 101. The procedure, with a complication rate of under 10% and a mortality rate of about 1% (SAFRANY 1978; SEIFERT 1978; LIGUORY et al. 1979; COTTON 1980) is much safer than re-exploration in such patients.

Bile duct and hepatic duct stones have been dissolved by perfusion with monooctanoin via a catheter inserted into the T-tube (THISTLE et al. 1978a; LEUSCHNER et al. 1979).

e) Gallstone Ileus

This is a rare but potentially dangerous complication of cholelithiasis, and occurs mainly in elderly women (KVIST 1979). The gallstone, over 2.5 cm in diameter, passes into small intestine or stomach via a fistula, and impacts most often in the ileum. Intestinal obstruction may be accompanied by features of cholangitis, and the previous history usually includes symptoms of chronic cholecystitis.

Diagnosis is usually made by X-rays of the abdomen, which may show distended bowel loops with fluid levels, air in the biliary tract, and possibly the offending gallstone; but any or all of these features may be absent and an emergency contrast examination may be needed (BALTHAZAR and SCHECHTER 1975). Pre-operative diagnosis is made in only a third of cases (KIRKLAND and CROCE 1961) but is more likely if the possibility is borne in mind when an elderly patient presents with small-bowel obstruction of obscure aetiology (SAFAIE-SHIRAZI and PRINTEN 1972).

Treatment is usually by enterotomy. The prognosis is poor; the mortality rate (25%) exceeds that for other causes of intestinal obstruction (MAINGOT 1964; MANAX 1969), although KVIST (1979) reported a mortality of only 12.5%. In successful cases a subsequent elective cholecystectomy is advised (THOMAS et al. 1962).

Rarely, an ischaemic bowel may be perforated by the gallstone (BROWN et al. 1966).

3. Cholecystitis

Acute or chronic cholecystitis is usually associated with gallstones and has an increased incidence in the elderly.

a) Acute Cholecystitis

This is often an exacerbation of chronic cholecystitis; it may be precipitated by interference of bile flow in the cystic duct, e.g. due to impaction of a gallstone at the neck of the gallbladder.

The organisms are usually *Escherichia coli, Klebsiella,* enterobacter, enterococci, streptococci or staphylococci. Anaerobes such as bacteroides and *Clostridia* often coexist.

α) Diagnosis. In the elderly, acute cholecystitis is usually accompanied by abdominal pain and perhaps tenderness; fever is less common and signs of peritoneal irritation are often absent. Mental confusion may be a prominent feature. Differentiation from other acute abdominal or cardiac emergencies may be difficult (HALASZ 1975) and diagnosis is often delayed (MORROW et al. 1978). Laboratory tests may be unhelpful.

Imaging techniques are invaluable in establishing the diagnosis (SELTZER and JONES 1980; ULREICH et al. 1980). Ultrasound is a valuable non-invasive primary screening procedure (MORROW et al. 1978; WOLSON and GOLDBERG 1978; SHERMAN et al. 1980; ULREICH et al. 1980) and may be helpful if gangrenous necrosis or empyema of the gallbladder complicates the picture (KANE 1980). The superiority of ^{99m}Tc-pyridoxylidene glutamate scanning over other techniques was claimed by DOWN et al. (1979).

β) Treatment. Supportive and symptomatic treatment (avoiding morphine) should be supplemented by broad-spectrum antibiotics (KUNE and BURDON 1975). The choice of antibiotics needs care: it will be difficult to achieve adequate concentrations of antibiotics in the bile (JÄRVINEN et al. 1978; KEIGHLEY 1978) and serum concentrations are more important (KEIGHLEY et al. 1976). Thus it is usual to recommend an aminoglycoside and a cephalosporin (or cephamycin antibiotic); newer broad-spectrum penicillins may also be helpful. Intravenous metronidazole had shown some promise (NIELSON and JUSTESEN 1977).

Surgical intervention is usually required at some time and much controversy has centered over its timing. The advocates of early cholecystectomy are supported by at least three controlled studies (LINDEN and SUNZEL 1970; MCARTHUR et al. 1975; LAHTINEN et al. 1978). It must be realized that "early" surgery may be as delayed as 7 days after the onset of symptoms because of delay in diagnosis; but some surgeons operate as soon after admission as feasible, once a diagnosis of acute cholecystitis has been made (SALLEH and BALASEGARAM 1974; MCARTHUR et al. 1975) and this was supported by MORROW et al. (1978) and BEVAN (1978). Meticulous pre-operative preparation is mandatory.

Delayed operation implies successful conservative management, followed by a delay of some months before cholecystectomy is performed. This course is fraught with difficulties – failure of medical treatment, development of complications – especially likely in the elderly – or recurrences of acute cholecystitis, and more difficult operation taking longer and requiring longer hospitalization with an increased incidence of postoperative complications (LAHTINEN et al. 1978).

Elderly patients with acute cholecystitis show greater postoperative morbidity and mortality than younger patients, and if the patient is considered too frail for early cholecystectomy, or if the operation is technically too ambitious in a partic-

ular aged patient, some surgeons favour cholecystostomy (GLENN 1977) as a compromise life-saving procedure which allows a safer wait for subsequent elective cholecystectomy. However, it should be noted that mortality may still be high, since the patients are selected because of their relatively poor prognosis (GAGIC and FREY 1975; GAGIC et al. 1975). Cholecystostomy is an inadequate procedure if suppurative cholangitis is present, since common bile duct decompression is then essential (RAINE and GUNN 1975; MORROW et al. 1978).

Complications of acute cholecystitis include gangrene, perforation, and empyema of the gallbladder, hepatic and subphrenic abscesses, bacteraemia, and internal biliary fistula. All these are commoner in the elderly, and most require emergency surgery, which is often poorly tolerated in these patients. Antibiotics may or may not prevent these complications; but prophylactic antibiotics given perioperatively in biliary tract surgery are certainly of value in reducing the incidence of wound infections (KUNE and BURDON 1975; CUNHA et al. 1978). Nevertheless, prophylactic antibiotics are recommended in biliary tract surgery if high-risk factors are present, such as: age over 70, stones and/or obstruction in common bile duct, jaundice, previous biliary-tract operation, recent rigors, emergency operation or operation within 4 weeks of an emergency admission (KEIGHLEY et al. 1976). The elderly are vulnerable because they often show several of these factors.

Acute acalculous cholecystitis is a serious illness; its incidence is increasing, especially in males aged 65 and above (GLENN 1979). It is particularly related to coincident significant disease of other systems, notably cardiovascular disease, or following surgery unrelated to the biliary tract; its aetiology is obscure.

Treatment is with early surgery; the mortality and morbidity are relatively high.

b) Chronic Cholecystitis

This occurs with cholelithiasis in most cases; it is therefore the commonest disease of the biliary system. The gallbladder becomes shrunken and fibrotic, the bile turbid. The onset is insidious, but acute exacerbations may occur. Symptoms are often vague ("flatulent dyspepsia"), especially after fatty food. There may be pain or discomfort in the right hypochondrium, scapular region or shoulder, and possibly tenderness over the gallbladder and a positive Murphy's sign.

Differential diagnosis is from peptic ulcer, hiatus hernia, colonic disorders, and urinary infections.

X-ray and imaging techniques help in diagnosis; but a normal oral cholecystogram does not exclude the diagnosis.

Treatment is medical or surgical. Medical treatment consists of weight reduction, fat restriction and symptomatic treatment of dyspepsia. However, it is used mainly for patients in whom cholecystectomy cannot be performed.

Cholecystectomy is the definitive treatment; it has been discussed above. Special consideration must be given to the possibility of common bile duct stones and their management.

4. Malignant Disease

a) Carcinoma of Gallbladder

This was once considered rare (NEWMAN and NORTHUP 1964) but is now being reported more commonly in the elderly (BRODÉN et al. 1978); it occurs two to four

times as frequently in women as in men, and becomes considerably more common during the 7th decade and thereafter (STROHL et al. 1964; BRODÉN et al. 1978). It is particularly associated with gallstones, which have been reported in from 54% (SOLAN and JACKSON 1971) to 99% (MITMAKER et al. 1964) of cases. Of patients aged over 70 years with biliary tract disease, up to 11% may have carcinoma (MCLAUGHLIN 1964). The risk is particularly high in calcified (porcelain) gallbladders, perhaps 12%–62% (BISMUTH and MALT 1979). A correlation between hepatobiliary carcinoma and the salmonella carrier state has been described (WELTON et al. 1979).

The tumour may be an adenocarcinoma, squamous, scirrhous or anaplastic. It is generally highly malignant, with early lymphatic spread to the porta hepatis, producing obstructive jaundice.

Pre-operative diagnosis is correct in only a minority of cases and is usually too late to allow complete removal of the growth. Suspicion should be aroused by a recent change in chronic symptoms, with persistent pain, weight loss, or debility, in a patient with a non-functioning and/or calcified gallbladder. While intravenous cholangiography is an appropriate investigation (and coeliac axis angiography may help), non-invasive techniques may be particularly valuable in the elderly, e.g. ultrasound or CAT scanning (CRADE et al. 1979; YEH 1979). Ultrasound may provide important information on tumour size and extension which other methods do not (YUM and FINK 1980), but these two techniques can complement each other (YEH 1979). Nevertheless, empyema of the gallbladder may only be distinguishable from carcinoma at laparotomy.

The prognosis is very poor; the 5-year survival rate is less than 3% (NEWMAN and NORTHUP 1964; SOLAN and JACKSON 1971). The outlook is best in patients with a small carcinoma found unexpectedly during elective cholecystectomy (NEVIN et al. 1976), especially if the diagnosis is made only on microscopy (BERGDAHL 1980). This occurs in 19% (PIEHLER and CRICHLOW 1978) to 33% (KEILL and DE WEESE 1973) of elective cholecystectomies.

Clinical diagnosis calls for early operation. If resection is impossible or inappropriate, various palliative procedures are possible (BISMUTH and MALT 1979).

Prophylaxis involves the prevention and treatment of gallstones, and particularly the use of elective cholecystectomy when the expectation of life is long enough to make the risk of carcinoma a significant hazard. The increasing possibility of medical management of gallstones adds to the opportunities for prophylaxis of this neoplasm.

b) Carcinoma of the Bile Ducts

This is a rarer neoplasm, which may affect extra and/or intrahepatic ducts. In the region of the ampulla it mimics carcinoma of the head of the pancreas; higher parts of the common bile duct are less often involved, but a main hepatic duct may be the site of origin. The cystic duct is never the primary site. In the Orient, liver fluke infection may predispose (BISMUTH and MALT 1979).

Males are affected more often than females, and the disease occurs in late middle or old age. Deep obstructive jaundice develops; occasionally it is intermittent (PHATAK 1974). Weight loss and hepatomegaly are marked and pain is mild.

Periampullary carcinoma has been reviewed by HERMANN and COOPERMAN (1979) and cholangiocarcinoma by MURRAY-LYON (1979).

Non-invasive scanning, hypertonic duodenography, and ERCP have aided in earlier diagnosis (OSNES et al. 1975; EVANDER et al. 1980).

The tumour grows slowly and is often small when diagnosed, but its site makes it frequently inoperable. Nevertheless, aggressive surgery has been advocated and has shown lower mortality, a better quality of life and shorter postoperative hospital stays than palliative surgery (EVANDER et al. 1980). Where necessary, various palliative procedures are available (BISMUTH and MALT 1979; MURRAY-LYON 1979; LAURENCE and COTTON 1980) and may be combined with radiotherapy. Chemotherapy has been discouraging generally, but some promise has recently been discerned (HALL et al. 1979).

The prognosis of carcinoma of the ampulla is better than that of carcinoma of the head of the pancreas, although the 5-year survival rate is only 11%–36% (BLUMGART and KENNEDY 1973; LONGMIRE 1973).

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Endocrine System

Hypothalamo-Hypophyseal-Adrenal Axis

A. V. Everitt and G. R. Andrews

A. Introduction

I. Adaptation to Stress, Such as Surgery

The hypothalamo-hypophyseal-adrenal axis is vitally concerned in the normal defence reaction of the body to stress, as in surgery. With the rise in the percentage of the elderly in Western populations, more and more geriatric surgery is being undertaken. Since such surgery is accompanied by a high rate of morbidity and mortality, it becomes important to understand the factors responsible. One of these factors may be an age-related change in the function of the hypothalamo-hypophyseal-adrenal axis.

II. Hypothalamic-Pituitary-Adrenal Interrelationships

The hypothalamus occupies a central position in controlling the secretion of anterior pituitary hormones, which in turn regulate the functions of the adrenal cortex (Fig. 1) as well as the thyroid, ovary, and testis. Neurohormones synthesized in the hypothalamus are liberated from nerve endings in the median eminence, enter the

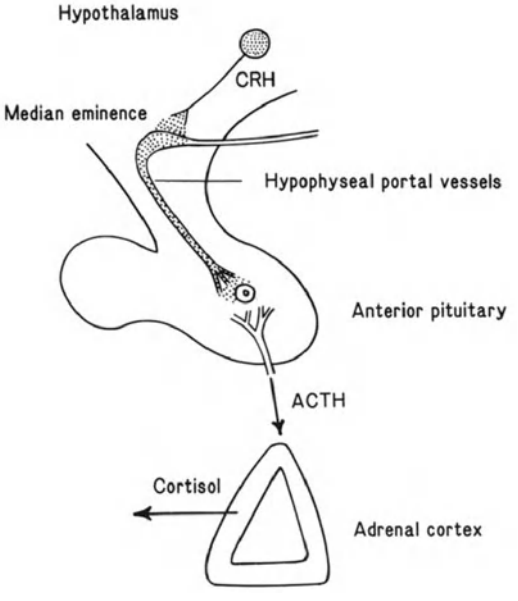

Fig. 1. The hypothalamo-hypophyseal-adrenal axis. Neurons in the median eminence of the hypothalamus secrete releasing hormones (e.g. CRH-corticotrophin-releasing hormone), which are transported by the hypophyseal portal vessels to the anterior pituitary, where they stimulate the release of the corresponding hormone (viz. ACTH) into the systemic circulation. On arrival at the adrenal cortex, ACTH stimulates the secretion of adrenocortical hormones such as cortisol

hypophyseal portal vessels, and then pass directly into the anterior pituitary (adenohypophysis), where they regulate its secretions.

The hypophysiotrophic area of the hypothalamus contains neurons which synthesize and secrete peptides which control the secretion of adenohypophyseal hormones. For each pituitary hormone there is a corresponding hypothalamic-releasing hormone or liberin, e.g. corticotrophin-releasing hormone (CRH) or corticoliberin, which brings about release of corticotrophin or the adrenocorticotrophic hormone (ACTH). In the case of pituitary growth hormone (somatotrophin) and prolactin there are also hypothalamic inhibitory hormones, viz. growth-hormone-inhibiting hormone (or somatostatin) and prolactin-inhibiting hormone (or lactostatin).

The secretion of the hypothalamic hormones appears to be controlled by neurotransmitters, but the mechanisms involved are complex (BROWNSTEIN 1977). Pharmacological studies indicate that basal ACTH secretion is maintained by cholinergic, noradrenergic, dopaminergic, and serotonergic influences, while ACTH stress responses appear to be determined by cholinergic and catecholaminergic mechanisms (ORDY and KAACK 1976).

The adrenal medulla, which also plays an important role in meeting emergencies, is controlled largely by sympathetic nerve pathways which have their origin in the hypothalamus. Thus the hypothalamus exerts a major influence over both regions of the adrenal.

The hypothalamus by mediation of hormones and sympathetic nerves regulates the majority of involuntary functions necessary for living and is especially important in coming to the defence of the organism in an emergency. Furthermore the hypothalamus is believed to regulate aging processes by mediation of the endocrine and nervous systems (DILMAN 1971; FROLKIS et al. 1972; EVERITT 1973; FINCH 1975; EVERITT and BURGESS 1976; DILMAN and ANISIMOV 1979).

B. Morphology

Morphological signs of aging can be seen in the hypothalamus, pituitary, and adrenals in elderly subjects.

I. Hypothalamus

Only limited data are available on morphological age changes in the human hypothalamus and consequently more extensive investigation is urgently required. BUTTLAR-BRENTANO (1954) investigated the supraoptic and paraventricular nuclei in 64 human brains ranging from an embryo of 6 months to old age at 100 years. In old age the two nuclei were enlarged up to tenfold the size in youth, but there were no signs of neuron loss or lipofuscin pigment accumulation frequently seen in other areas of the brain.

In aging laboratory animals there are reports of disruption of hypothalamic architecture in mice (MACHADO-SALAS et al. 1977); loss of neurons (HSU and PENG 1978), and neurosecretory changes (FROLKIS et al. 1972) in the rat; and accumulation of lipofuscin in the guinea-pig (HASAN et al. 1974).

II. Pituitary

Whole pituitary weight undergoes a progressive decrease after age 40 years in males but not in females (Roessle and Roulet 1932; Rasmussen 1928, 1938; Verzár 1966). Such changes in aging men are mainly due to decreases in the anterior lobe (Shanklin 1953) and may be related to decreases in body weight and height (Calloway et al. 1965; Fazekas and Jobba 1970).

In both sexes between ages 20 and 70 years, fibrous tissue gradually replaces parenchymal cells in the anterior pituitary (Fazekas and Jobba 1970; Greenberg 1975). In subjects over 90 years of age, the anterior and posterior lobes are largely intact, although anterior lobe cells are surrounded by bundles of connective tissue (Greenberg 1975). However, this slow loss of glandular tissue does not seriously impair pituitary function since the surviving cells are quite active. Immunocytological studies reveal normal secretory activity in old age of anterior pituitary cells secreting prolactin (Kovacs et al. 1977), growth hormone (Calderon et al. 1978), thyrotrophin (Ryan et al. 1979), and corticotrophin (Gaal et al. 1980). Earlier studies with conventional staining techniques had shown a high secretory activity of pituitary cells in postmenopausal women (Severinghaus 1944) in association with the increased secretion of gonadotrophins.

Pituitary adenomas are seen in about 20% of pituitaries examined at unselected autopsies on elderly subjects (Costello 1936; McKeown 1965; Duchen and Schurr 1976; Kovacs et al. 1980).

The principal morphological age changes in the posterior pituitary are the invasion of basophil cells from the anterior pituitary (Rasmussen 1938) and the reduced vascularity in old age (Xuereb 1954).

The pharyngeal hypophysis, the volume of which is only one-thousandth that of the sellar hypophysis, shows an increase in volume at about age 50 years in the human female (McGrath 1971).

III. Adrenal

Adrenal weight was not found to change significantly with age in two series of 154 (Haugen 1973) and 400 (Calloway et al. 1965) necropsies on patients who died between ages 20 and 90 years. However, it has to be understood that the observed weights were probably increased by the terminal disease and the stresses associated with dying.

Histological age-related changes were described by Cooper in 1925 (see Blichert-Toft 1978). Fibrous tissue proliferates, replacing both cortical and medullary parenchymal cells. In the cortex there is a loss of steroid-containing lipid in the zona fasciculata and an accumulation of pigment cells containing lipochrome granules.

Adrenocortical nodular hyperplasia is a common feature of the aging adrenal. This condition was first described by Letulle in 1889 and has more recently been studied in two autopsy series by Dobbie (1969). In the first series of 71 autopsies, abnormal adrenals were found in 50 patients, 80% of which belonged to the age group between 50 and 80 years. In the second series of 113 consecutive autopsies from patients dying between ages 25 and 82 years, 35% of adrenals showed normal cortical structure, 50% mild nodularity and 14% distinct nodularity. Dobbie sug-

gests that in the majority of patients the nodular hyperplasia is a result of focal ischaemia due to arteriopathy caused by systemic hypertension.

C. Basal Function

There is no gross disturbance of the hypothalamo-hypophyseal-adrenocortical functions in old age, although the secretion of corticosteroids is reduced.

I. Hypothalamus

The secretion of ACTH and adrenocortical steroids is governed mainly by a biological clock in the hypothalamus, which causes hormones to be secreted in episodes mainly occurring at the end of normal sleep. This sleep-related episodic secretion produces peak plasma levels of ACTH and cortisol at about 7 a.m. (BERSON and YALOW 1968; KRIEGER et al. 1971). The nyctohemeral rhythmic secretion of ACTH and cortisol was found to be similar in seven young and four healthy elderly subjects (BLICHERT-TOFT and HUMMER 1977). This study suggests that the adrenocortical biological clock in the hypothalamus functions normally in healthy old age. Abnormal rhythms in episodic secretion of ACTH and cortisol in the elderly may be due to insomnia, psychic stress, and cardiac insufficiency (BLICHERT-TOFT 1978.

Significant age changes occur in the metabolism of hypothalamic neurotransmitters which modulate the secretion of hypothalamic hormones. Catecholamine systems, particularly dopaminergic ones, are highly vulnerable to age changes (FINCH 1976). In the human hypothalamus significant age-associated decrements occur in the activity of enzymes concerned with the metabolism of catecholamines, γ-aminobutyric acid and acetyl choline (MCGREER and MCGREER 1975). In the rat there is a reduction with age in the hypothalamic content of noradrenaline and dopamine (MILLER et al. 1976; SIMPKINS et al. 1977). There is evidence of depressed catecholamine and enhanced serotonin metabolism in aging male rats (SIMPKINS et al. 1977). The effect of these neurotransmitter changes on the secretion of ACTH is unknown.

II. Pituitary

There is no evidence of a change in plasma ACTH levels with age. In a study of 115 fasting healthy subjects of both sexes aged 20 to 94 years the morning level of serum immunoreactive ACTH showed no age relationship (BLICHERT-TOFT 1975).

III. Adrenal Cortex

Basal plasma cortisol levels show no change with age, but the 24-h cortisol secretion rate is reduced in old age. Plasma aldosterone and adrenal androgen levels are lowered significantly in healthy subjects in old age.

1. Glucocorticoids

BLICHERT-TOFT (1975) measured the basal morning plasma cortisol level in 182 healthy subjects (70 female and 112 male) aged 14 to 94 years and found no signif-

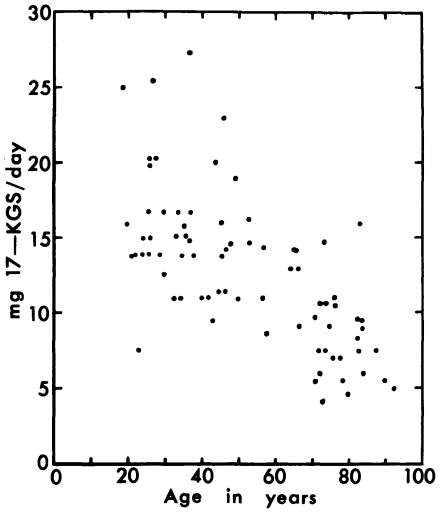

Fig. 2. Urinary 17-ketogenic steroid (17-KGS) excretion per day obtained under basal conditions from 83 healthy male subjects of different ages. Data redrawn from BLICHERT-TOFT (1975)

icant age differences. Similar findings were reported in earlier studies where relatively few elderly subjects were examined, including in some series patients with chronic diseases.

The cortisol secretion rate per day was measured by ROMANOFF et al. (1961), who studied the metabolism of cortisol-4-^{14}C injected intravenously into eight young men aged 21 to 35 years, and eight healthy older men aged 65 to 73 years. They found no qualitative variation in cortisol metabolism in old age. These workers estimated that the 24-h secretion rate of four cortisol metabolites in 23 elderly men was 70% of the rate in 23 young men. Their observations are in agreement with other studies showing a 30%–40% decline (Fig. 2) between maturity and old age in the 24-h excretion of urinary 17-hydroxycorticosteroids (17-OHCS) (HOCHSTAEDT and REICHENBACH 1961) and 17-ketogenic steroids (17-KGS) (BLICHERT-TOFT 1975). Within the physiological range there is fairly good correlation between the excretion of urinary 17-OHCS and the secretion rate of cortisol (JAMES and CAIE 1964). When the excretion of cortisol metabolites is expressed per unit of urinary creatinine there is no age-associated change. Thus the age-related decrement in the secretion of cortisol appears to be related to the fall in total muscle mass which determines creatinine excretion. The diminution of muscle mass in old age may in some way be correlated with a slower cortisol utilization by the tissues. WEST et al. (1961) found a half-life of exogenously administered cortisol of 112 minutes in young men compared with 169 minutes in elderly men. Animal studies have shown reduced corticosteroid binding to muscles in old age (ROTH 1974).

2. Mineralocorticoids

The secretion rate of aldosterone in nine healthy elderly males aged 67 to 88 years was about half that in seven young males aged 18 to 35 years (FLOOD et al. 1967). Intermediates in the aldosterone pathway, deoxycorticosterone, and corticosterone, were likewise excreted at a slower rate in seven elderly men compared with six young men (ROMANOFF and BAXTER 1975). The metabolic clearance rate and

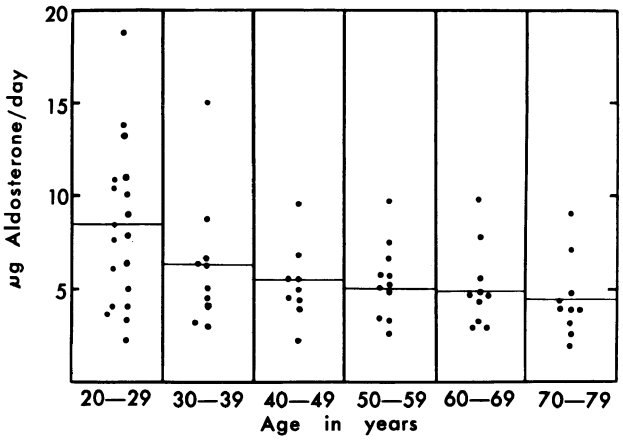

Fig. 3. Urinary aldosterone excretion per day at each decade of life from 20 to 79 years with male subjects on unrestricted sodium intake. Data redrawn from CRANE and HARRIS (1976)

the plasma level of aldosterone were also reduced in these elderly subjects. In normotensive healthy individuals older than 60 years, both aldosterone excretion (Fig. 3) and plasma renin activity were about 60% of the values in young normotensive males (CRANE and HARRIS1976; NOTH et al. 1977).

3. Androgens

The plasma levels of dehydroepiandrosterone and androsterone are found to decrease with age in both sexes (MIGEON et al. 1957; YAMAJI and IBAYASHI 1969). A large age-associated decline in both sexes in the urinary excretion of these and other androgens collectively termed 17-ketosteroids has been shown by many workers (HAMBURGER 1948; KIRK 1949; KOWALEWSKI 1950; BORTH et al. 1957).

IV. Adrenal Medulla

Several studies (ZIEGLER et al. 1976; PRINZ et al. 1979) suggest that plasma noradrenaline levels are increased in older subjects, but adrenaline remains unchanged. The age effect appears to be greatest at night and is correlated with poor sleep in elderly subjects (PRINZ et al. 1979). Plasma noradrenaline levels may reflect sympathetic activity rather than adrenomedullary secretion.

The urinary excretion of the catecholamine metabolite 4 hydroxy-3 methoxy mandelic acid (VMA) in 50 hospital patients aged 69 to 96 showed no change with age (FISHER 1971), whereas an age-related decrease in urinary catecholamines had been reported in earlier studies (KARKI 1956; MASSE 1960).

D. Dynamic Function

The secretory reserve of the hypothalamo-hypophyseal-adrenocortical axis can be assessed with the aid of a number of provocative and suppression tests. The

adrenocortical response is measured by estimating plasma cortisol levels or the excretion of cortisol metabolites such as the 17-KGS or 17-OHCS.

I. Insulin Tolerance Test

Hypoglycaemia produced by intravenous insulin stimulates the hypothalamus to secrete corticotrophin-releasing factor, which in turn increases pituitary ACTH secretion and thence cortisol secretion from the adrenal. Thus this test assesses the integrity of the entire hypothalamic-pituitary-adrenocortical axis. A number of studies clearly indicate that the rise in plasma cortisol in response to insulin-induced hypoglycaemia does not decrease with age (Friedman et al. 1969; Cartlidge et al. 1970; Muggeo et al. 1975; Blichert-Toft 1978). Although insulin tolerance is the test of choice, it is often unpleasant for the patient, requires strict supervision and is not without cardiac risk in old age (Blichert-Toft 1978). With the same insulin tolerance test it is possible to assess the growth hormone secretory response (Cartlidge et al. 1970; Muggeo et al. 1975).

II. Metyrapone Test

Metyrapone inhibits 11β-hydroxylation in the adrenal cortex, thus reducing cortisol synthesis. The resultant fall in plasma cortisol by negative feedback on the hypothalamus tests the physiological reserve capacity of the hypothalamic-pituitary-adrenocortical axis. Indices of adrenocortical secretory response are the rise in plasma total corticosteroids (11 deoxycortisol plus cortisol) and the increase in the excretion of urinary 17-OHCS or 17-KGS. Jensen and Blichert-Toft (1970) have successfully used intravenous metyrapone to test the adrenocortical response in elderly patients. They found no significant difference in adrenocortical response between 11 young and 12 elderly patients as shown by an equal rise in plasma total corticosteroids. This was confirmed in a later study (Blichert-Toft 1975). Measurements of the immunoreactive-ACTH response to intravenous metyrapone also showed no difference between young and old subjects (Blichert-Toft and Hummer 1977).

Oral metyrapone may give unreliable results. Jensen and Blichert-Toft (1970) maintain that the intravenous metyrapone test is the safest test of hypothalamic-pituitary-adrenocortical axis. They believe that the insulin hypoglycaemia, the vasopressin and the pyrogen tests are potentially dangerous.

III. Dexamethasone Suppression Test

Friedman et al. (1969) showed that oral dexamethasone (250 µg at 6-h intervals for 2 days) produced a fall in plasma cortisol levels in 20 elderly hospital patients similar to that in a young control group.

IV. ACTH Test

The responsiveness of the adrenal cortex to ACTH stimulation as measured by the rise in plasma corticosteroid level does not appear to change with age (West et al. 1961; Blichert-Toft et al. 1970). However, when allowance is made for the slower

disposal of cortisol in the elderly, an equal plasma cortisol response to ACTH stimulation in young and aged subjects implies that the old adrenal cortex secretes less cortisol (WEST et al. 1961). Further evidence for diminished adrenal responsiveness to ACTH in old age is the lower urinary excretion of 17-OHCS in the aged to ACTH challenge (MONCLOA et al. 1963).

V. Surgery

Major surgery produces intense stimulation of the hypothalamic-pituitary-adrenocortical axis, leading to increased secretion of cortisol. This reaction is essential for survival after surgical trauma and consequently an assessment of adrenocortical reserve should precede major surgery in the elderly.

BLICHERT-TOFT (1975) studied the ACTH and cortisol responses during and after elective major surgery in 18 young and 14 elderly patients. The immunoreactive ACTH was not impaired during surgery on elderly patients and there was no evidence of exhaustion of ACTH reserve in the postoperative period (BLICHERT-TOFT and HUMMER 1976). The rise in plasma cortisol during surgery was the same in both groups, and on the fifth postoperative day a metyrapone test resulted in a significantly greater elevation of the plasma cortisol level in the older group. Thus there was no evidence of exhaustion of adrenocortical reserve after surgery in aged patients (BLICHERT-TOFT 1975). However, it must be emphasized that elderly patients who are chronically ill or suffer from chronic malnutrition may have a diminished adrenocortical reserve (COOKE et al. 1964).

E. Clinical

There are no characteristic features of disease affecting the hypothalamo-hypophyseal-adrenal axis which are specific for the elderly. The classical descriptions of clinical syndromes associated with hyper- or hypofunction of the component parts of the axis apply to elderly patients suffering those disorders as much as to those who are younger. HALL (1978) points out, however, that many elderly people do display features such as increased pigmentation, loss of body hair, hypotension and mental confusion which may be confused with hypofunction of the adrenal or the hypophysis, and care should be taken in the clinical assessment of these patients to exclude the possibility of such hypofunction as a cause. There are some specific aspects of disorders of the hypophyseal-adrenal axis worthy of note by those responsible for the assessment and care of elderly patients.

I. Anterior Pituitary

Syndromes associated with hyperfunction of the anterior pituitary do not as a rule present in old age, though acromegaly may rarely be diagnosed in late life. The clinical features and treatment are the same as for younger patients (ASCH and GREENBLATT 1978). Hypopituitarism sometimes occurs in old age and may be due to a pituitary adenoma, may be postsurgical or may be the result of auto-immune hypophysitis. Very rarely hypopituitarism following postpartum haemorrhage

may first present in old age. The occurrence in old age of "microadenomas" (small tumours constituting less than one-quarter of the anterior pituitary) may be more frequent than previously realized. One post-mortem study revealed 9% of females and 17.5% of males over 80 years of age at death had pituitary adenomas, usually prolactinomas diagnosed at post-mortem, though no significant clinical correlations were found (Singer et al. 1979; Kovacs et al. 1980). The approach to diagnosis and management of panhypopituitarism or selective hypopituitarism in the elderly should not differ from that taken in the case of younger patients.

II. Posterior Pituitary

The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) has been increasingly recognized in recent years (De Troyer and Demanet 1976). In this condition, there is continual release of antidiuretic hormone without relationship to plasma osmolality. The patients who have been described with this disorder are commonly elderly. The clinical picture described is due primarily to water intoxication and may include disordered consciousness, extrapyramidal signs, and epileptic seizures. Lethargy, muscle cramps, nausea, and anorexia may be complained of by the patient. Hypokalaemia or hypocalcaemia commonly accompany the characteristic hyponatraemia. The disorder needs to be differentiated from other causes of hyponatraemia. In contrast to patients with salt depletion, they are usually well hydrated, normotensive and have normal or low plasma creatinine (Miller and Moses 1977).

Malignancy, particularly oat-cell carcinoma of the lung is the most common cause, but the disorder may also be seen with cerebral tumours, cerebrovascular accidents, hypothyroidism, pulmonary tuberculosis, pneumonia, and drugs including morphine, barbiturates, and chlorpropamide.

The hyponatraemia does not respond to sodium replacement and as a rule, fairly severe water restriction is necessary to raise the plasma sodium concentration (Schwartz et al. 1957).

Thus the features of SIADH that serve to distinguish it from other causes of hyponatraemia are low serum osmolality with less than maximally dilute urine, absence of hypotension, dehydration, azotemia or oedema; continued renal excretion of sodium, reflecting sodium intake; persistence of hyponatraemia even when large quantities of sodium are given; and correction of hyponatraemia by vigorous water restriction alone.

In severe and prolonged cases, frusemide, given together with a small volume of hypertonic (3%) saline, is recommended (Hantman et al. 1973). The use of the antibiotic dimethylchlortetracycline, which interferes with the renal action of ADH has also been shown to be effective in some cases where water restriction has not been possible (Schrier 1978).

III. Adrenal Cortex

The incidence of both adrenal hyper- and hypofunction in the elderly is low and generally when either does occur, the clinical picture is similar to that occurring in younger patients. Cushings syndrome in particular, is relatively rare, but improved

methods of diagnosis and treatment have meant the survival of an increasing number of patients into older age (ORTH and LIDDLE 1971). When the diagnosis is made for the first time in older age, adrenal carcinoma or ectopic ACTH production should be considered, although both pituitary and adrenal Cushings disease may very rarely occur per se.

Addisons disease is more common, but is not frequently diagnosed in old age. The disease is due usually to auto-immune phenomena and may be associated with other endocrine antibodies and the presence of hypothyroidism or thyrotoxicosis (IRVING 1975). While the clinical manifestations and treatment are similar for both old and younger patients, particular care must be taken in the elderly with this disease, to avoid excessive salt and fluid retention by overzealous use of replacement drugs with mineralocorticoid activity.

Hyperaldosteronism may occur as a primary disease due most commonly to a benign adenoma of the adrenal cortex and less often due to hyperplasia or carcinoma of the gland, or it may occur secondarily on cirrhosis of the liver, with other forms of hepatic disease, cardiomyopathies, nephrosis or malignant hypertension. The secondary form is more common in the elderly.

IV. Adrenal Medulla

Phaeochromocytoma may occur in the aged, though it is a rare occurrence. In one series of 58 patients, only four were aged over 60 years at the time of diagnosis (MODLIN et al. 1979). Non-functioning or unrecognized, but clinically functioning, phaeochromocytoma may be discovered at autopsy and several such instances were described in older people in a recent retrospective clinicopathological analysis conducted at one centre (MELICOW 1977).

V. Ectopic Humoral Syndromes

Malignant tumours of non-endocrine origin have been shown to be frequently capable of secreting endocrine polypeptides. The occurrence of otherwise inexplicable metabolic changes consistent with excess hormone secretion should give rise to the suspicion of ectopic production from a solid malignancy. In this context, tumours secreting ectopic ACTH, ADH, gonadotrophins, growth hormone, and melanocyte-stimulating hormone, have all been reported (GOMEZ-URIA and PAZIANOS 1975). This may occur in aged patients at a time when the tumor is still small and has not metastasized, so that it remains clinically occult with only the hormonal effects in evidence.

VI. Iatrogenic Disease

Glucocorticoid therapy is not infrequently used in the elderly. The use of such drugs is particularly hazardous in the aged and the risk of hypercorticoadrenalism is greater than in younger subjects. There is also a risk with more prolonged use of hypothalamic-pituitary-adrenal suppression and consequent acute adrenocortical insufficiency on cessation of therapy. In general, to avoid these hazards, corti-

costeroids should be used only when there is a clear-cut indication and then in as small an effective dose as possible and for as short a time as possible.

The syndrome of inappropriate secretion of antidiuretic hormone resulting from chlorpropamide and other therapy has already been discussed.

F. Conclusions

Morphological age-related changes can be identified at all levels of the hypothalamo-hypophyseal-adrenocortical axis.

Basal secretory functions are diminished at least at the adrenocortical level. Under basal conditions the cortisol secretion rate is reduced in old age, and this appears to be the result of a slower tissue utilization of cortisol acting via a feedback mechanism. The secretion rates of aldosterone and androgen are also reduced in healthy elderly subjects.

Dynamic function tests fail to demonstrate any age-related changes in the ability of the adrenal cortex to raise the plasma cortisol level. Elderly patients exposed to the stress of major elective surgery show no evidence of impaired adrenocortical secretion either during the operation or postoperatively.

Clinically there is no sign of endocrinopathy of the hypothalamic-pituitary-adrenal axis which is specifically associated with old age.

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The Aged Thyroid Gland

H. WAGNER, K. HENGST, and TH. HOSSDORF

After diabetes mellitus, thyroid diseases are one of the most frequent endocrine disorders. There are established age-related changes in hyperthyroidism, hypothyroidism, and cancer of the thyroid, with hyperthyroidism and hypothyroidism giving rise to special diagnostic problems.

A. Morphology of the Elderly Thyroid

The adult thyroid has a mean weight of 20–30 g in nongoitrous areas and is subject not only to considerable regional variations but also to phase-type fluctuations. The shape, weight, and position of the thyroid vary according to genetic factors. In the aging process, however, a change in shape and weight can be detected in both the healthy and the diseased thyroid. Systematic studies on weight changes in the thyroid in the aging process have been carried out in particular by ASCHOFF (1928); KLÖPPEL (1910); WEGELIN (1926) and BREITNER (1928); and by RÖSSLE and ROULET (1932).

After the age of 50 the overall size of the normal thyroid decreases (as can be seen in Fig. 1) because it is then that the thyroid – like numerous other organs – is subject to an involutional process that can affect the isthmus in particular (WEGELIN 1926).

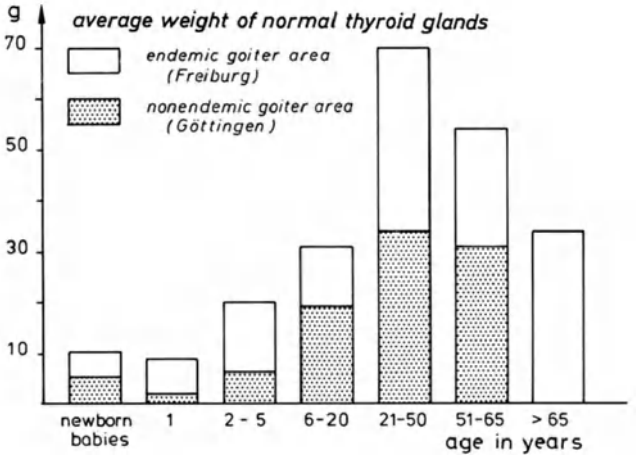

Fig. 1. Changes in weight of the normal thyroid gland in dependency of age in an endemic and a nonendemic goiter area

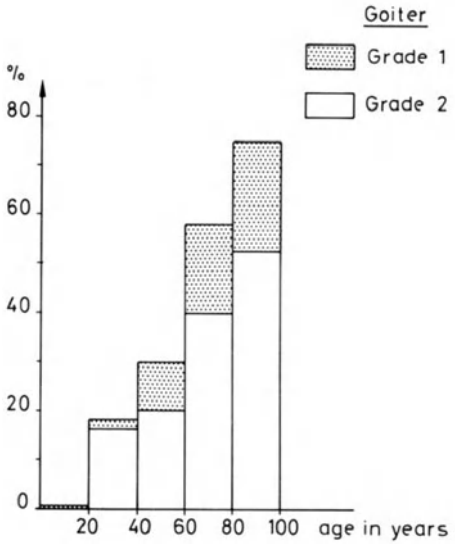

Fig. 2. Frequency (in percentage) of goiters dependent on age in an endemic area of Switzerland (GEISER et al. 1978). Demonstrated are the magnitudes of goiters, which were divided into grade 1 (small-medium size) and grade 2 (large goiters) by GEISER and BÜRGI

It has furthermore been ascertained that goitrous growth, and thus the weight of the thyroid, increases during middle age and into the 6th or 7th decade in endemic areas, as the number of nodules usually increases and the individual nodules tend to become enlarged with increasing age. After the age of 70, the weight of the thyroid has been found to decrease also in these areas. As the overall size and goitrous growth of the thyroid develop contrary to each other in advancing age, goiter evolution is not to be regarded as an expression of the normal aging process; rather it is a sign of morbid change in advancing age. Figure 2 shows the age-dependent behavior of goitrous growth in an endemic area in Switzerland (GEISER et al. 1978).

Histological examinations of the human thyroid have shown that the formation of microfollicles increases during the aging process. According to CLERC (1912) the mean diameter of the follicles decreases in advancing age. DOGLIOTTI and NIZZI (1935) also observed a reduction in the number and size of follicles in conjunction with a reduction in colloid and secretory granulae, at the same time establishing an increase in the height of the otherwise flat epithelial cells of the thyroid. These findings were interpreted by the authors as an expression of thyroid hypersecretion in the elderly.

On the other hand, interfollicular connective tissue shows signs of increase during the aging process. An increased number of thyroid cysts, in conjunction with increased infiltration of the interfollicular connective tissue by small round cells, are found. Comparable changes can be established in the less-marked immunothyroiditis. This disease, however, is accompanied by increased antibody formation that cannot be detected in lymphocytic infiltration of the thyroid in the elderly (HOLLIS 1968).

Experiments on rats and guinea pigs have produced results confirming the reduced number and size of the follicles. At the same time, colloid and nuclear abnormalities together with progression in the fibrotic processes were observed (FROLKIS et al. 1973; RIES and ALLEGRETTI 1965).

B. Physiology of the Aged Thyroid

Increasing insight has been gained into the function of the thyroid and its regulation since the introduction of radioactive iodine and of hormone determination by radioimmunoassay. It is conceivable that the aging process may be influenced by the overall thyroid function at almost every level. For example, the superordinate central regulatory mechanisms, the formation and regulation of thyrotrophin-releasing hormone (TRH), and thyroid-stimulating hormone (TSH) may be subject to an aging influence. An age-related influence on the iodine metabolism of the organism and on hormone production and secretion in the thyroid itself and on the formation and degradation rate of connective proteins is also conceivable. Other age-related changes may appear in the conversion of thyroid hormones in the periphery, which takes place essentially in the liver. Studies investigating the influence of the aging process on the thyroid function must take into account the age-related changes in the metabolizing organs such as the liver, peripheral body cells, or kidneys. Among the elderly, the liver in particular may display numerous age-related and disease-related changes and lesions that must be taken into account in relevant studies. The corresponding tests and their results are considered in detail below.

I. Iodine Metabolism

Iodine as an essential element of the thyroid hormone is assimilated with the diet. Intestinal absorption processes are known to be less efficient in the elderly. As the iodine content of the diet remains constant, impaired assimilation in the elderly would be conceivable. The daily iodine uptake from the diet, however, is observed to increase from 150 μg to 200 μg in the elderly, the iodine content of the thyroid nevertheless decreasing with increasing age.

Initial studies with radioisotope to clarify a significant influence of age on iodine uptake by the thyroid were carried out in 1949 by PERLMUTTER and RIGGS (1953). They found the iodine concentration in the thyroid to be significantly lower in the elderly than in younger euthyroid subjects. Numerous other investigators (QUIMBY et al. 1950; KLEIN 1960; MCGAVACK and SEEGERS 1959; GAFFNEY et al. 1973; GREGERMAN 1976; ODDIE et al. 1968; PETERSEN 1978; WAYNE et al. 1964) have measured the iodine uptake of the aging thyroid, the iodine metabolism in the thyroid, and iodine excretion. Although some results have been conflicting, the overall conclusion is that the ability of the thyroid to assimilate iodine (so-called iodination) is slowed down in elderly subjects but is certainly not decreased in the long term. Twenty-four hours after application of a radioisotope, the concentration in the thyroid is not subject to any definite age-related influence, according to critical evaluation of relevant literature. Investigations reporting an impaired ability of the aged thyroid to assimilate iodine are frequently based on measurements taken above the thyroid after 2 or 6 h (GAFFNEY et al. 1973; ODDIE et al. 1968; PERLMUTTER and RIGGS 1953; PETERSEN 1978; WAYNE et al. 1964). An age-related decrease in iodination can be established with certainly only when extremely young and very old subjects are compared (GREGERMAN 1976).

Another factor influencing the thyroidal uptake of iodine is the amount of iodine excreted by the kidneys. This is subject to a continuous decrease with increasing age, amounting in 80–90 year old patients to only 55% of the output attained

by 50–60 year old subjects (ACKERMANN and IVERSEN 1953; GAFFNEY et al. 1973; HANSEN et al. 1975). This result is in close correlation with the known regression of insulin clearance in advancing age, one of the factors characterizing the aging process of the kidney. Iodine clearance is thus decreased in the elderly, i.e., the fact that less iodine is excreted by the kidneys in advancing age results in iodine being retained longer in the blood stream. Actually delayed iodination as described in studies after 2–6 h could thus be compensated over a longer period. This would explain the fact that no significant age-related decrease in iodine uptake was found after 24 h in certain investigations. In order to solve this problem HANSEN et al. (1975) investigated the absolute thyroidal iodine uptake by measuring the thyroidal uptake of ^{131}I, determining the plasma iodine at the same time. Their findings showed that the absolute iodine uptake is markedly reduced after the 65th year as compared with young normal subjects. This result is interpreted as a compensatory mechanism on the reduced hormone production of the thyroid with advancing age (cf. p 106).

II. Thyroid Hormones

Prior to the measurement of total T_4 and T_3 being introduced, the proportion of hormones circulating in the blood stream was determined by means of plasma-bound iodine (PBI). T_4 was generally assumed to account for the greater part of PBI. MCGAVACK and SEEGERS (1958); ODDIE et al. (1968); DAILEY and SKAHAN (1956), and GAFFNEY et al. (1960) found no age-dependent changes in the level of the PBI concentration when studying large numbers of cases. These findings are confirmed by other investigators on smaller groups of subjects (PERRY and COSGROVE 1949). An age-specific reduction in PBI was reported by some investigators, with a preponderance being established in the female sex (KOUNTZ et al. 1949; REED et al. 1972; TUCKER and KEYS 1951). Others again detected an increased PBI concentration in the elderly (SCAZZIGA et al. 1955). Evaluation of the findings must take account of the fact that PBI is influenced by a wide range of factors as demonstrated in a survey by DAVIS (1966). All in all, a correlation between PBI and age is now regarded as a certainty.

As with PBI, literature relating to the influencing of the total thyroxine concentration and free T_4 in the serum during the aging process is not consistent. In many studies hitherto published on physiological changes in the hormone parameter in the blood, critical consideration must be given to the fact that although attention was paid to elderly subjects being euthyroid, too little attention was paid to whether latent or manifest extrathyroid diseases were present. The latter are known to occur more frequently with increasing age (so-called multimorbidity in advanced age).

Some studies ascertained that no significant changes in free and total T_4 occur during the aging process (BRAVERMANN 1966; LEMARCHAND BERAUD and VAENOTH 1969; OHARA et al. 1974; SAN MARCO et al. 1972; WAGNER et al. 1979; WESTGREN et al. 1976) (Fig. 3).

Other investigators on the other hand report a 20% decline in the thyroxine concentration (HERRMANN et al. 1974; HESCH et al. 1976; WENZEL and HORN 1975). A 60% decrease in thyroxine secretion has been observed in old female rats (VERZAR and FREYDBERG 1956).

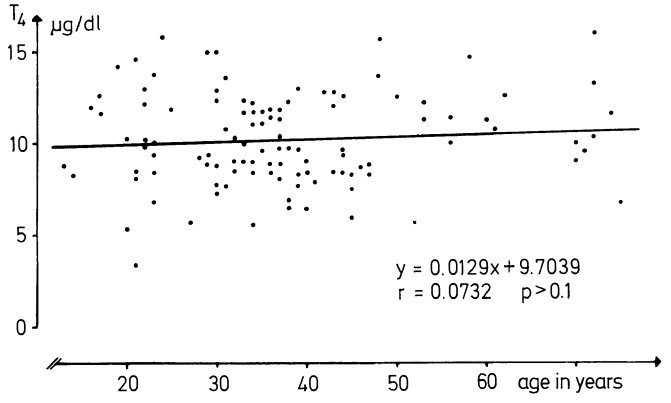

Fig. 3. Age independency of total serum-thyroxine values in healthy men and women aged 15–75 years. The regression line is nearly parallel to the axis of age

These conflicting findings may be due to unsystematic selection of the test subjects. This is verified by the results of detailed investigations in the representative English town of Wickham (EVERED et al. 1978). In this study, thyroid diseases and any known extrathyroid influences were carefully excluded. The results showed that among men in an absolutely normal random population, the T_4 serum concentration increased with increasing age whereas no dependency on age was established among women. With no selectivity, the T_4 increase in elderly men (above 65 years) was less marked; among elderly women there was a decline in T_4 concentration in comparison with those women under the age of 45. These findings were explained by the proportion of pregnant women and by contraceptives being taken by younger women, whose T_4 serum concentrations were significantly higher than those of young men.

T_4 turnover studies with intravenous injection of radioactive thyroxine have shown that the production rate of T_4 and the absolute thyroidal uptake of iodine decline with advancing age (HANSEN et al. 1975; RUBENSTEIN et al. 1973). Similar observations have been made in experiments on animals (VERZAR and FREYDBERG 1956; GRAD 1969; GRAD and HOFFMANN 1955). Studies of this kind have shown that the metabolic clearance rate of T_4 declines significantly in healthy elderly subjects. The absolute thyroidal uptake of iodine is decreased as a response to hormone production declining in advanced age. At the same time the secretion of thyrosine from the thyroid is increased and the degradation rate in the periphery reduced. It is pointed out once again that extrathyroid diseases in particular, such as liver diseases, may give rise to conflicting results and have led to findings such as increased metabolic activity and a decreased T_4 concentration. The fact is, however, that T_4 production is decreased and degradation retarded. The absolute thyroxine concentration thus remains constant, as demonstrated by turnover tests (GREGERMANN et al. 1962; ODDIE et al. 1968; WENZEL and HORN 1975).

With measurements in the serum, there may be a gradual, marginal decline in the total T_4 concentration, whereas the free T_4 remains at a normal level even at advanced age owing to a slight increase in the percentage of free T_4.

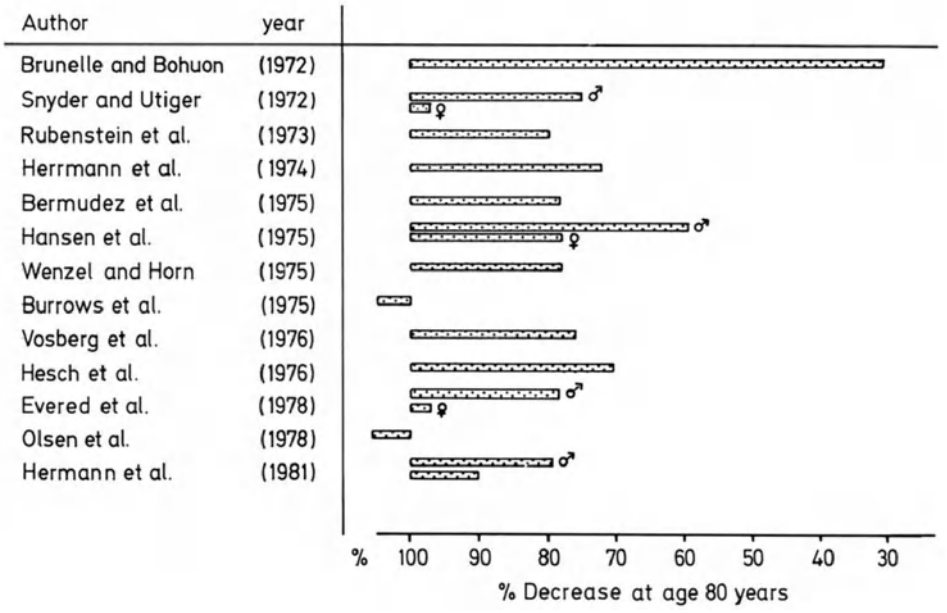

Fig. 4. The decrease in serum-triiodthyronine concentration at the age of 80 is compared with the values at the age of 30 as reviewed from the literature. (HERRMANN et al. 1981)

The behavior of the triiodothyronine concentration (T_3) with increasing age is assessed differently by different teams. A general survey of the relevant literature is given in Fig. 4. A large number of teams report a continuous decline in the concentration of total and free T_3. Many of the elderly subjects were living in homes for the aged or were euthyroid patients undergoing inpatient or outpatient treatment for other illnesses (BERMUDEZ et al. 1975; BRUNELLE and BOHUON 1972; BURROWS et al. 1975;EVERED et al. 1978; HANSEN et al. 1975; HERRMANN et al. 1974 a, b;-HESCH et al. 1976; MØHOLM HANSEN 1978; RUDORFF et al. 1977; HOSSDORF et al. 1980; RUBENSTEIN et al. 1973; SAN MARCO et al. 1972; VOSBERG et al. 1976; WAGNER et al. 1975; WENZEL and HORN 1975). One single team reports unchanged T_3 concentrations from adolescence until the age of 80 and only then a sharp decline (WESTGREN et al. 1976). Special attention was paid in this study to blood samples being taken only from nonfasting patients. This was not taken into account in other studies. It is pointed out, however, that the T_3 serum concentration can frequently be lowered considerably by malnutrition (POTTNAY et al. 1974) or by various chronic and acute system diseases (BERMUDEZ et al. 1975; BURGER et al. 1976; WEISSEL et al. 1978). Some investigations have indeed found triiodothyronine levels corresponding to those of young adults in elderly subjects with a good general state of health (AZIZI et al. 1975; OLSEN et al. 1978). These findings are confirmed by the Wickham study (EVERED et al. 1963) already quoted.

The conclusion must be drawn from these investigations that the total and free hormone concentrations of T_4 and T_3 are unchanged in advancing age and that the changes described are due to an extrathyroid disease in advancing age (ENGLER et al. 1978).

Table 1. Serum T_3, T_4, and reverse T_3 values in elderly patients of different states of health compared with younger healthy probands. HERRMANN et al. (1981)

	Women				Men			
	Age	T_3(ng/dl)	T_4(μg/dl)	RT_3(ng/dl)	Age	T_3(ng/dl)	T_4(μg/dl)	RT_3(ng/dl)
Young controls Blood donors	30±11	112±32 (47)	8.7±1.9 (47)	22±12 (47)	35± 8	117±23 (62)	7.4±1.7 (62)	19±8 (58)
Private nursing Home; healthy s.	79± 7	101±20 (45)	8.6±1.7 (45)	26±16 (45)	77±13	94±13 (20)	8.4±2.7 (20)	23±7 (20)
Geriatric psychiatry Amb. "healthy" s.	76± 6	103±27 (123)	9.0±2.0 (128)	–	75± 8	94±27 (38)	9.0±2.2 (38)	–
Municipal nursing Home; chron. ill s.	77± 6	94±22 (97)	7.4±2.6 (97)	–	–	–	–	–
Hospital patients Moderately ill	76± 5	83±23 (20)	8.9±1.7 (20)	26±12 (20)	75± 6	85±19 (21)	8.8±1.9 (21)	28±12 (21)

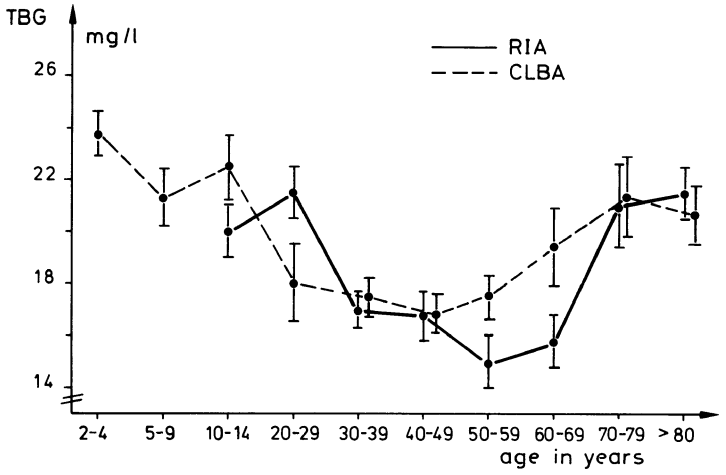

Fig. 5. Dependency of TBG (thyroxine-binding globulin) concentrations on age ($\bar{x} \pm SEM$) as measured by RUDORFF et al. (1981) with RIA-TBG (radioimmunoassay) and CLBA-TBG (competitive ligand binding assay)

Correspondingly, turnover tests as carried out by WENZEL and HORN (1975) and by HERMANN et al. (1981) have shown no age-related change in the metabolic clearance of T_3. With an unchanged metabolic T_3 clearance in the elderly organism and a proven decline in metabolic T_4 clearance in advancing age, this could only be explained by increased hormone conversion in the periphery or by increased secretion of T_3 by the thyroid. Both alternatives seem extremely unlikely, especially as no increased secretion or conversion could be detected in experiments on animals (RUDORFF et al. 1981). Summing up, it is emphasized once again that the age-dependent 20% decrease in T_4 secretion and the corresponding age-dependent decline in the T_3 concentration can by no means be regarded as proven, since studies based on carefully selected subjects were unable to detect any age-related changes. Table 1 shows a compilation of various thyroid function parameters related to age and state of health of the subjects.

III. Binding Proteins

An age-related change in thyroid function due to changed binding of the hormones to their specific binding proteins and a corresponding change in the free biologically effective hormone concentration is conceivable. A continuous decline in thyroxine-binding globulin (TBG) after the age of 9 months with a minimum level between the 20th and 45th years and a renewed rise in advancing age has indeed been observed (HESCH et al. 1976; PICKARDT et al. 1977; RUDORFF et al. 1972, Fig. 5). Other teams report that the TBG level remains constant from adolescence into advanced age (BRAVERMAN et al. 1966; WAGNER et al. 1977, 1979). One team from the United States (JEFFREYS et al. 1972) reports a decreased TBG level in advancing age. It must, however, be noted that this observation was made on a small group of subjects. This study also reports a decreased albumin concentration among the subjects, possibly due to reduced synthesis for extrathyroid reasons.

A corresponding age correlation is also described for the maximum binding capacity of TBG for T_4. The maximum binding capacity of thyroxine-binding prealbumin for T_4, on the other hand, increases with increasing age, reaching a maximum between the ages of 20 and 50, and then declines again in advanced age (BRAVERMAN et al. 1966). A difference between the sexes is described. Among 20–30 year old women, the T_4-binding capacity of TBG is raised and that of thyroxine-binding prealbumin lowered. A conflicting influence of estrogens and testerone is discussed. The differences between the sexes are marginal and lead to no significant differences in the overall binding capacity of the thyroid hormones. The overall binding capacity of the serum for thyroid hormones thus undergoes no age-related change (RUDORFF et al. 1981).

IV. Regulation by the Hypothalamic Anterior Pituitary System

Some teams point out an unchanged basal TSH level in advancing age (BERMUDEZ et al. 1975; VOSBERG et al. 1976; WEST and CHAVRÉ 1964). Other investigators report a marginally increased TSH level that is, however, still within the normal range (LEMARCHAND BERAUD and VAENOTH 1969; OHARA et al. 1974). There are further observations that the basal TSH concentrations in adults are higher between the ages of 20 and 50 than in subjects over the age of 65 (WENZEL et al. 1974). Many studies quote only small numbers of cases, which may explain the discrepancies in the findings reported. We found no age correlation in the basal TSH concentration of our subjects (Fig. 6).

The maximum rise in the TSH level after stimulation with TRH occurs in the blood after 30 min. After a dose of 400–500 µg TRH intravenously injected, the maximum rise in the TSH level in advancing age is significantly lower at this stage than among 20–50 year old normal subjects (SNYDER and UTIGER 1972; WAGNER et al. 1974; WAGNER et al. 1975; WENZEL et al. 1974). The reason for the reduced

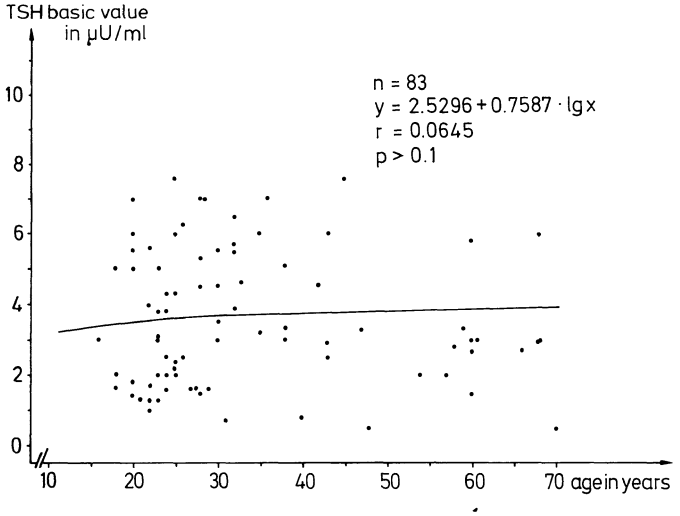

Fig. 6. Age independency of basal TSH values in serum in healthy men aged 15–70 years

TSH increase in advancing age is unknown. The pituitary may possibly react less sensitively to TRH or more sensitively to the suppressive effect of the thyroid hormone. Also in experiments on animals, older animals were found to have decreased thyroid secretion rates after stimulation (CHEN and WALFISH 1978; NARRANG and TURNER 1966; KORRENCHEWSKY et al. 1953; GRAD 1969). No change is known in the basal TSH level or in reaction to stimulus by TRH during chronic diseases. The ability of the aged thyroid to secrete T_3 on endogenic and exogenic TSH stimulation does, however, remain unchanged even in advancing age (GREGERMAN 1976; SCAZZIGA et al. 1955).

C. Nontoxic Goiter

Nontoxic goiter is defined as a noninflammatory and nonmalignant enlargement of the thyroid gland that is present in an euthyroid metabolic situation.

It is well known how frequently long-standing goiter may lead to complaints in advancing age even in nonendemic areas. In general, goiters tend to grow and to become increasingly nodular in elderly subjects, particularly in women. This is a result of the changed hormone balance during the menopause, which also leads increasingly to recurrent goiter. Progressive changes are accompanied by an increase in the size of the colloid adenoma. Whereas the normal thyroid – as mentioned in the section on morphology – loses weight with increasing age and the tendency is rather toward regressive changes (MCGAVACK and SEEGERS 1959), a marked increase in the incidence and the size of goiters can be observed, above all in endemic areas (GEISER et al. 1978; DE GÊNNES et al. 1961; HELSLOOT et al. 1976).

The majority of long-standing goiters consist of a number of different, large full nodules. The trachea is occasionally subject to considerable constriction, being frequently not only displaced laterally but more or less incised. The cervical vessels may be clearly congested. In all events it is essential to control to what extent substernal parts are responsible for the respiratory tract being further constricted. Elderly patients with tracheostenosis have more difficulty in breathing, so that global emphysema may occur, which can result in right ventricular heart failure with the pulmonary circulation being overstrained. Patients complain furthermore of decreased vitality, sensory disturbances, and insomnia.

The diagnosis of nontoxic goiter depends first and foremost on excluding other thyroid diseases by differential diagnosis. The number of goiters with a hyperthyroid metabolic condition undoubtedly increases in advancing age (DE GÊNNES et al. 1961; HELSLOOT et al. 1976; COPE et al. 1947). Basic diagnosis consists in determining the total thyroxine concentration in the serum and carrying out a binding test. Further diagnosis should include a TRH-TSH test. This is positive in 80% of all cases, i.e., a normal increase in the TSH concentration is registered after a dose of 400–500 μg TRH (BRITTON et al. 1975; ORMSTON et al. 1971).

Irregular activity is frequently registered by scintigram, particularly with elderly patients. An increased number of autonomous regions are found among extensive regressive areas (SCHAUER et al. 1972; WOOLNER 1971). It is pointed out that autonomous areas in euthyroid goiters degenerate more rapidly into hyperthyroidism under exposure to iodine in elderly patients (SCHAUER et al. 1972). The

potential malignancy of regressive areas is often hard to assess. Needle biopsy may be indicated for further diagnostic clarification and represents very little strain on the patient.

Signs of malignancy at an early stage, such as nuclear abnormalities, irregular overall structure, and growth into the vessels and surrounding tissue, are frequently detected histologically. For this reason a decision on actually malignant growth is not easy in elderly patients even with histological methods. If there are, however, localized adherent glands, e.g., at the rear edge of the sternocleidal mastoid process, if radiating pain occurs in the ears, and if the thyroid is fused with the trachea and a sudden acceleration in thyroid growth has been noticed, suspicion of a malignant growth is fully justified.

In general, nontoxic goiter can be treated by medication, by surgery, or with radioiodine. In cases of life-threatening tracheostenosis, an operative approach, i.e., subtotal resection of the thyroid, is desirable. Elderly patients, on the other hand, may have contraindications in high-risk second illnesses, such as cardiac insufficiency, decompensated emphysematous heart, general angiosclerosis, and hypertension, which raise the risk of anesthesia and surgery beyond an acceptable limit. In such cases a surgical indication should be regarded with reserve. If a malignant growth is furthermore definitely suspected, the decision on the therapeutic approach will be even more difficult. Following resection, relapse prophylaxis by means of replacement therapy is recommended (BANSI 1967; OBERDISSE 1980).

Life-threatening tracheostenosis can be avoided in elderly patients – particularly when the patient emphatically refuses surgery – by shrinking the thyroid with radioiodine. This treatment is frequently unsatisfactory from the cosmetic point of view but it does succeed in stopping the risk of suffocation and can be repeated if necessary. Subsequent relapse prophylaxis by means of replacement therapy with synthetic thyroid hormones is recommended in this case too.

If the elderly patient notices sufficiently early that his goiter is becoming enlarged, one single treatment with hormones can be tried out. The indication must, however, be very strict, since the potential risks of thyroid hormone therapy with advancing age must be carefully considered. They are expressed above all in possible cardiac strain with symptoms such as angina pectoris, palpitations, tachycardia, and insomnia.

Treatment with a pure L-thyroxine preparation or with a mild compound preparation with a 10:1 ratio of T_4 to T_3 (e.g., Prothyrid) is advantageous. Compound preparations with higher T_3 concentrations lead to peak serum concentrations accompanied by an increased cardiac risk (PICKARDT et al. 1981). In advancing age the full maintenance dose must be built up very carefully over a long period. Therapy should be as consistent as possible, with success being controlled on clinical findings.

The main cause of nontoxic goiter developing is generally assumed to be an inadequate dietary iodine supply, although many other goitrogens are known.

In endemic areas (e.g., in Switzerland and Austria) prophylaxis with iodized salt has been implemented for some considerable time with success (CONNOLLY 1970; STUDER et al. 1978). This is not without risk for the goiter of the elderly subject. As already mentioned, autonomous areas in euthyroid goiters of elderly patients may degenerate more rapidly on exposure to iodine. All in all, the aged

thyroid is markedly incapable of coping with an inadequate supply of iodine. In Switzerland, STUDER et al. (1978) investigated the significance of iodine application in such cases of subclinical or preclinical hyperthyroidism in advancing age and drew attention to the potential risks; autonomous tissue regions in so-called nontoxic goiters, a frequent occurrence in elderly patients, do not lead to metabolic imbalance until provided with sufficient iodide as a substrate for hormone synthesis. Another study failed, however, to confirm this risk of prophylaxis with iodized salt (JOSEPH et al. 1979).

D. Hypothyroidism in Elderly Subjects

Some 0.2% of the adult population suffers from hypothyroidism. Hypothyroidism is a typical disease of old age; its increased incidence among elderly subjects has become particularly evident now that various investigators have recognized the significance of screening tests, for it is significant how frequently hypothyroidism fails to be diagnosed in practice among elderly patients owing to most of the patients appearing merely to have aged prematurely on superficial observation. LLYOD et al. (1961) found 1.5% of manifest cases of hypothyroidism among 3,417 geriatric patients. Over a 3-year period in a geriatric ward of one hospital, 1.4% of the patients were found to be suffering from thyroid diseases, 3.9% of these from hypothyroidism (GATTI and POZZI 1975). In 1975, hypothyroidism was detected in 2.3% of 2,000 geriatric patients (BAHEMUKA and HODGKINSON 1975). A German multicenter study recently confirmed these data (HERRMANN et al. 1981). Prevalences determined prior to the introduction of screening tests were considerably lower (MCGAVACK and SEEGERS 1959).

When cases of hypothyroidism among elderly patients are divided according to sex, there is a definite preponderance among women (BAHEMUKA and HODGKINSON 1975; LLOYD and GOLDBERG 1961), the ratio being 5:1.

With elderly patients suffering from hypothyroidism, a distinction must be made on principle between cases of hypothyroidism that developed in youth and have extended into advanced age and those that have only developed in advanced age.

In the large majority of cases, hypothyroidism has not developed until more advanced age, spontaneous hypothyroidism apparently taking first place (BASTENIE et al. 1973; MCCONAHEY 1978; OWEN and SMART 1958), with between 90% and 100% (BASTENIE et al. 1973; INGBAR 1978; LLOYD and GOLDBERG 1961) (Fig. 7). The cause of spontaneous hypothyroidism is suspected to be autoimmune thyroiditis that has subsided (OWEN and SMART 1958). It is assumed to be a variant of Hashimoto's thyroiditis (MCCONAHEY 1978). BASTENIE et al. (1973) did in fact identify thyroid antibodies in 91% of cases of spontaneous hypothyroidism in elderly subjects. The remaining cases of hypothyroidism occurring in elderly subjects are due to thyroid destruction, e.g., by radioiodine treatment and surgical intervention. Percentage data on such cases of "post-therapeutic" hypothyroidism vary between 3% and 30% of those treated (BERTHEAUX and BRIBET 1968; BURKE and SILVERSTEIN 1969; EINHORN and WICKLUND 1966; SHAFER and NUTALL 1975; TROTTER 1965; MARKSON and FLATMAN 1965) with no unequivocal correlation with age. BLAHOS AND SOUMAR (1975), however, established the 55th year as the critical age

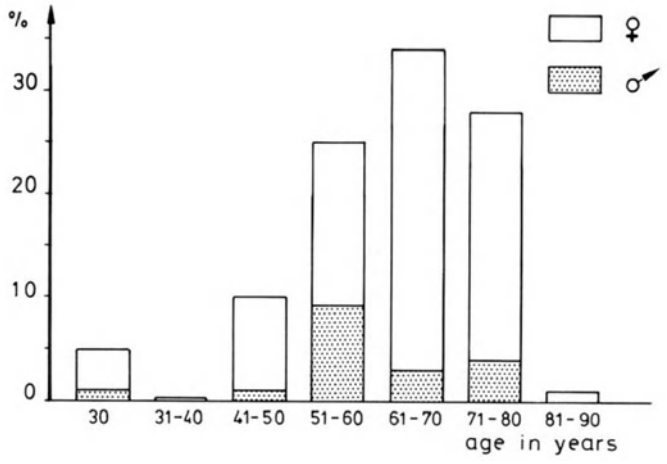

Fig. 7. Distribution of age and sex in patients with the diagnosis of spontaneous hypothyroidism

for destructive therapy. Prior to the 55th year, the rate of post-therapeutic hypothyroidism is claimed to be 11% and after the 55th year 31% (mean value 26%). They assumed the cause of the increase in iatrogenic hypothyroidism in elderly subjects to be age-related anatomical factors or sensitization of the aged thyroid to radioactive iodine. This might be due to frequent long-standing hypothyroidism among elderly patients prior to therapy.

The initial occurrence in advanced age of secondary hypothyroidism due to pituitary disorders must be regarded as extremely rare (McCONAHEY 1978). No cases of secondary hypothyroidism were observed among those cases of hypothyroidism discovered in geriatric patients in various field studies (BAHEMUKA and HODGKINSON 1975; EVERED and HALL 1972).

There is no great difference in principle between younger and older patients in clinical symptomatology (INGBAR 1978). In adulthood the insidious onset of the disease in general rarely permits early diagnosis. The boundaries between euthyroidism and hypothyroidism are fluid. With increasing age, the signs and symptoms of the disease are more subtle and of even slower progression (MORROW 1978). This accounts for less than one-third of patients displaying classical symptoms in early screening tests and a general feeling of illness, weakness or a poor general state of health being marked (BAHEMUKA and HODGKINSON 1975). The insidious progress of the disease and the fluid transitions also explain the shortage of precise data on the incidence of individual symptoms in the elderly. Investigations nevertheless repeatedly point out that individual symptoms may be prominent in the disease (monosymptomatic or oligosymptomatic presentation) (BAHEMUKA and HODGKINSON 1975; MORROW 1978). The fact must not be overlooked here that the physiological aging process may mask the symptoms and make classification difficult for the physician (HOLLIS 1968). On superficial observation the patients generally appear merely to be prematurely aged (MORROW 1978). For this reason it is not surprising that attention is constantly being drawn to the significance of screening tests in the diagnosis of hypothyroidism. A physician not think-

ing of hypothyroidism will not consider it as a possible diagnosis and will fail to have corresponding laboratory tests performed.

Changes in the integument and in physical appearance are especially inclined to be interpreted as premature aging. The incidence of obesity, withdrawal behavior, lethargy, dry thin hair, and loss of the lateral eyebrows increases with advancing age. Dry, scaly, cool skin loses reliable diagnostic significance in view of senile atrophic changes in the skin (MORROW 1978). It is pointed out that patients with long-standing diabetis mellitus or nephrotic syndromes may have a similar physical appearance (MCCONAHEY 1978).

Then there is a large number of symptoms that are almost physiological in the elderly, such as reduced resilience and activity, impaired faculties of hearing (syringitis and middle-ear catarrh resulting from myxedema in the tympanic cavity), persistent constipation, sluggish reflexes, and increased sensitivity to cold.

Intolerance to cold is almost always a symptom of elderly patients suffering from hypothyroidism (HENGST et al. 1980). Hypothermia can be verified clinically. Exacerbations of the disease occur most frequently in winter among elderly patients (MCCONAHEY 1978). Many elderly patients not suffering from hypothyroidism, on the other hand, complain of intolerance to cold due to the blood circulation being inhibited by arteriosclerosis. Eighty-six percent of elderly hypothyroid patients complain of persistent constipation (BAKER and HARVEY 1971; HENGST et al. 1980). In our western affluent society with its low-bulk diet, however, persistent constipation is an extremely frequent clinical symptom among elderly women in particular. The possibility of hypothyroidism should nevertheless always be considered in cases of persistent constipation. Extreme cases are accompanied by severe abdominal cramps and meteorism going as far as paralytic ileus (BASTENIE et al. 1973).

As already mentioned, resilience and activity decline with advancing age. It is thus hardly surprising that too little importance has been attached to lack of drive and to apathy in the diagnosis of hypothyroidism. Mental and physical slowness in conjunction with depressions and dysmnesia is wrongly interpreted in many cases as senile dementia, neurotic depression, or chronic schizophrenia. This accounts for the constant flow of investigations reporting cases of nondiagnosed hypothyroidism among psychiatric patients (ASHER 1949; BAHEMUKA and HODGKINSON 1975; HENSCHKE and PAIN 1977; SAVAGE 1880; TONKS 1964). A systematic examination of these publications shows that the patients concerned are almost always over 60 years of age. Mental changes in particular are frequently the outstanding symptoms in the elderly. BAHEMUKA and HODGKINSON (1975) report that 22% of their patients undergoing screening tests displayed only mental changes. This percentage has been confirmed by other studies (ASHER 1949; BEUMONT 1972; CROPPER 1973; HENSCHKE and PAIN 1977; TONKS 1964). The patients concerned are almost exclusively women. The cause is assumed to be an impaired blood supply to the brain or reduced cardiac output (SCHEINBERG et al. 1964). In many cases the patients are first seen by a psychiatrist. As elderly patients in particular may display dysmnesia and changes in character due to cerebral sclerosis, the diagnosis is often overlooked in these cases unless the symptoms are accompanied by a typical physical appearance. A dramatic improvement frequently occurs after adequate replacement therapy unless irreversible damage has been caused by metabolic changes

during illness (ASHER 1949; HENSCHKE and PAIN 1977; TONKS 1964). The sluggish reflexes, above all the delayed ankle reflex, used to be evaluated as diagnostic criteria, a delayed ankle reflex time appearing to correlate well with the severity of the hypothyroidism in 90% of cases (CROPPER 1973). This examination method should now be regarded as outdated. The lack of a delayed reflex time in 40% of elderly patients is also reported (MORROW 1978).

Other investigators draw attention to the increased occurrence of paresthesia; at the same time there was a marked tendency among elderly patients to myogelosis and muscle spasms (BASTENIE et al. 1973; HENSCHKE and PAIN 1977).

Being subjected to little strain, the cardiovascular system shows no marked signs of deficiency symptoms in elderly subjects. Arteriosclerosis and the development of coronary heart disease are encouraged by disturbances of the lipometabolism in hypothyroid patients (BAHEMUKA and HODGKINSON 1975; VANHAELST et al. 1967). Complaints by elderly patients of angina pectoris are also being increasingly reported (MCCONAHEY 1978). On the other hand, the rate of cardiac infarction among elderly hypothyroid patients is the same as among euthyroid subjects of the same age (BASTENIE et al. 1973). With reduced vitality due to slowing of the metabolic process and reduced strain on the heart due to concomitant anemia, the hypothyroid elderly patient is not subject to an increased risk of infarction despite severe pathological changes in the heart. The blood pressure is rarely high; the ECG displays low voltage amplitude and disturbed intraventricular conduction. Ischemic S-T depression changes, however, occur 10% more frequently than in euthyroid subjects of the same age (VANHAELST et al. 1967).

In screening tests on geriatric patients, special attention has been drawn to concomitant pernicious anemia and rheumatoid arthritis (BAHEMUKA and HODGKINSON 1975; BANSI 1967). Pathogenetic-type immunological mechanisms are suspected.

Suspected hypothyroidism diagnosed by means of the clinical syndrome is nowadays confirmed in the chemical laboratory by determination of the total thyroxine concentration in the serum and performance of a binding test. If the total T_4 concentration is low, medication with diphenylhydantoine, androgens, or large doses of salicylates must be meticulously excluded (MCCONAHEY 1978). Determination of the basal TSH concentration is recommended for more advanced diagnosis. The TRH-TSH test is performed in selected cases only, e.g., to differentiate cases of secondary hypothyroidism (HENGST et al. 1980).

Treatment of hypothyroidism is simple and effective. Adequate replacement with synthetic thyroid hormones produces a positive and convincing improvement in the symptoms and diseases. It must be borne in mind when treating elderly patients with long-standing diseases and previous cardiac damage that they have adapted to their metabolic state and cannot cope so fast with an improved metabolism. The coronary vessels may be narrowed and their function just sufficient with the reduced cardiac output and reduced systolic volume, so that there might be a risk of angina pectoris under therapy (HOLLIS 1968).

Replacement therapy using a pure T_4 preparation is preferable in advanced age to administration of a compound preparation (HENGST et al. 1980). Owing to the shorter half-life period and faster assimilation of triiodothyronine, preparations of this type lead to varying blood levels with increased T_3 concentrations when the

tablets have been taken, accompanied by an increased cardiac risk and by complaints such as angina pectoris, palpitations, tachycardia, and insomnia.

One single early-morning dose of a T_4 preparation produces a sufficiently consistent blood level. 25 μg/day should be taken as a starting dose, the dose being increased by 25 μg/day at intervals of 2–3 weeks. Experience shows that elderly patients require less thyroid hormone for complete compensation, so that the maintenance dose of 100–125 μg/day for elderly patients is lower than that for younger patients (150–200 μg/day) (SHOCK et al. 1974). To check for sufficient replacement, determination of the total thyroxine concentration in the serum, which should be absolutely normal, is advisable. In some instances the TSH concentration can also be determined or a TRH-TSH test performed, in which the TSH serum concentration should be within the normal range or marginally suppressed after administration of TRH (HENGST et al. 1980; MORROW 1978).

Although mean maintenance doses have been stipulated, individual requirements may fluctuate in elderly subjects. If complications arise before a euthyroid state is attained, the dose must be reduced immediately to a previous symptom-free status and retained at that level for several weeks. Therapeutic complications include first and foremost angina pectoris complaints. BAHEMUKA and HODGKINSON (1975) reported two serious cases of myocardial infarction under replacement therapy. Muscle cramps and loss of scalp hair, sometimes complained of when therapy is started, are fully reversible after some time (MCCONAHEY 1978).

D-T_4 preparations used to be administered freely, especially to patients with a coronary heart disease (STARR 1960; SCHNEEBERG 1964) as these preparations were thought to be better tolerated. The effectiveness of this substance, however, is only 7%–10% of that of L-T_4, so that treatment with dextrorotatory T_4 preparations has not asserted itself.

I. Myxedema Coma

The hypothyroid or myxedema coma is an extremely severe form of the disease, occurring most often in elderly patients, especially in women (MCCONAHEY 1978). The peak incidence is in the 7th decade (BASTENIE et al. 1973) and the female:male ratio 4:1. One reason for the increased incidence of the coma in senescence may be that the hypothyroid syndrome is more rarely diagnosed in old age on account of its symptomatic similarity with the physiological aging process and its insidious development. The symptoms might furthermore be aggravated by the concomitant presence of basic illnesses such as cerebrovascular or pulmonary dysfunction (INGBAR 1978). Some 150 cases have been reported in international literature up to date. The incidence of myxedema comas appears to have been on the increase in recent times, possibly as a delayed consequence of radioiodine therapy for hyperthyroidism (BASTENIE et al. 1973).

Exacerbation shows increased incidence in winter. The triggering factors must be assumed to be: severe exposure of infections to cold, severe traumata, cardiac decompensation, and furthermore the administration of certain preparations, such as opiates, barbiturates, phenothiazine, imipramine, phenylbutazone, and para-aminosalicylic acid (SOTOMAYER and BOWERS 1964). Other factors may be apoplexia, hypoxia, hypercapnia, and hypernatremia (MCCONAHEY 1978).

The clinical syndrome is that of severe myxedema and generally not difficult to recognize owing to its classic presentation (McCONAHEY 1978). It is a deep, calm coma with hypoventilation, hypotension, and hypothermia. Apart from signs of peripheral low voltage there are no specific changes in the ECG. No special signs of neurological disturbance can be detected (BASTENIE et al. 1973). Nor are any age-specific features of this disease – which occurs anyway almost exclusively in elderly patients – known to us. It is essential for diagnosis to be confirmed without delay. The mortality rate is quoted in relevant literature at 50%–70% (BASTENIE et al. 1973; McCONAHEY 1978).

As no studies covering large numbers of cases are available and most authors have used a therapeutic approach based on their own experience, therapeutic directives cannot necessarily be given for elderly subjects. Unlike the treatment of hypothyroidism, fast full replacement is essential for elderly patients in myxedema coma (McCONAHEY 1978). Relevant literature quotes dosages of 10 μg/12 h to 100 μg/6 h of L-triiodothyronine given intravenously or by nasogastric tube (BLUM 1972; CATZ and RUSSEL 1961; McCONAHEY 1978; DOW and LERMAN 1965; HAUSMANN 1970; IVY 1965) or 300–500 μg/day L-thyroxine given intravenously (HOLVEY et al. 1964; MENENDEZ and RIVLIN 1973; ROSENBERG 1968). Therapy is continued orally after 4–7 days with 100 μg/day L-thyroxine.

Hydrocortisone (100–300 μg/day) is administered as an adjunctive. Complications such as respiratory insufficiency, hypoglycemia, hypothermia, hyponatremia, and shock should be kept under control by measures that are standard practice today in any intensive care unit.

E. Hyperthyroidism in Elderly Subjects

Hyperthyroidism as a disease occurring in elderly patients has been gaining significance. The peak incidence has shifted from the 20th–40th year to the 40th–50th year (IVERSEN 1953; RONNØV-JESSEN and KIRKEGAARD 1973; WERNER 1962; YOUNG 1941). Figure 8 shows the age-related distribution of hyperthyroidism according to OBERDISSE (1980). Retrospective studies report the proportion of elderly patients in the total number of cases at 12%–15% (BARTELS 1954; COOKSON 1939; DE GÊNNES et al. 1961; HELSLOOT et al. 1976a; HELSLOOT 1976; SCHULTZ 1978). Higher percentages (27%–50%), however, are quoted in more recent reports (BRUN et al. 1978; GUINET and BORY 1973; RONNØV-JESSEN and KIRKEGAARD 1973). Some authors even assume hyperthyroidism to be far more frequent among elderly subjects than among younger persons as it is often not detected (RONNØV-JESSEN and KIRKEGAARD 1973). In systematic large-scale field studies on several thousand patients, 0.5%–1.1% of elderly patients were found to have undiagnosed hyperthyroidism (LLOYD and GOLDBERG 1961).

Whether the apparent shift in the age groups corresponds to actual fact is questionable. The possibility of a general increase in the proportion of elderly patients is contemplated as an explanation for the increased number of elderly patients among the total number of hyperthyroid cases (BRUN et al. 1978; IVERSEN 1953). In addition, diagnosis has been improved by the introduction of more sophisticated laboratory methods (BRUN et al. 1978; IVERSEN 1953; RONNØV-JESSEN and KIR-

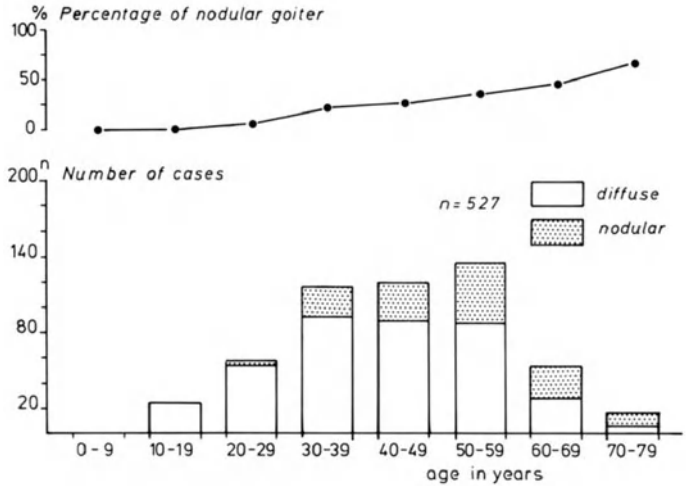

Fig. 8. Distributions of goiters in patients with hyperthyroidism dependent on age (OBERDISSE 1980). The percentage of nodular goiters is shown in the upper part of the figure

KEGAARD 1973) so that oligosymptomatic forms of hyperthyroidism among elderly subjects are now more reliably covered. As with younger patients, the incidence is greater among women. Data on the male:female ratio of patients above the age of 60 suffering from the disease vary among different authors from 1:4 to 1:9.6 (DAVIS and DAVIS 1974; DÖPKE 1964; GUINET and BORY 1973; SCHULTZ 1978). Among younger patients the male:female sex ratio is 1:7.5 (OBERDISSE 1980).

Research into the causes of hyperthyroidism in senescence suggests that only 1.3% of patients had once had a compensated autonomous nodule (KÖBBERLING et al. 1980). Of those affected, 33% had antecedent goiter. In 16% of the cases, recurrent hyperthyroidism was reported. The incidence of nodular goiter in hyperthyroid subjects over the age of 70 is outstanding high (BARTELS 1954). There is thus a "Basedowification" of previously nontoxic goiters during later decades (OBERDISSE 1980). The triggering factor in 82%-95% of the patients was established by some authors as antecedent exposure to iodine (DAVIS and DAVIS 1974; KÖBBERLING et al. 1980; BLUM et al. 1974). One series of investigations showed that the quantities of iodine triggering off hyperthyroidism are lower among elderly patients than among young people (BRUN et al. 1978). We must point out that elderly patients are more frequently exposed to iodine through the administration of radiological contrast media within the diagnostic framework of concomitant diseases. It has already been claimed that every case of nodular goiter eventually develops into hyperthyroidism under corresponding exposure to iodine provided that the patient lives long enough (BARTELS 1954).

Clinical diagnosis of hyperthyroidism in elderly subjects is by no means elusive in severe, typical cases. Symptoms and presentations that may mask the clinical picture as such do, however, occur more frequently in senescence. The obvious signs – increased irritability, restlessness, hyperkinetic activity, and cardiovascular hyperactivity (warm skin and fast pulse) – may be masked or completely absent. Monosymptomatic or oligosymptomatic presentations of the disease are so

frequent among elderly subjects that individual syndromes may well be predominant.

One of the leading syndromes among elderly patients is thyrocardiopathy. Such symptoms as palpitations, extrasystoles, and tachycardia are reported by more than 60% of all elderly hyperthyroid patients, and by 42% as the primary complaint (DAVIS and DAVIS 1974; MCMILLAN and WENDLOS 1937). The clinical symptoms of angina pectoris are present in 20% of all cases. LEVINE and STURGES (1924) described a group of thyroxic patients whose cardiac symptoms were so prominent that hyperthyroidism could not readily be diagnosed. BARTELS (1954) claims that cardiac symptoms are almost inevitable among hyperthyroid elderly patients. Constant tachycardia is by no means always present in these patients; varying incidences are given by different authors. For instance, BARTELS (1954) diagnosed significant constant tachycardia in 70% of cases, DAVIS and DAVIS (1974) in 59%, MOREAU (1966) in 100%, and IVERSEN (1953) in only 20%. Absolute arrythmia with atrial fibrillation is diagnosed among elderly patients with the same incidence as tachycardia and was registered, for example, by DAVIS and DAVIS (1974) in 39% of cases, by STIEL et al. (1972) in 13%, and by SEED and LINDSAY (1949) in 72%. Atrial fibrillation appears to increase continuously among hyperthyroid patients with each decade. The incidence of atrial fibrillation is furthermore believed to be associated with the autonomous nodule, with the age of the patient, and with the severity and duration of the disease (SEED and LINDSAY 1949). Symptoms in the sense of cardiac insufficiency (dyspnea on exertion, edema and/or ascites, nycturia) are quoted in 14%–60% of cases (BARTELS 1954; DAVIS and DAVIS 1974; SEED and LINDSAY 1949). A primary cardiac disease (hypertension, coronary sclerosis, vitia, etc.) is always present in elderly patients with thyrocardiopathy (OBERDISSE 1980). The occurrence of hyperthyroidism with a higher metabolic rate and an increased O_2 requirement leads to an increase in the cardiac output and the myocardial effort. The heart may occasionally be able to compensate this, but cardiac failure will occur sooner or later owing to the limited cardial reserve. This is often difficult to treat and may prove to be refractory if the hypermetabolism is very marked. The same may apply to arrythmia. Treatment involves high digitalization. Adequate treatment of hyperthyroidism as a primary disease, however, is less problematic (GUINET and BORY 1973; SCHULTZ (1978). Congestive heart failure of unclarified genesis, therapy-refractory congestive cardiac failure, and paroxysmal atrial fibrillation of unclarified genesis should suggest hyperthyroidism in elderly subjects (MCMILLAN and WENDLOS 1937; SCHULTZ 1978). Ineffectiveness of digitalization may also be a valuable clue.

We should mention at this point that myocardial infarction is, if anything, rare among hyperthyroid elderly patients despite the increase in angina pectoris symptoms (BRUN et al. 1978; DAVIS and DAVIS 1974; GUINET and BORY 1973; LITTMAN et al. 1957; SCHULTZ 1978; SEED and LINDSAY 1949). Only a Scandinavian team headed by BURSTEIN (1960) reports an increased incidence of myocardial infarctions in thyrotoxic patients. There is, however, a conspicuously increased incidence of coronary diseases in the area under review, so that the thyrotoxicosis probably overburdens an already stressed heart in these cases.

Among elderly hyperthyroid patients, electrocardiography furthermore shows a prominent P wave and an upright-type heart stimulation pattern that is quite un-

common for the advanced age of the patient. There are also drops in ST segments, T flattening, and negative T waves. Atrial fibrillation or flutter, as already mentioned, is another frequent occurrence. The sinus rhythm can be restored therapeutically in many cases (DÖPKE 1964). DAVIS and DAVIS (1974) reported atypical systoles in 69% of cases and diastoles in 10% being determined by ascultation.

Hypertension is a frequent symptom among elderly hyperthyroid patients (COOKSON 1939; WISHAW 1946) and can be explained in 23% of cases (DAVIS and DAVIS 1974; GUINET and BORY 1973; SEED and LINDSAY 1949). One conspicuous feature is a high amplitude of blood pressure without any valvular defect in the case history pointing to an aortic disorder.

Apart from cardiac manifestations, other clinical features and subjective complaints by older thyrotoxic patients are easily overlooked. Typical changes in the skin, such as a fine texture, hyperthermia, and moistness, occurred in 81% of those elderly patients examined by DAVIS and DAVIS. These authors did emphasize, however, that age-dependent changes among an elderly euthyroid population also include a thinner and finer skin texture and may thus mask the signs of hyperthyroidism. The normal skin in senescence is cool, dry, wrinkled, and hyperpigmented. On the other hand, the warm moist skin of elderly thyrotoxic patients may not be prominent in cases of vasoconstriction due to cardiac failure (HOLLIS 1968). A fine tremor is also observed in 89% of cases (DAVIS and DAVIS 1974) but is frequently overlooked as a diagnostic pointer owing to fine muscular tremor being a frequent symptom of senility (DAVIS and DAVIS 1974; HOLLIS 1968).

Among the more subjective data, the fact is conspicuous that an increased appetite is confirmed only rarely (approx. 22%) (BANSI 1967; DAVIS and DAVIS 1974; HOLLIS 1968), but a relatively large number of elderly hyperthyroid patients complain of impaired appetite that reaches anorexial proportions in up to 36% of cases (BARTELS 1954; DAVIS and DAVIS 1974; DE GÊNNES et al. 1961; GUINET and BORY 1973). Loss of weight is more considerable in elderly patients (mean loss 11 kg) than among younger ones (mean loss 4 kg) (DE GÊNNES et al. 1961; MOREAU 1955; RONNØV-JESSEN and KIERKEGAARD 1973).

One French team headed by DE GÊNNES (1961) even reports loss of weight as the only constant symptom in all elderly hyperthyroid patients. There is a close correlation between the duration of the disease and the extent of the loss in weight (GUINET and BORY 1973). Serious loss in weight and myopathies may be the major symptoms if the patient is unable to cover the loss of metabolic energy by an increased caloric intake, as may be the case in the elderly patient due to associated diseases, anorexia, or weakness.

Diarrhea is an occasional manifestation and may also result in a loss in weight. In general, however, the elderly patient complains of changed bowel habits rather than of watery stools. Two to six well-formed or pultaceous stools are reported in 24% of cases (DAVIS and DAVIS 1974; SCHULTZ 1978). A comparably large number of patients on the other hand complain of constipation, a frequent symptom in old age (BAKER and HARVEY 1971). Constipation persisting despite hyperthyroidism has already been reported. Syndromes covering loss of weight, anexoria, and constipation are observed in 14% of cases and wrongly interpreted as a gastrointestinal carcinoma (DAVIS and DAVIS 1974).

Table 2. Frequency of symptoms (in %) in young and old patients with hyperthyroidism.

Authors	No of cases	Age	Symptoms in percentage of cases				
			Heat intolerance	Increased sweating	Increased appetite	Reduced appetite	Loss of weight
BANSI (1967)	?	55	49	53	22	–	80
RØNNOV-JESSEN and KIRKEGAARD (1973)	28	60	46.4	35.7	–	57.1	100
IVERSEN (1953)	?	60	–	60	–	–	86.8
STIEL et al. (1972)	126	60	6	–	–	–	24
HELSLOOT et al. (1976)	179	60	67	66	10	39	83
BANSI (1967)	?	40	77	86	75	–	81
RØNNOV-JESSEN and KIRKEGAARD (1973)	21	60	61.9	66.6	–	9.5	100
IVERSEN (1953)	?	60	–	52	–	–	79.4
STIEL et al. (1972)	?	60	6	–	–	–	30
HELSLOOT et al. (1976)	?	60	73	78	50	12	74
Mean percentage of symptoms							
Old persons			42.1	53.6	16	48	74.7
Joung persons			54.4	70.6	62.5	10.7	72.9

Hepatomegaly was reported by DAVIS and DAVIS (1974) in 45% of cases, and hepatosplenomegaly in 9%. Of these cases, 60% are the result of right-sided cardiac failure due to cardiac insufficiency.

Heat intolerance, a tendency to excessive sweating, low-grade pyrexia, and hot flushes are reported only infrequently and appear rather to be ambiguous (BRUN et al. 1978; BÜRGI et al. 1978; DÖPKE 1964). DAVIS and DAVIS (1974) report, however, that heat intolerance was affirmed by two-thirds of the patients in their own systematic examinations.

Differential diagnosis of hyperthyroidism in the elderly patient is particularly difficult if the superficial signs of hyperkinetic activity are replaced by nonactivation as a dominant clinical feature. LAHEY (1931) coined the term "apathetic hyperthyroidism" for this type of thyrotoxicosis. The patient's behavior is quiet and disinterested. Dominant features are depression, changes in the general behavior pattern, emotional instability, and irritability (SCHULTZ 1978). Other dominant features such as tachycardia and warm moist skin may be absent in many cases. LAHEY (1931) found that all these patients were already elderly and had small thyroids. Although they did not appear to be seriously ill, they lapsed into coma within a short time and died. Other authors have meanwhile reported this feature in up to 37% of hyperthyroid elderly patients (DAVIS and DAVIS 1974; MCGEE et al. 1959; HAY 1936). Occurring almost exclusively in senescence, this apathetic form could indeed almost be termed senile hyperthyroidism. On the other hand, not all elderly hyperthyroid patients are apathetic. Some are similarly hyperactive and excitable to 16-year-olds (SEED and LINDSAY 1949). The transitions between hyperkinetic and apathetic hyperthyroidism are fluid. Changing symptomatology may be observed at times (LAHEY 1931) and has been reported as occurring particu-

Data were obtained from authors who examined young as well as old patients

Symptoms in percentage of cases											
Nervousness, hyperkinesis	Diarrhoea frequent stool	Palpitations consciousness	Dyspnoea	Loss of hair	Tremor	Typical skin signs	Palpable thyroid	Tachycardia	Auricular fibrillations	Systolic murmur	Eye symptoms
86	24	51	57	42	66	57	94	46	27	53	55
35.7	14.2	–	–	–	–	–	71.4	39.2	25	–	3.5
–	28.6	–	–	–	79	–	–	–	25	–	48.1
15	3	–	–	–	–	–	34	–	13	–	4
85	12	–	–	–	60	73	–	–	50	–	4
99	36	73	49	51	71	73	96	44	1	41	62
85.7	38	–	–	–	–	–	71.4	66.6	14.7	–	19
–	25.5	–	–	–	71	–	–	–	2	–	64.8
52	8	–	–	–	–	–	16	–	1	–	5
90	30	–	–	–	71	80	–	–	15	–	25
55.4	16.3	51	57	42	68.3	65	66.4	42.6	28	53	22.9
81.6	27.5	73	49	51	71	76.5	61.1	55.3	6.7	41	35.2

larly often with hyperthyroid multinodular goiter (THOMAS et al. 1970). DAVIS and DAVIS (1974) report asthenia and weakness in 28% of cases. Of elderly hyperthyroid patients, 10% display syncopes, somnolence, mental confusion, and behavioral disturbances (DEWIND et al. 1958). It must, of course, be borne in mind that a large number of senile, arteriosclerotic, and psychological reactions impair the normal function of the psyche (HOLLIS 1968). Mental confusion, irritability, and anxiety do, however, occur more frequently among elderly hyperthyroid patients than among their euthyroid contemporaries (DAVIS and DAVIS 1974; DEWIND et al. 1958).

The incidence of symptoms and complaints among elderly and among younger hyperthyroid patients as reported by different authors is summarized in Table 2. The survey covers only those authors who also examined correspondingly younger patients, which is not often the case. It becomes evident that the wealth of symptoms undergoes a percentage decline with increasing age. The incidence of absolute arrythmia and anorexia, on the other hand, is clearly higher than among young patients. The investigations listed are specially directed,systematic records of findings in patients known to be thyrotoxic. It is pointed out once again that there are not more than one or two dominant features in most cases. In some 10% of cases, the disease occurs characteristically in advanced age without any of the symptoms and complaints and may therefore be discerned only by routine screening (BARTELS 1954; OBERDISSE 1980). It is thus hardly surprising that hyperthyroidism is diagnosed in only 25% of elderly patients by means of clinical indices such as the Newcastle thyrotoxicosis index or the Crooks, Murray, and Wayne index (DAVIS and DAVIS 1974). This also explains why the prediagnosis duration of the disease is lon-

ger among elderly patients, with a median of 25.3 months (SEED and LINDSAY 1949) as opposed to 6–9 months for younger patients (BARTELS 1954).

The disease generally develops more slowly in old age, so that it may often be more advanced by the time diagnosis is made. BÜRGI et al. (1978) attribute this primarily to an increased incidence of autonomous nodules in old age. They found that diagnosis was delayed by 1–5 years regardless of age in all cases handled by them of autonomous nodules with an insidious onset and slowly progressing symptomatology. Failure to diagnose an autonomous nodule is accordingly believed to be a frequent occurrence among all age groups (HORST et al. 1967).

As far as the distribution of diffuse goiter and autonomous nodules among young hyperthyroid patients is concerned, 78% of cases are reported to occur with diffuse goiter, 21% with autonomous nodules, and 1% without goiter (SEED and LINDSAY 1949). No distinction is made here, however, between autoimmune hyperthyroidism and disseminated autonomy. It is only in recent times that more attention has been paid to these distinctions. The incidence of diffuse goiter undergoes a marked decrease with advancing age, whereas the autonomous nodule or hyperthyroid nodular goiter attain their peak incidence after the age of 40. Figure 8 shows a summarized age distribution and the distribution of different types of goiter. On surveying relevant literature, a marked increase in multinodular toxic goiters from 3% to 32% is conspicuous (BARTELS 1954; BRUN et al. 1978; BÜRGI et al. 1978). In data relating to the distribution of nodular goiters and diffuse goiters among the elderly, account must be taken of whether the data are based on scintiscan findings or on palpation. It must be borne in mind that palpation findings are considered highly unreliable in old age (BRUN et al. 1978), failing to correlate with scintiscan findings in 70% of cases. It is only with the introduction of scintillation scanning that the former assumption that diffuse goiter occurs only in younger patients and autonomous nodules only in elderly patients has been proved wrong. Both types occur, as mentioned above, in both age groups despite the increased incidence of nodular goiter among the elderly population arousing the impression that autonomous nodules are confined to old age. Scintillation scanning has shown, however, that autonomous nodules may also occur in non-nodular goiters. The autonomous areas in the nodular goiter have frequently been found to occur between the nodules, with the nodules themselves being less active. Palpation alone is insufficient to ensure diagnosis of an autonomous nodule. Pathologically also, the autonomous nodule in elderly subjects has special features. Within a hot nodule of a younger patient, histological examination reveals a structure consisting of microfollicles with capsules formed of normal thyroid tissue, whereas the findings may be simple regional hyperplasia in a multinodular goiter in the case of elderly patients. Histologically, various types of autonomy are obviously concerned. Even in multinodular goiters, one single hyperactive area can often be observed (BLUM et al 1975; BRUN et al. 1978). An ever-increasing number of follicles become autonomous, however, in nodular goiter with increasing age (STUDER et al. 1978).

The theory that the number of autonomous areas increases with advancing age has recently been refuted by JOSEPH et al. (1979a, b). All in all, the number of autonomous areas remains constant before and after the 40th year. An increase in nodular and a decline in disseminated autonomy, however, can be ob-

served after the 40th year. In these studies also, a higher incidence of decompensation of autonomous areas was shown with advancing age.

The significance of concomitant diseases should be dealt with briefly at this point. Apart from cardinal cardiovascular diseases, it is exacerbation of old-age diabetes that is most frequently observed. Concomitant diabetes is easier to cope with when the thyrotoxic patient receives adequate treatment (SEED and LINDSAY (1949). Increased susceptibility to infection and the detection of chronic foci, e.g., of tonsillogenic or otogenic character, are also factors of significance with elderly hyperthyroid patients (DÖPKE 1964). The importance of scintillation scanning in the differential diagnosis of autonomous nodules among elderly patients has been mentioned above. In addition it should be stated once again that irregular distribution of activity is also found in thyrotoxic multinodular goiter. There are also regressive areas with decreased activity in hyperthyroidism, suggesting concomitant presence of a carcinoma. It should therefore be emphasized that thyrotoxicosis and carcinomas are rarely concomitant (DEWIND et al. 1958).

Diagnosis of hyperthyroidism is nowadays substantiated by determination of total serum thyroxine concentration and performance of a binding test as well as by determination of the total serum triiodothyronine concentration. Performance of a TRH-TSH test is advisable to exclude hyperthyroidism.

The problematic nature of interpreting diagnostic data in old age was mentioned elsewhere in this chapter (p 129). Widely differing teams have reviewed the valency of the individual tests with regard to diagnosing hyperthyroidism in old age. There is an established decrease in the serum triiodothyronine concentration in old age, most probably due to the concomitant presence of severe nonthyroidal illnesses (cf. p 106). TURNER et al. (1975), KIRKEGAARD et al. (1975), and BRITTON et al. (1975) describe this laboratory constellation of T_4 thyrotoxicosis in elderly hyperthyroids with severe nonthyroid illnesses. KIRKEGAARD et al. (1975) concluded a diminished conversion of T_4 into T_3 from their investigations. Furthergoing investigations, e.g., including the simultaneous measurement of reverse T_3, are not known to us. In cases of discrepant findings and suspected thyrotoxicosis, a TRH-TSH stimulation test should be performed.

A review of relevant literature shows that no false-negative laboratory results occur in the average elderly thyrotoxic patient. In elderly patients, however, there are relatively more diagnostic failures (BRITTON et al. 1975; HELSLOOT et al. 1976b; KIRKEGAARD et al. 1975; TURNER et al. 1975). All authors therefore agree that not only one test should be performed (BÜRGI et al. 1978; CAPLAN et al. 1978; HARVEY 1971; STIEL et al. 1972). Free T_4 determination (BÜRGI et al. 1978; HARVEY 1971; RONNØV-JESSEN and KIERKEGAARD 1973) and performance of a TRH-TSH stimulation test (BÜRGI et al. 1978; GEMSENJÄGER et al. 1976; KÖBBERLING et al. 1980) are quoted as being most reliable. There is no difference between younger and elderly patients in laboratory data on the extent and severity of hyperthyroidism. Nor do there appear to be any specific laboratory distinctions in apathetic thyrotoxicosis (RONNØV-JESSEN and KIERKEGAARD 1973; THOMAS et al. 1970).

The TRH-TSH test is regarded as the most reliable and precise diagnostic measure even in the early diagnosis of so-called subclinical or preclinical hyper-

thyroidism (GEMSENJÄGER et al. 1976). The significance of the preclinical disease can be summed up with the following problems: The severity of hyperthyroidism may fluctuate. The symptoms of the disease may be masked by concomitant diseases. In patients with concomitant diseases, clinically quiescent hyperthyroidism may suddenly become a serious factor. Rapid treatment cannot then always be given in the short time required (STUDER et al. 1978). Subclinical hyperthyroidism is a warning signal and should be kept under constant control and observation.

Treatment of hyperthyroidism in senescence involves no special problems. In general, radioiodine therapy is given absolute preference for elderly people with any type of hyperthyroidism since it is safe and reliable (DEWIND et al. 1958). The disadvantages of this treatment, such as potential genetic injury to the genital system and the risk of a thyroid carcinoma developing, are inconsequential in senescence.

The initial effects of radioiodine treatment cannot be expected within 8 weeks of iodine application. For this reason some authors prefer treatment with thyrostatic drugs and first aim for a euthyroid state (SCHULTZ 1978), whereas others (DÖPKE 1964) start treatment with radioiodine supported by sedative drugs until the effects become apparent (RONNØV-JESSEN and KIERKEGAARD 1973; THOMAS et al. 1970).

Treatment with thyrostatic drugs alone is not successful with elderly people, who frequently – as already stated – have autonomous nodules and areas. The punctual taking of drugs and regular control of old patients may also prove difficult over a long period. No increased incidence of side effects of thyrostatic drugs in old age has come to our notice.

The general condition of the elderly patient permitting, an operative approach can be discussed. Some physicians treat any autonomous nodule with surgery on principle (SCHULTZ 1978; YOUNG 1941), even in senescence. After the age of 50, however, surgical intervention involves a marked risk of mortality (NOFAL et al. 1966). GREENE and HURXTHALL (1941) performed operations on 469 elderly patients with hyperthyroidism and concomitant cardiac failure. Only one patient survived the mean life of healthy subjects.

Surgery in an euthyroid state also reduces mortality in senescence. SEED and LINDSAY (1949) demonstrated that the mortality rate is higher among elderly euthyroid than among young euthyroid patients.

Hypothyroidism may occur as a later complication of any destructive therapy of the thyroid gland, whether by radioiodine or by surgical intervention. In respect of this the risks of radioiodine are age dependent and are greatest between the ages of 30 and 40. After the age of 60 hypothyroidism rarely occurs (GUINET and BORY 1973; NOFAL et al. 1966; SILVER 1962). All in all, the incidence of hypothyroidism is considerably lower after surgery (BERGER et al. 1968), even in old age. Surgical mortality, however, increases as stated above in senescence. Now that lower doses of radioiodine are being given and fractionary therapy (repeated application of small doses of radioiodine) is applied in some instances, the rate of post-therapeutic hypothyroidism has undergone a marked decrease (GOLDEN and FRASER 1969; HAGEN et al. 1967). Although hypothyroidism is undesirable, it is as a rule easily controlled. It usually occurs 3–6 months after treatment. Elderly patients may be unwilling to carry consistent substitution through over a long period (HOLLIS

1968), so that they need regular follow-up examinations. SCHULTZ (1978) therefore suggests starting routine substitution by giving 50 μg thyroxine/day immediately on conclusion of radioiodine treatment.

Cardiac manifestations of hyperthyroidism, such as congestive heart failure and atrial fibrillation, require consistent treatment. Heart failure in particular should be recompensated prior to radioiodine therapy, because ^{131}I therapy may cause a temporary metabolic increase. If cardiac failure and atrial fibrillation cannot be controlled, treatment with thyrostatic drugs should first be considered (SCHULTZ 1978).

The prognosis of hyperthyroidism is somewhat less favorable in elderly subjects than in young patients. Apart from any therapy-related factors, the mortality rate increases sharply after the age of 60, being 0.2% in persons under the age of 30, 2%–7.3% in 60-year-olds, and 20% in 70-year-old subjects (CLUTE and SWINTON 1935; CRILE 1938; SEED and LINDSAY 1949).

F. Endocrine Ophthalmopathy

Endocrine orbitopathy is now thought to be a disease per se of autoimmune character, often associated with Graves' disease without there being any direct connection between the two diseases. The assumption that there is a specific exophthalmos-producing factor (EPF) from the anterior lobe of the pituitary gland is now outdated.

Cardinal symptoms are considerably rarer in senescence. For example, the combined symptoms of exophthalmos, goiter, and tachycardia (also known as Merseburg triad) are hardly ever found in senescence (DÖPKE 1964). Whilst endocrine orbitopathy still occurs in 68% of young patients with Graves' disease, it is found in only 26% of patients over the age of 60 (SEED and LINDSAY 1949). Percentage data on endocrine orbitopathy in old age vary between 9.5% and 33% among different authors (BRUN et al. 1978; DE GÊNNES et al. 1961; HOLLIS 1968; LAZARUS and HARDEN 1969; RONNØV-JESSEN and KIERKEGAARD 1973; SEED and LINDSAY 1949).

No distinction is made between young and old patients in diagnostic procedure and treatment of endocrine ophthalmopathy.

G. Thyroiditis

Inflammatory diseases of the thyroid are classified into acute suppurative and non-suppurative thyroiditis; infectious and parainfectious subacute thyroiditis; chronic thyroiditis of the lymphocytic type (Hashimoto's thyroiditis), the fibrous-strophic type, or the fibrous-invasive type (Riedel's disease); and chronic-specific forms such as lues and tuberculosis. Although more attention has been paid in recent times to clinical forms of inflammatory thyroid disease, only few authors report on this aspect in senescent patients. BANSI (1967) discerned signs of thyroditis lymphomatosa Hashimoto among 5% of his elderly patients with goiter. This disease is a genuine immunological process with antibody formation against thyroglobulin

and microsomal antigens. One variant of this disease is the asymptomatic atrophic thyroiditis, which is of increased significance in senescence (BASTENIE et al. 1977). It is regarded as a preclinical disease of spontaneous hypothyroidism in elderly patients and is therefore also referred to in literature as premyxedema (BASTANIE et al. 1977; BONNYNS and BASTENIE 1967; BRAVERMAN et al. 1971; BUCHANAN et al. 1965; MCGAVACK and SEEGERS 1959; FOWLER 1972).

No distinction is made between young and elderly patients in the diagnostic procedure and treatment.

H. Struma Maligna

The term struma maligna covers all malignant neoplasms of the thyroid. The system developed by the thyroid division of WHO is now generally accepted for histological classification of thyroid tumors (BÖRNER et al. 1978) and has also been adopted with slight modifications by the German thyroid division (REINERS and BÖRNER 1980). The classification system is shown in Table 3. Four types of tumor above all are of clinical significance; with malignancy in ascending sequence they are papillary carcinoma, follicular carcinoma, C-cell carcinoma, and anaplastic carcinoma.

These clinically relevant types display different age and sex distribution patterns (see Fig. 9). While papillary carcinomas are also frequent in young people, follicular and anaplastic carcinomas are predominant among subjects between 50 and 60, or 60 and 70 years of age respectively.

Suspicion of malignancy is clinically confirmed by rapid growth of solitary indolent nodules, especially in recidivant goiters or under therapy with thyroid hormones. With regard to elderly goitrous patients this diagnostic criterion may be problematic, as nodularity and goitrous growth are known to increase in old age (BANSI 1967; MCGAVACK and SEEGERS 1959; HOLLIS 1968). In Germany, however, the incidence of malignant tumors in nodular goiters is claimed to undergo an age-

Table 3. Classification of thyroid carcinomas

I. Epithelial tumors
  A. Benign tumors
    1. Follicular adenoma
    2. Others
  B. Malignant epithelial tumors
    1. Follicular carcinoma
    2. Papillary carcinoma
    3. Squamous carcinoma
    4. Undifferentiated (anaplastic) carcinoma
      a) Spindle cellular type
      b) Gigantocellular type
      c) Microcellular type
    5. Medullary carcinoma

II. Nonepithelial tumors
  A. Benign tumors
  B. Malignant tumors
    1. Fibrosarcomas
    2. Other sarcomas

III. Different tumors
  1. Carcinosarcoma
  2. Malignant hemangioepithelioma
  3. Malignant lymphoma
  4. Teratoma

IV. Secondary (metastatic tumors)

V. Unclassifiable tumors

VI. Tumor-like changes in thyroid tissue

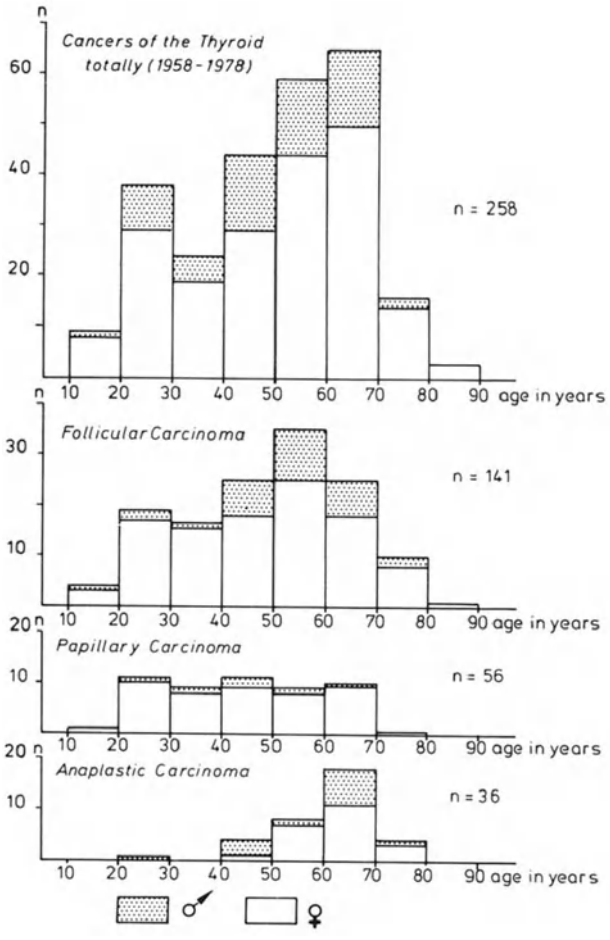

Fig. 9. Distribution of thyroid carcinomas at different ages dependent on histological type of cancer. (REINERS and BÖRNER 1980)

dependent change (BANSI 1967), being 45% prior to the age of 35 and 28% after the age of 35. These data from 1959 are open to comparison with a more recent study quoting a thyroid carcinoma incidence of about 2% in a German endemic goiter area. In the United States, MCGAVACK and SEEGERS (1959) found a malignancy incidence of 9% among their patients over the age of 60 (REINERS and BÖRNER 1980). In one endemic goiter area in the States, 5.7% of elderly subjects with multinodular goiter were found to have thyroid carcinomas; among those with uninodular goiter the incidence was 10% (CAVANAGH 1958). Clinically the diagnosis of thyroid cancer is considerably more difficult in the numerous elderly people with multinodular goiter. With regard to malignancy, infiltrative goitrous growth especially into the soft parts of the neck and increasing pressure on the tracheal band are of major importance. The presence of cervical lymph glands should be checked. Hoarseness, paresis of the recurrent laryngeal nerve, and painfulness of the goiter strengthen the suspicion of malignancy. A conspicuously solid to hard goiter with impaired mobility should also arouse suspicion. Horner's syndrome is often found in cases of anaplastic carcinoma (REINERS and BÖRNER 1980).

The occurrence of metastases in cervical lymph nodes, in the lungs, or in bones facilitates differential diagnosis.

Scintigraphic scanning with ^{131}I confirms the tentative diagnosis of thyroid cancer. Malignant areas of the thyroid are usually represented in the scintiscan as inactive or "cold" areas, i.e., with no iodine uptake. Areas showing no radioiodide uptake in scintiscans of elderly thyroids do not necessarily imply malignancy since large colloid cysts or regressive areas frequently have no hormonal activity either and may appear as cold areas in scintiscans. The elderly thyroid gland therefore displays irregular distribution of activity. In all events, scintillation scanning should be used to detect ^{131}I-marked metastases. Needle biopsy may support diagnosis. It also represents very little strain on elderly patients and is highly accurate with regard to sensitivity and specificity when performed by an experienced cytologist. An absolutely certain diagnosis, however, can be provided only by surgical intervention.

Suspected struma maligna is treated with surgical intervention, preferably total thyroidectomy, regardless of the age of the patient. Surgery should also be given serious consideration for elderly patients if there is a strong suspicion of infiltrative goitrous growth or if metastases are confirmed. The rapid progress of the malignant tumor cannot be stopped by any other treatment and compression of the tracheal band eventually proves fatal (BANSI 1967). Differential diagnosis is facilitated by the fact that other nodular goiters, even with some areas suspected of malignancy, never display malignant growth. Cervical lymph nodes, as mentioned above, are always of significance. Postoperative follow-up treatment is the same in young and old patients.

Apart from the extent of the tumor on being diagnosed and the histological type of tumor, the age of the patient is of prognostic importance. The prognosis for patients below the age of 40 is distinctly more favorable than for older patients (WOOLNER 1971).

I. Laboratory Diagnosis of Thyroid Diseases in Geriatric Patients

Thyroid diseases are nowadays diagnosed by clinical evidence and confirmed by biochemical in vitro methods. Further diagnostic procedure includes in vivo tests.

In order to assess the thyroid function of a patient, a precise case history and clinical evidence are still indispensable, especially with regard to a critical assessment of thyroid function tests. There is no pathognomic syndrome enabling thyroid dysfunction to be diagnosed with certainty. Nevertheless, specific case histories and clinical diagnosis are the first indications of thyroid diseases.

Assessment of anamnestic statements and physical features is not easy for a physician dealing with geriatric patients. Hypothyroidism in particular correlates to a large extent with the physiological aging process. It is conspicuous how frequently hypothyroidism fails to be diagnosed in elderly patients as superficial examination often merely suggests premature aging (GREGERMAN 1976; INGBAR 1978). Additional problems arise from special presentation of thyroid dis-

eases (Bahemuka and Hodgkinson 1975; Charcot 1885; Dewind 1958; Seed and Lindsay 1949). Hypothyroidism and hyperthyroidism in old age have a marked tendency to monosymptomatic or oligosymptomatic presentation (Bürgi et al. 1978; Gurney et al. 1970; Helsloot et al. 1976a; Hollis 1968, Stiel et al. 1972). This means that single symptoms may be predominant and suggest thyroid dysfunction, causing a delay in exact diagnosis. A physician dealing with geriatric patients should therefore be alert to thyroid disease. The clinical diagnosis must be confirmed by biochemical tests.

It should be mentioned briefly that it was the basal metabolism rate, blood cholesterol levels, and deep tendon relaxation time that confirmed the diagnosis of thyroid dysfunction prior to the introduction of thyroid in vitro tests. Age-dependent changes had long been known with these methods (Aub and Du Bois 1917; Binet and Bourlière 1951; Boothby and Sandiford 1929; Davis and Davis 1974; McGavack and Seegers 1959; Goldberg and Larson 1963; Harris and Benedikt 1919; Keys et al. 1973; Reed et al. 1972; Shock 1955; Shock and Yiengst 1952). Today they are of no significance in the diagnosis of thyroid diseases.

Interpretation of in vitro test results in old age is problematic. As already stated in the section on the physiology of the thyroid, different teams report varying results on the correlation of thyroid hormone concentrations with age in euthyroid subjects. Those divergent results must be due to the groups investigated not being comparable or to the subjects not having been strictly selected with regard to their state of health. Thorough examination of elderly euthyroid people shows no changes in total and free serum thyroid hormone concentrations in comparison with young euthyroid subjects (Rudorff et al. 1981). In practice, however, physicians are dealing with a mixed standard population and must take certain changes in thyroid hormone parameters into account.

I. TSH and the TRH-TSH Test

Reports on investigations into the age dependency of basal TSH values are extremely conflicting (Azizi et al. 1975; Bermudez et al. 1975; Lemarchard Beraud and Vaenoth 1969; Ohara et al. 1974; Vosberg et al. 1976; Wagner et al. 1974, 1975; Wenzel et al. 1974; Wenzel and Horn 1975). All in all, a slight decrease in basal TSH concentrations in serum can be expected with advancing age in an elderly standard population. In all events the increase in the TSH concentration after intravenous administration of thyrotrophin releasing hormone (400–500 μg TRH) is significantly lower (Snyder and Utiger 1972; Wagner et al. 1979; Wagner et al. 1975; Wenzel et al. 1974) (Fig. 10). The practical consequence is that the lower borderline value of the maximum TSH increase, showing a positive response of TSH to TRH, must be reduced from 2.5 μg TSH/ml in young patients to 1.5 μg TSH/ml in elderly subjects. Borderline results should be controlled by an oral TRH-TSH test. The TSH concentration is measured 3–5 h after oral administration of 40 mg TRH. In cases of negative intravenous TRH-TSH tests, the oral TRH-TSH test often produces positive results, so that an accurate distinction can be made between euthyroidism and hyperthyroidism (Hoenle 1980).

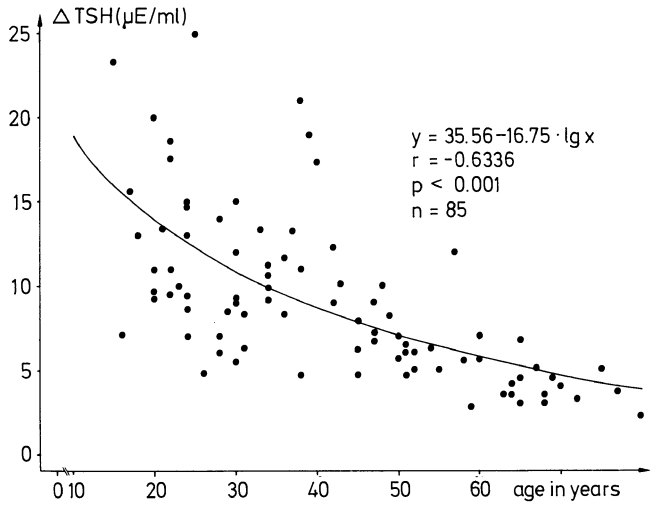

Fig. 10. Decrease in secretion of TSH from the adenohypophysis after intravenous stimulation with 500 μg TRH. The Δ TSH of healthy women aged 15–75 years is shown. Δ TSH, difference between basal TSH value and TSH concentration 30 min after i.v. application of TRH

II. Total Serum Thyroxine Concentration, Free Thyroxine, Binding Proteins, and Parameters for Determination of Free T_4

The total serum thyroxine concentration shows no significant changes from adolescence into senescence (BRAVERMAN et al. 1966; LEMARCHAND BERAUD and VAENOTH 1969; OHARA et al. 1974; SAN MARCO et al. 1972; WAGNER et al. 1979; WENZEL and HORN 1975; WESTGREN et al. 1976) (Fig. 3).

In senescence the serum TBG value increases once again (RUDORFF et al. 1981), though opinions on this are also divergent. Some authors report almost unchanged TBG concentrations from adolescence onwards (BRAVERMAN et al. 1966; HESCH et al. 1976; WAGNER et al. 1979).

The development of the T_4:TBG ratio as a parameter for determination of free T_4 is accordingly assessed in different ways. In old age, both a decrease and unchanged values are reported (HESCH et al. 1976; PICKARDT et al. 1977; RUDORFF et al. 1972). Figure 11 shows the age-dependent curve of the T_4:TBG ratio according to RUDORFF et al. (1981).

The free thyroxine binding capacity of the serum is not age-correlated in euthyroid male subjects, whereas a slight decline is registered with advancing age among euthyroid female subjects (Fig. 12). These findings can be interpreted as confirming that there are connections between estrogenic hormones and free thyroxine binding capacity and that a decrease in these hormones with advancing age correlates with the declining free thyroxine binding capacity (RUDORFF et al. 1981).

The FT_4 index, combining the results of total serum thyroxine determination with those of the T_3 in vitro test (T_3 test, R T_3 U) is thought to increase again in old age (INGBAR 1978; PICKARDT et al. 1977), the renewed increase being due to the

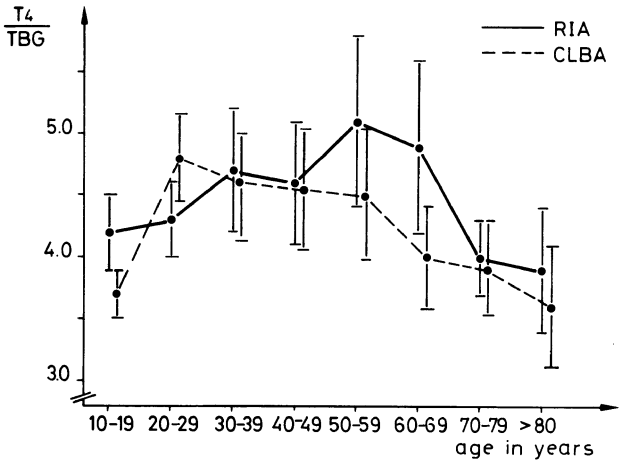

Fig. 11. Dependency of T/TBG ratio on age according to RUDORFF et al. (1981). Demonstrated are the mean values (±SEM) measured by radioimmunoassay (RIA) and competitive ligand binding assay (CLBA)

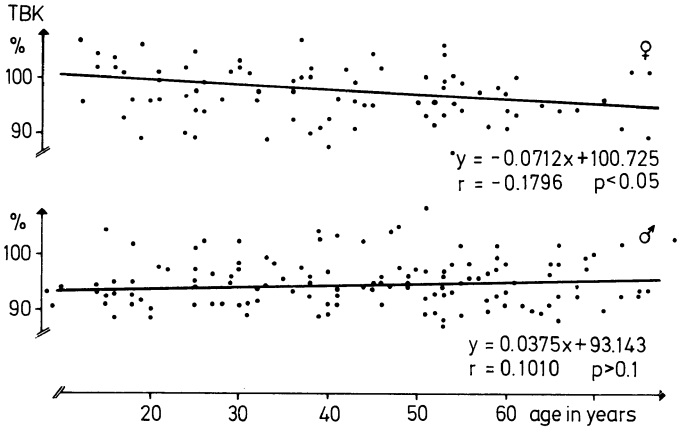

Fig. 12. Free serum thyroxine binding capacity is not age-dependent in healthy men, while there is a slight decrease during aging in healthy women

T_4 concentration increasing in elderly subjects. These findings have, however, yet to be confirmed by other teams, so that the age correlation of the FT_4 index remains uncorroborated in other publications (HANSEN et al. 1975; WAGNER et al. 1979; WAGNER et al. 1975). The effective thyroxine ratio (ETR) or nominal thyroxine ratio (NTR), in which the T_4 test and the T_3 test are combined into one single test, show no age correlation in advanced age (RUDORFF et al. 1981). The divergent observations illustrate that ratios or products formed from parameters based on methods independent of each other must be interpreted with caution.

III. Total Triiodothyronine, Free T_3, and Thyroid Antibodies

An assessment of the T_3 serum concentration in elderly patients is of great practical significance. Recent investigations suggest that T_3 concentrations decline only marginally, if at all, in healthy elderly subjects (OLSEN et al. 1978; EVERED et al. 1978). On the other hand, patients living in homes for the aged, as well as out-

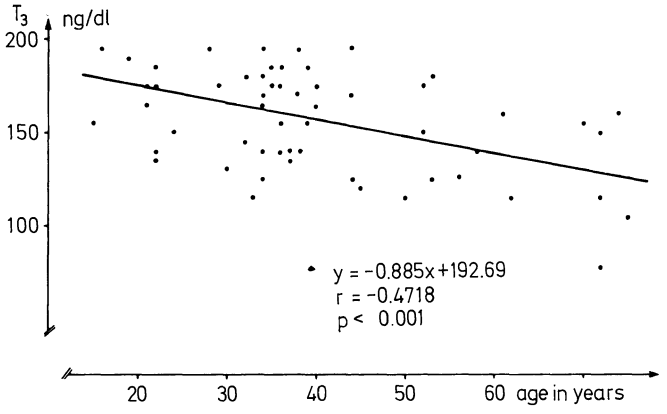

Fig. 13. Decrease in serum triiodthyronine concentration with increasing age

patients and inpatients with minor nonthyroid illnesses, have significantly lower T_3 serum concentrations than young normal subjects. There is thus a sex-independent decline in the triiodothyronine level by approximately 0.08–0.1 mg/ml per decade among the patients from an average population (BERMUDEZ et al. 1975; BURROWS et al. 1975; HERRMANN et al. 1974a, b; RUBENSTEIN et al. 1973; SAN MARCO et al. 1972; WAGNER et al. 1979; WENZEL and HORN 1975; WESTGREN et al. 1976) (Fig. 13). A decreased production rate and an increased degradation rate have both been put forward as possible causes. The fact that the reverse T_3 concentrations in the serum are simultaneously increased suggests that one cause of the lower T_3 serum concentrations might be a dysfunction in the conversion of T_4 into biologically active T_3 (HERRMANN et al. 1974a; INGBAR 1978; RUDORFF et al. 1981; WAGNER et al. 1979). Some two-thirds of the T_3 produced daily is formed in the peripheral tissue by the diodination of T_4, about one-sixth by the intrathyroidal conversion of T_4 to T_3 and another mere one-sixth by thyroglobulin hydrolysis (LARSEN 1972). This explains why extrathyroid illnesses may have a marked influence on the T_3 serum concentration or on the conversion of T_4 into T_3. Advanced age thus appears not to be the only factor responsible for the classical "low T_3 syndrome," in which a strongly reduced serum T_3 concentration is found with a normal T_4 concentration.

It is for these reasons that the patient's general state of health must be taken into consideration for diagnostic assessment of the disease. Nutritional deficiency and various chronic and acute system diseases can lower the serum triiodothyronine concentration. In practice the T_3 serum concentrations can be assumed to be within the lower normal range among outpatients and inpatients, with absolutely healthy elderly subjects being the exception. Completely normal or slightly increased T_3 serum concentrations should not be interpreted in senescence without the result of a TRH test being available, particularly in cases of an extrathyroid disease being present with clinically suspected hyperthyroidism.

No age-specific influences are known to us in the determination of thyroid antibodies (antibodies against thyroglobulin and against microsomal antigens).

IV. In Vivo Diagnostic Techniques

Scintigraphic scanning of the elderly thyroid reveals no special features, but assessment is more difficult – as mentioned in the section on struma maligna – in cases of nodular goiters with regressive areas and cystic degeneration.

The radioiodine test is the only functional test which directly and dynamically provides data on thyroid iodine metabolism. It is used today as a supplement to in vitro diagnostic techniques in preparing radioiodine treatment. Although the absolute iodine uptake is indeed clearly diminished in the aged thyroid (HANSEN et al. 1975), the 24-h iodine uptake is little changed (GAFFNEY et al. 1973; GREGERMAN 1976; PETERSEN 1978; QUIMBY et al. 1950). The radioiodine test thus necessitates no change in evaluation in the diagnosis of diseases among elderly thyroid patients. There is no significant age-related change in the plasma-bound ^{131}I (DAILEY and SKAHAN 1956; MCGAVACK and SEEGERS 1959; ODDIE et al. 1968; PERLMUTTER and RIGGS 1953; PERRY and COSGROVE 1949). The significance of the thyroid hormone suppression test and the TSH stimulation test remains unchanged in old age, for some investigations have shown that the functional response of the thyroid tissue undergoes no change with advancing age (GREGERMAN 1976; HOLLIS 1968).

Needle biopsy is a supplementary measure for diagnosing thyroid diseases in elderly patients. It involves an experienced cytologist and can provide reliable evidence in cases of suspected carcinomas (DROESE 1979; LÖWHAGEN and SPRENGER 1974; MÜLLER 1980).

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Diabetes Mellitus in Advanced Age

H. WAGNER, TH. HOSSDORF, and K. HENGST

A. Definition and Classification

Diabetes mellitus is a chronic hereditary metabolic disease due to absolute or relative insulinopenia. The symptoms are characterized by hyperglycemia and – though not necessarily – by glycosuria. The insulinopenia leads not only to a disturbed carbohydrate metabolism but also to pathological changes in the lipometabolism and the proteometabolism known as a metabolic precursory syndrome.

In the course of the diabetic dysbolism there may be acute metabolic imbalances and vascular complications typical of diabetes (late diabetic syndrome) in various organ systems.

In 1978 the National Diabetes Data Group of the NIH (NDDG 1979) worked out new criteria for classification of diabetes mellitus; these criteria were designed to differentiate the symptoms according to clinical aspects:

I. Primary Diabetes Mellitus

A distinction is made here between insulin-dependent, ketosis-prone diabetes mellitus (IDDM) or juvenile onset diabetes (JOD), also referred to as type I diabetes mellitus, and noninsulin-dependent diabetes mellitus (NIDDM) or maturity onset diabetes (MOD), otherwise known as type II diabetes mellitus, adult onset diabetes, or old-age diabetes. Type II diabetes may start with obesity, but this is not necessarily the case. Adult onset diabetes occasionally occurs in juveniles (MODY = maturity onset type diabetes of the young).

II. Secondary Diabetes Mellitus

Secondary diabetes mellitus includes diabetic dysbolism following traumatic destruction or surgical removal of the pancreas, after recurrent pancreatitis or due to hemochromatosis. This type is also observed with hyperfunction of extrapancreatic endocrine glands, such as with acromegalia, Cushing's syndrome, pheochromocytoma, or with long-term steroid therapy. In addition, a diabetic carbohydrate dysbolism may occur with glycogenosis, insulin receptor abnormalities as found in congenital lipodystrophy, and as a drug-induced hyperglycemia.

III. Subclinical Diabetes Mellitus

Patients with subclinical diabetes mellitus have fasting blood glucose levels within the normal range. After oral or intravenous glucose administration, however, the

Table 1. Diagnostic criteria of impaired glucose tolerance in nonpregnant adults. (National Diabetes Data Group 1979)

	Glucose tolerance		
	Fasting value mg/dl (mmol/liter)	$^1/_2$-h, 1-h, or $1^1/_2$-h oral glucose tolerance test mg/dl (mmol/liter)	2-h oral glucose tolerance test mg/dl (mmol/liter)
Venous plasma	140 (7.8)	200 (11.1)	140–200 (7.8–11.1)
Venous whole blood	120 (6.7)	180 (10.0)	120–200 (6.7–10.0)
Capillary whole blood	120 (6.7)	200 (11.1)	140–200 (7.8–11.1)

blood glucose levels rise to pathological values (Table 1). This symptom is known as impaired glucose tolerance. Relevant international literature also uses the terms: borderline diabetes, asymptomatic diabetes, and chemical, latent, or subclinical diabetes mellitus. Agreement has yet to be reached, however, on the question of whether the symptom of impaired glucose tolerance can be equated with the subclinical precursory stage of diabetes mellitus.

Those forms of diabetes occurring in *advanced age* can be summarized as follows:

1. Type I diabetes

Patients suffering from this type of diabetes can nowadays reach an advanced age under good metabolism control.

2. Adult onset or maturity onset diabetes, type II diabetes mellitus

This becomes manifest only in advancing age. Among these patients we find a group whose metabolism cannot be stabilized by dietary means or with oral antidiabetic drugs despite a correct preliminary diagnosis. Ten percent of all type II diabetics belong to these so-called primary therapeutic failures (CLARKE and DUNCAN 1967). After a more extensive duration of the disease, another 4%–10% of those patients treated with sulfonyl ureas have to be insulinated after all (BERNHARD 1965; CAMERINI-DAVALOS et al. 1962; MEHNERT 1967; PFEIFFER et al. 1957). This group is termed secondary failures.

3. Subclinical diabetes mellitus

Subclinical diabetes mellitus, with the initial symptom of pathological glucose tolerance, is found mainly with adiposity, in advanced age, or as a result of medication.

B. Epidemiology of Maturity Onset Diabetes

Diabetes mellitus is one of the most frequent metabolic diseases. An increase in the number of diabetics is being recorded in all social classes in countries with an in-

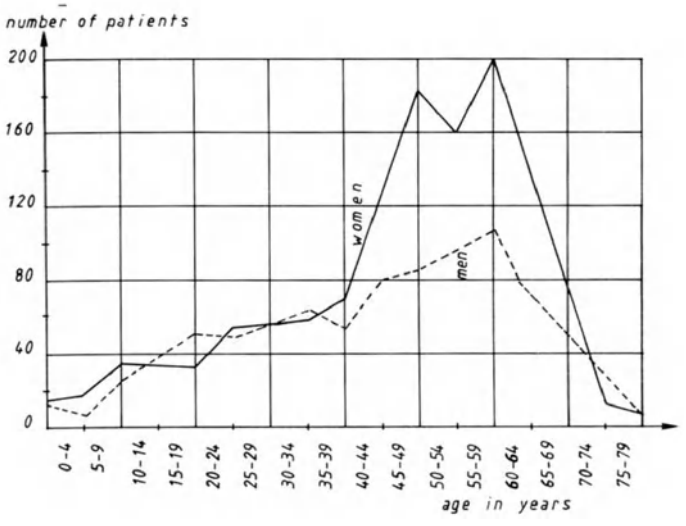

Fig. 1. Onset of diabetes mellitus in 2,132 diabetics. (HARRIS 1950)

creasing degree of civilization and a rising standard of living. It is in both young and elderly age groups that the disease is on the increase. The increasing incidence of diabetic diseases can thus not be due to the changing age structure of a population alone. Investigations carried out by MEHNERT et al. (1968) suggest that between 2% and 3% of the population of the Federal Republic of Germany suffer from manifest diabetes mellitus. Another 8%–10% of the population have impaired glucose tolerance, a metabolic abnormality that may be connected with the preliminary stage of diabetes mellitus.

Eighty percent of male and 85% of female diabetics are over the age of 45, according to BAUER (1967), MCDONALD (1970), SCHLIACK (1971), and a report published in 1967 by the National Center for Health Statistics (1967). Among those subjects over the age of 45, the disease is found considerably more often among women than among men. This situation is illustrated in Fig. 1, based on an investigation of over 2,000 diabetics published by HARRIS (1950): the diabetes morbidity rate rises after the age of 40 in both sexes, the female: male incidence ratio being 3:2 (MARKS et al. 1971). The incidence of the disease is observed by the above-stated teams to be highest between the ages of 60 and 70 (HARRIS 1950; MARSHALL 1930). BAUER (1967) quotes an incidence of some 5%–6% in this age group.

The already-mentioned Munich Early Diagnosis Survey by MEHNERT et al. (1968), showed that manifest diabetes is to be expected in every tenth person above the age of 65 years.

C. Etiology and Pathogenesis

The symptoms of maturity onset diabetes (type II diabetes) are marked by hereditary and environmental factors. The disease becomes manifest through various diabetogenic factors (manifestation factors) coinciding with a genetic disposition.

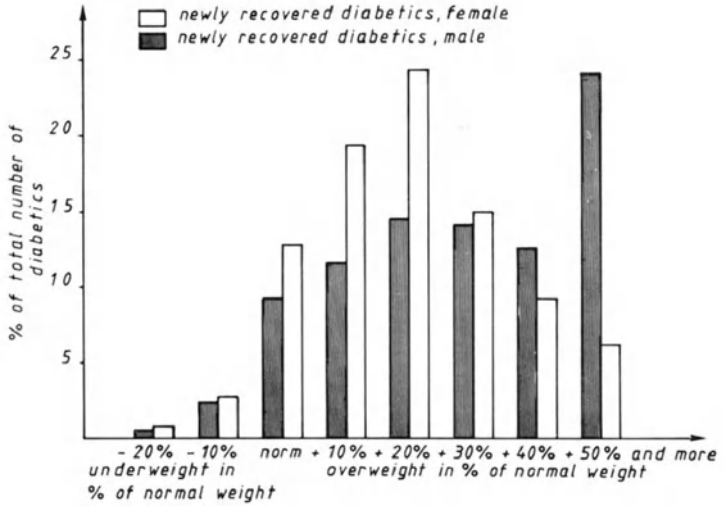

Fig. 2. Excess weight as a percentage of normal weight (according to BROCA) in newly detected diabetics of both sexes. (Munich Early Diagnosis Survey by MEHNERT et al. 1968)

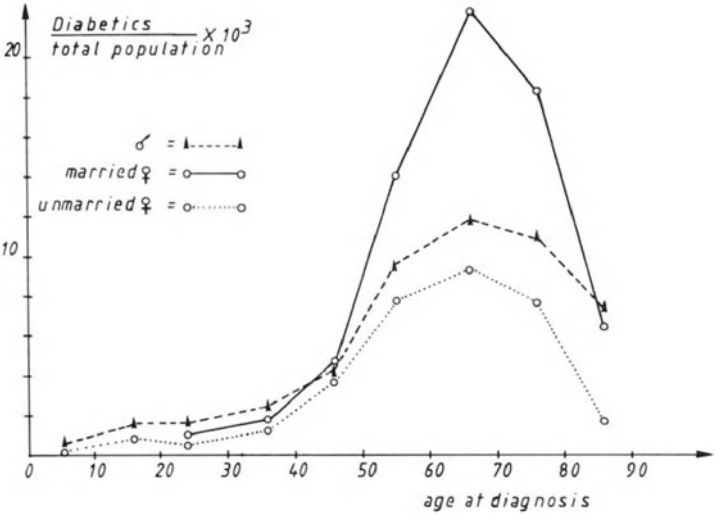

Fig. 3. Relative incidence of newly diagnosed cases of diabetes in men and in married and unmarried women in relation to total population. (FITZGERALD et al. 1961)

The pathogenesis is obviously marked by genetic and exogenous factors interacting multifactorally, without any specific hereditary process or any specific triggering factor being responsible for the outbreak of the disease.

In noninsulin-dependent type II diabetics, an unequivocal genetic disposition to the disease can be established. Twenty-three percent of parents, 39% of siblings, and 21% of children of type II diabetics also develop manifest diabetes mellitus (JARRETT and KEEN 1975; KÖBBERLING et al. 1969; POMBO 1977). The most significant factor furthering manifestation is obesity, as is illustrated by the Munich Ear-

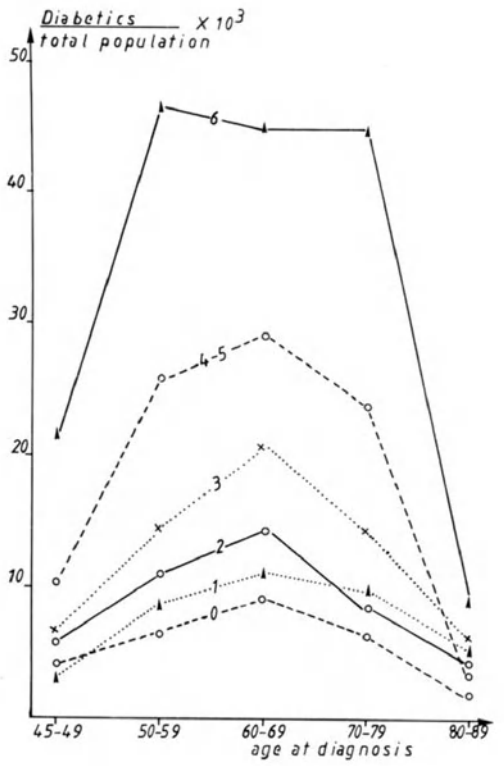

Fig. 4. Relative incidence of diabetes mellitus in women of different age groups and with different numbers of pregnancies. (FITZGERALD et al. 1961)

ly Diagnosis Survey by MEHNERT et al. (1968) (Fig. 2). At the time of diagnosis, 40%–50% of noninsulin-dependent patients are obese, whereas adiposity is registered in 80% of advanced-age diabetics, as the body weight continues to increase in the course of the disease.

Married women contract type II diabetes mellitus in advanced age considerably more frequently than men and unmarried women (Fig. 3). FITZGERALD et al. (1961) showed that one cause of this may be the number of earlier pregnancies. Figure 4 illustrates clearly that the risk of diabetes in women after six pregnancies is 6 times greater between the ages of 50 and 59 than among women of the same age who have had no pregnancies.

An annual increase in metabolic decompensation with hyperglycemia, glycosuria, and loss of weight is observed in a small percentage of patients who were not insulin-dependent at the onset of diabetes. MEHNERT and REISNER (1969) quotes the incidence among the patients observed by them at 4% in 10 years, BERNHARD (1965) at 10.6% in 6 years, and CAMERINI-DAVALOS et al. (1962) at 8% per year. The reason seems to lie in the natural progress of the disease.

The origin of insulin-dependent diabetes in juveniles (type I diabetes) is generally assumed to be a genetically impaired immunological system that can lead to an outbreak of the disease in conjunction with, for instance, an infection by Coxsackie, ECHO, or mumps viruses. This immunological false regulation is probably due to an antipancreatic immunoresponse passed on by lymphocytes or to the for-

Table 2. Pathogenesis of type I diabetes mellitus

Genetic predisposition (Human leukocytic blood-group system)		Virus infection
Primary	HLA-B8 HLA-B15	
Secondary	HLA-DW3 HLA-CW3 et al.?	Autoimmune disease = insulinitis Destruction of β-islet cells Special (weakened) instantaneous immunological defensive condition

mation of an immunoglobulin G antibody. This autoimmune reaction directed against pancreatic tissue may possibly be induced by the HLA B8 or the HLA B15 alleles that occur frequently in insulin-dependent diabetes (NERUP et al. 1974; SOLOW et al. 1979) (Table 2).

D. Pathophysiology

In juvenile insulin-dependent diabetics (type I) the number of β-cells at the onset of the disease is only about 10% or less of the normal level (GEPTS 1965). The β-cells disappear completely in the course of the disease. The histopathological diagnosis is an infection of the islets of Langerhans, so-called insulinitis, characterized by lymphocytic infiltrations and in subsequent phases by fibrosis and islet cell atrophy. On the basis of this morphological substrate it was assumed that type I diabetes becomes manifest when a virus infection in conjunction with reduced immunological resistance leads to an autoimmune disease and to the destruction of β-cells, resulting in the absolute insulinopenia of the type I diabetic.

In maturity onset diabetes (type II diabetes) occurring between the ages of 30 and 70, the average decline in the number of β-cells is only between 50% and 60% of the normal value (GEPTS 1965). This decline alone is not as a rule sufficient to cause diabetes. There are only few indications, if any at all, of hyperactivity of the cells, and there is no degranulation at all (LAZARUS and VOLK 1962). Investigations by PFEIFFER (1963), YALOW and BERSON (1960), and CERASI and LUFT (1967a) in particular have shown that it is a matter of dynamic insulin secretion dysfunction, otherwise termed "insulin rigidity." The theory put forward by LAZARUS and VOLK (1962) that the hyalinosis and fibrosis of the islet cells found in the maturity onset diabetic disturb the insulin secretion is no longer accepted. Fibrosis and hyalinosis are rather to be regarded as a consequence of the diabetic dysbolism and not as the cause of it. Histopathological findings do not permit the deficient insulin secretion to be interpreted conclusively.

In a normal-weight diabetic with a mildly disturbed metabolism, insulin secretion is reduced and above all delayed in comparison with a healthy contemporary (KIPNIS 1968). Even under nondiabetic conditions, glucose tolerance declines dis-

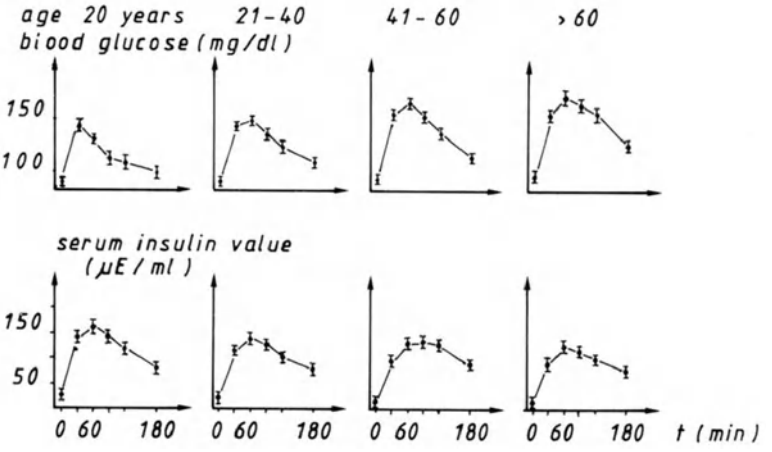

Fig. 5. Decline in oral glucose tolerance with increasing age. The *top line* shows the elevated blood glucose concentration after an oral glucose challenge, and the *bottom line* the corresponding decline in insulin secretion. (HAUPT 1979)

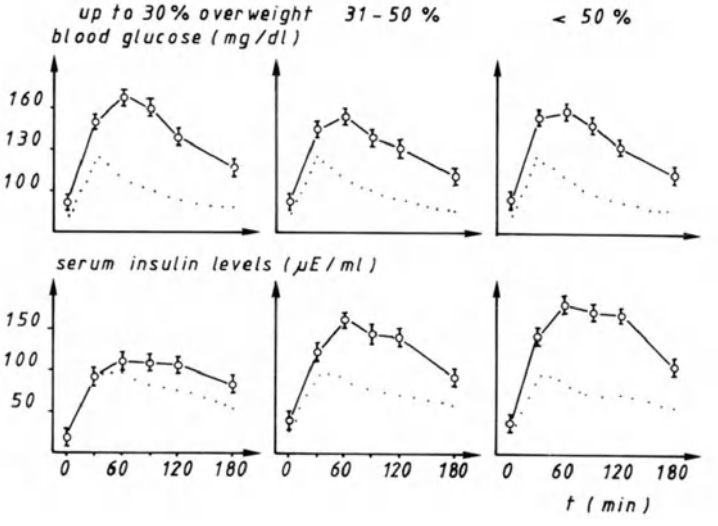

Fig. 6. Rising insulin secretion depending on degree of obesity (according to BROCA). Standard values are plotted as *points* below the curves. (HAUPT 1979)

tinctly with increasing age. As Fig. 5 (HAUPT 1979) shows, the blood glucose levels rise and insulin secretion undergoes a marked decline in the higher age groups.

The site of the defect in the insulin secretion mechanism and its relation to a pathological genetic change is not yet clarified. Maturity onset diabetes (type II) can accordingly be due either to a reduced islet cell capacity and/or to a decrease in the insulin sensitivity of the target organs (insulin resistance).

A peripheral, age-related insulin resistance is present in the normal-weight, noninsulin-dependent maturity onset diabetic. DEFRONZO (to be published),

HARANO et al. (1977), GINSBERG et al. (1974), REAVEN and OLEFSKY (1977), and ORSKOV and CHRISTENSEN (1969) found a strong insulin resistance with gravely impaired glucose tolerance.

In contrast to nonadipose maturity onset diabetes, insulin production and secretion are increased in the noninsulin-dependent so-called "old-age diabetes" with concomitant adiposity. Even the nondiabetic adipose subject displays distinct hyperinsulinism, as illustrated in Fig. 6 (HAUPT 1979).

Relevant literature provides numerous theories on the causes of hyperinsulinism. It can be regarded as proven that the increased insulin secretion is a consequence of hyperalimentation and not a cause of it. Insulin in incubation media of hepatic cells, lipocytes, myocytes, and monocytes reduces the number of insulin receptors so that insulin resistance is triggered off (BJORNTORP et al. 1971; BLACKARD and GUZELIAN 1978; LIVINGSTON et al. 1978). A reduction in weight is known from clinical investigations (BERGER et al. 1976; GARCIA et al. 1974; IRSIGLER and WALDHÄUSL 1969; JEANRENAUD 1979) to lead to improved glucose tolerance. Obviously the number of receptors increases again after a decline in the elevated insulin level induced by the reduction in body weight.

The intercorrelations between peripheral insulin resistance under hyperalimentation and adiposity, which eventually result in a diabetic metabolic condition, may be explained as follows:
Hyperalimentation causes the glucose level to rise, with a consequent increase in the mass of adipose tissue. The increased level of glucose stimulates increased insulin secretion. The hyperinsulinism for its part induces a reduction in the number of receptors and the associated reduction in insulin sensitivity of the target organs. This reduced reactivity, on the other hand, causes a rise in the glucose level and increased insulin secretion, which lead to consecutive exhaustion of the β-cells if the genetic disposition is present.

E. Diagnosis

Diagnosis of manifest juvenile (type I) diabetes mellitus is unproblematic. Symptoms such as polydipsia, polyuria, glycosuria, and hyperglycemia as well as rapid loss of weight accompanied by lassitude and decreased vitality are unequivocal indications of manifest diabetes.

Maturity onset diabetes (type II), in contrast, is often diagnosed only by chance. The insidious progress of the disease, the little-marked clinical symptoms and the fact that the complaints involved can frequently not be definitely classified may give rise to diagnostic problems in cases of hitherto undiagnosed adult onset or maturity onset diabetes. Investigations by the Joslin Clinic (JOSLIN et al. 1936) and by MEHNERT (1979) suggest that increasing lassitude, depressive psychosis, polydipsia, increased appetite, increased urine output, pruritis ani et vulvae, or balanitis are conspicuous symptoms. Polyneuropathies are a significant precursory symptom. Recurrent infections of the bronchial system or of the urinary tract accompanied by a high temperature may also indicate manifest maturity onset diabetes, particularly if they have led to a so-called initial coma without diabetes having hitherto been diagnosed.

Acute cerebrovascular or cardiac events such as ischemic cerebral insultus or myocardial infarction may lead to acute decompensation of a hitherto undiagnosed diabetes. Between 3.8% (JAHNKE 1977) and 6% (PENSE and PANZRAM 1962) of these complications induce a diabetic coma.

Glucose utilization is known to decrease with increasing age (ANDRES 1971; BRANDT 1960; BURCH and O'MEALLIE 1967; CROCKFORD et al. 1966; GOTTFRIED et al. 1961; GRIES et al. 1980; MARIGO et al. 1962; METZ et al. 1966; O'SULLIVAN et al. 1961; SILVERSTONE et al. 1967; SWERDLOFF et al. 1967; ZEYTINOGLU et al. 1969), so that also healthy elderly subjects have higher fasting blood glucose levels than younger subjects. Extensive investigations (ALBANESE et al. 1968; BUTTERFIELD 1964; CALLOWAY and KUJAK 1971; DAVIDSON 1979; GRAF et al. 1978; MAHLER to be published, MARIGO et al. 1962; MARSHALL 1930; OLEFSKY and REAVEN 1974; Report of the CGP 1963; SCHNEEBERG and FINESTONE 1952; University Group Diabetes Program 1970) however, indicate that age-related changes in the fasting blood glucose levels are considerably less marked than those measured after an oral glucose challenge. If the result is assessed by the widely used Fajans-Conn criteria (FAJANS and CONN 1959), which conform esssentially with those of the US Public Health Service (REMEIN and WILKERSON 1961), the British Diabetes Association (FITZGERALD and KEEN 1964), and the World Health Organisation, 50% of elderly adipose subjects display pathological glucose tolerance (BRANDT 1960; BURCH and O'MEALLIE 1967, CHESROW and BLEYER 1954; DEREN 1936–1937; FUTCHER and MARCUS 1956; GOTTFRIED et al. 1961; HAYNER et al. 1965; HOFSTATTER et al. 1945; HORVATH et al. 1947; JOHN 1934; KINGSBURY 1968; KÖBBERLING 1980; MAHLER to be published; METZ et al. 1966; SILVERSTONE et al. 1957; SIMON and GARVEY 1951; SIPERSTEIN 1975; SIPERSTEIN et al. 1978; SINHA et al. 1974; SMITH and HALL 1973; STREETEN et al. 1965; WAGLE and ASHMORE 1964; WEST et al. 1980; YALOW et al. 1965). The Bedford, Tecumseh, and Kristianstad studies and numerous other investigations, e.g., by WELBORN et al. (1969), by O'SULLIVAN et al. (1971), and by the University Group Diabetes Program (1970), show that blood glucose levels are between 4 and 14 mg/dl higher per decade of life, i.e., 9.5 mg/dl on average, 1 h after an oral glucose challenge. The 2-h blood glucose concentrations are between 1 and 11 mg/dl higher per decade (ANDRES 1971; DUCKWORTH and KITABCHI 1972).

Glucose metabolization following intravenous glucose administration also decreases with increasing age, as reported by ANDRES (1971); SMITH and SHOCK (1949), SCHNEEBERG and FINESTONE (1952), CROCKFORD et al. (1966), WAGNER et al. (1977), and CERASI and LUFT (1967 a, b). The ageing process in conjunction with stress factors such as recurrent infections with an increased production of contrainsulin hormones should be given consideration as a cause of this change, as described by MEHNERT (1974). One essential factor is adiposity, which predisposes to diabetes mellitus in advancing age. Insufficient physical exercise or a low-carbohydrate diet also lead to reduced glucose tolerance. Some of the studies listed above, on the other hand, indicate that reduced glucose utilization remained in elderly subjects despite both factors being corrected during the investigation period.

It should not be deduced from the test results described that age-related evaluation of oral or intravenous glucose tolerance tests should be introduced into diagnostic techniques for diabetes. According to MEHNERT (1974), diagnosis and therapy would then be omitted in an increasing number of diabetics.

When assessing the fasting blood glucose levels and those following an oral glucose challenge, medication must be taken into account in the multimorbidity rate among elderly subjects. A substantial number of diuretics and antihypertensive agents, such as chlorthalidone, clonidine, diazoxide, furosemide, and above all thiazides, induce increased blood glucose levels and pathological glucose tolerance. Psychoactive agents such as haloperidol, lithium carbonate, and phenothiazines, as well as glucocorticoids, may cause manifest diabetes mellitus (ALAVI et al. 1971; NDDG 1979). On the other hand, aminosalicylates, levodopa, methyldopa, nalidixic acid, propylthiouracil, and tetracycline reportedly produce misleadingly high values in some laboratory blood glucose tests (NDDG 1979). A false diagnosis should be prevented by discontinuing these drugs and chemical agents in accordance with the half-life period.

The latest WHO directives, based essentially on suggestions by Anglo-American teams (NDDG 1979), state that manifest maturity onset (type II) diabetes mellitus must be suspected under the following conditions:

1. When classic symptoms of diabetes are present with unequivocal elevation of fasting blood glucose levels. Fasting blood glucose concentrations of 140 mg/dl and more (around 8 mmol/liter) and random venous blood glucose concentrations of 200 mg/dl (approximately 11 mmol/liter) and more are regarded as diagnostic verification.
2. In the absence of unequivocal diabetes symptoms, a 75 g oral glucose challenge at various intervals under standard conditions is recommended. In this case, a 2-h value of 200 mg/dl (11.1 mmol/liter) and more in venous plasma or capillary whole blood, or of 180 mg/dl (10 mmol/liter) and more in venous whole blood permits manifest diabetes to be diagnosed.

From the aspect of differential diagnosis, medication with various agents affecting the blood glucose concentration must be taken into account in elderly subjects with hyperglycemia. A temporary low-calorie diet in response to gastrointestinal complaints or to general lassitude with anorexia leads to transitory hyperglycemia or impairment of oral glucose tolerance just as immobilization does (GANDA et al. 1978; VINNIK et al. 1962).

Apart from in various forms of diabetes mellitus that are, however, diagnosed mainly in younger age groups, nondiabetic glycosuria occurs in elderly subjects through ascending pyelitis. This is frequently diagnosed when an adenoma of the prostate gland leads to ischuria.

Conversely, aglycosuria with hyperglycemia may occur in the elderly patient, owing to the renal threshold for glucose rising in advancing age (MEHNERT 1974). Screening techniques for early diagnosis of diabetes may provide false diagnoses on this account. Elderly diabetics with a restricted renal function due to a Kimmelstiel-Wilson nephropathy furthermore display a marked reduction in glycosuria.

F. Diabetes Therapy in Advanced Age

In diabetes stabilization at advanced age, special consideration must be given to the overall situation of the patient, his constitution, and concomitant diseases. In general, diabetes therapy is aimed at attaining normal glycemia and agly-

cosuria values. The older the diabetic, the more broadly stabilization criteria are set by the doctor in charge, in order not to expose the patient to hazardous side effects of therapy and not to impair his lifestyle.

Nor is rigid control of the metabolism in advanced age to be recommended in view of the delayed complications to be feared in the juvenile, type I diabetic. Good diabetes stabilization with exclusively dietary methods is regarded as a fasting whole-blood glucose concentration of 110 mg/dl, with 1-h postprandial values of 120 mg/dl. The postprandial values may increase to 140 mg/dl under medication with oral antidiabetic agents. The fasting blood glucose levels in insulinated patients are around 120 mg/dl, with 2-h postprandial values of approximately 130 mg/dl with good insulin stabilization; under moderate therapy the values are approximately 130 mg/dl (basal) and 150 mg/dl (2-h postprandial). Fasting blood glucose concentrations of 140 mg/dl are considered a sign of adequate stabilization. In the complication-free elderly diabetic patient, 140–160 mg/dl before meals is regarded by PETZOLDT (1981) as a relatively good metabolic compensation.

In the younger diabetes patient, whether insulinated or under treatment with oral antidiabetic agents, a metabolic process as rigidly controlled as possible is aimed at, to avoid or delay later complications. In the old-age diabetic, in whom the carbohydrate metabolism imbalance has not become manifest until after the age of 60, less rigid therapy can be applied. On the other hand, some form of treatment is essential in cases of manifest diabetes in old age on account of the risk of a coma.

I. Dietary Measures

The basis of diabetes therapy also in the elderly subject is diet. The energy content of the food is generally distributed in a carbohydrate : protein : fat ratio of 40% : 20% : 40%; this also applies to the elderly diabetic patient.

A low-calorie diet with a reduced carbohydrate and a proportionately increased fat and protein percentage, as recommended by RABAST et al. (1976), is necessary for most diabetics because of their obesity. This also applies to numerous type I diabetics who are already obese or can be expected to become so with increasing age (PETZOLDT 1981). Diets with a low saturated fatty acid content induce a decline in low-density lipoprotein (LDL) cholesterol, a rise in high-density lipoprotein (HDL) cholesterol, and a fall in triglycerides (SAUER and GRÜN 1980). Such diets may have a prophylactic effect on artery occlusion, which represents the main cause of death in the type I diabetic over the age of 35–40 years. Although saturated fats cannot be shown to have a negative influence on the development of arteriosclerosis despite detailed investigations, most authors recommend reducing them in favor of highly unsaturated fatty acids (BERGER et al. 1980; JARRETT and KEEN 1975b, 1976).

In the maturity onset or type II diabetic too, calorie restriction for obese patients is one of the crucial therapeutic measures. Increased insulin resistance with a reduced number of receptors can be improved considerably by a decrease in weight. High-bulk foods improve glucose tolerance and lead to a fall in triglycerides and serum cholesterol and to a rise in HDL cholesterol, according to recent reports by JENKINS et al. (1980) and ANDERSON and WARD (1978).

This high-bulk food reduces the oral antidiabetic and insulin requirement. It must be provided in an easily digestible form such as vegetables or stewed fruit for the elderly patient, as coarse food is frequently avoided in old age owing to the problems of chewing.

In the elderly adipose diabetic, weight reduction should be given priority over any other treatment. A low-calorie diet should be tried out in all events, but not insisted on with very elderly patients as the general state of health can be considerably impaired by subjective displeasure. Value must be attached to an adequate intake of protein, vitamins, and calcium, since elderly subjects tend to restrict their intake of these dietary components in particular, owing to their reduced calorie requirements. All in all, the diet of the elderly diabetic patient should have a low calorific value and should avoid easily absorbed fats and carbohydrates.

II. Muscular Exercise in the Elderly Diabetic Patient

In physical activity, a distinction must be made between acute effects of myokinesis and long-term effects of physical exercise. The latter effects are of greater significance in the positive effect on the diabetic metabolism. The positive effects of physical exercise on cardiovascular (CLAUSEN 1977; MORSE 1974) and on pulmonary (VINNIK et al. 1962) functions are well known. It is also generally accepted today that a decline in the triglyceride concentration and an increase in the HDL cholesterol level can be induced by regular exercise (AHLBORG et al. 1974; BERGER and BERCHTOLD 1980; HALMOS et al. 1970; ISSEKUTZ et al. 1963, 1965). In experiments on animals and clinical investigations it has been shown, however, that insulin sensitivity may be increased by physical exercise (BJÖRNTORP et al. 1971, 1977; MONTOYE et al. 1977; VRANIC and BERGER 1979; ZINMAN et al. 1979). According to PRUETT and MAEHLUM (1973), the hypoglycemic effect of muscular exercise can be detected as much as 14 h after the last injection of a medium-term insulin. These findings are compatible with the clinical experience that muscular exercise lowers the daily blood glucose level, reduces the urinary glucose concentration, and lowers the daily insulin requirement (REAVEN and MILLER 1979; SALTIN et al. 1979; STRUWE 1977; WAGLE and ASHMORE 1964; ZIERDEN et al. 1977).

Whether this effect is due to an increased affinity of insulin to its receptor, to an increased number of insulin receptors, or to primarily metabolic factors remains to be clarified. In view of the cardiovascular risk to which type II diabetics are subject, the prophylactic measures included in cardiovascular prophylaxis and rehabilitation programmes must be taken into account in physical training programmes. Only a carefully selected group of type II diabetics can be considered for a physical training programme as it is among just these patients that cardiovascular diseases are most prevalent (BERGER et al. 1980; SOLER et al. 1974).

Regular sporting activity is quite feasible for the elderly diabetic too. Regular long walks, simple gymnastics, and swimming are suitable forms of physical exercise for the fully mobile elderly diabetic patient. In MEHNERT's experience (1974), bowling and cycling are also to be recommended, particularly if the patient had occasionally pursued these activities prior to his illness. Intensive physiotherapy can be of value for almost every patient who is confined to bed or is temporarily immobilized on account of concomitant diseases or after an operation. A reversible

deterioration in glucose tolerance is known to be inducible by immobilization, as was proved by VRANIC and BERGER (1979) in experiments on animals. Our own experience shows that diabetics with concomitant diseases such as neuropathies or peripheral circulatory disturbances are not easily persuaded to do regular exercises, owing to the pain involved. They do the exercises conscientiously, however, as soon as they are aware of an alleviation of their complaints.

Physical activity and sport are known to lead to low-grade hypoglycemia even in healthy subjects. In the diabetic patient, a disproportionately greater decline in blood glucose can be observed, with severe hypoglycemia occasionally occurring (PRUETT and MAEHLUM 1973). Diabetic patients undergoing only dietary or biguanide therapy are less susceptible to hypoglycemia. Mobilization of endogenous insulin by sulfonyl ureas or by exogenous insulin administration may lead, in conjunction with muscular activity, to hypoglycemia. Extreme physical strain is therefore not advisable for the elderly long-term diabetic and the maturity onset diabetic.

III. Oral Antidiabetic Agents

1. Sulfonyl Ureas

Apart from diet as the most important basis of diabetes therapy and regular physical activity, medication has been available as a form of therapy for some 25 years, using essentially two types of substances: sulfonyl ureas and biguanides.

Those sulfonamides used in diabetes therapy have a β-cytotropic effect by increasing insulin secretion (CREUTZFELDT and BÖTTCHER 1956; CREUTZFELDT and SCHLAGINWEIT 1957; KRACHT and RAUSCH-STROOMANN 1956; MALINS 1968; WAGLE and ASHMORE 1964). Direct evidence of an aggressive effect by the sulfonyl ureas immediately at the β-cells of the pancreas has been provided through hyperplasia being detected by LOUBATIÈRES (1946), hyperemia by KRACHT and RAUSCH-STROOMANN (1956), and degranulation by GEPTS (1958).

The mode of action can be divided into three components:

1. Stimulation of secretion of stored insulin drug and i.v. glucose administration;
2. Augmentation of glucose-induced insulin secretion;
3. Lowering of the threshhold of sensation for glucose-induced insulin secretion (SCHÖFFLING 1980).

An extrapancreatic mode of action of sulfonyl ureas may be an augmentation of insulin receptors in muscle, liver, and fat tissue, especially in Type II diabetes (BACHMANN et al. 1979; OLEFSKY 1981; SKILLMANN and FELDMANN 1981).

These findings show clearly that blood glucose levels can be depressed by sulfonamide derivatives only in type II or maturity onset diabetics whose insulinogenesis is maintained.

Individual drugs in this substance group display a varying period of activity or metabolization characteristics that should be taken into account in the elderly subject. Restricted renal function, for instance, may result in the active substance accumulating, so that hypoglycemic reactions have been observed (GOTTESBÜREN et al. 1970; HASSLACHER and WAHL 1971; SCHÖFFLING 1978). This applies in particular to long-acting preparations such as glibenclamide. When renal function is restricted, sulfonamides with essentially enterobiliary elimination, such as gliqui-

done, can be used, as recommended by SCHÖFFLING (1978). Shorter-acting sulfonyl ureas such as tolbutamide or glymidine can be given to maturity onset diabetics with a risk of hypoglycemia. In cases of nocturnal glycosuria, CLARKE and DUNCAN (1967) recommend medication with sulfonamide derivatives with a long plasma half-life period and thus an extended active period, such as glibenclamide, gliburonide, or glisoxepide.

For sulfonyl urea derivative therapy of the maturity onset diabetic, special care must be taken in selecting the preparation, owing to the nontoxic and toxic side effects.

The nontoxic side effects include leukopenia and thrombopenia as well as skin allergies; these are reversible after discontinuing or changing the preparation. Gastrointestinal complaints such as anorexia and nausea, or less frequently vomiting and diarrhea or a sensation of weakness and dizziness with no evidence of hypoglycemia are a strain on the patient in many cases. CLARKE and DUNCAN (1967) and SCHÖFFLING et al. (1974) report that these gastrointestinal side effects occur in some 1%–3% of treated patients within some weeks of therapy being started and disappear spontaneously or on reduction of the dosage. If the tablets are taken after a meal or with an antacid agent, these concomitant symptoms recede into the background (CLARKE and DUNCAN 1967).

Toxic effects of sulfonyl ureas are observed only when concomitant diseases are present or other drugs have also been prescribed. A special risk to the elderly diabetic patient from sulfonyl ureas can be observed with concomitant cardiac or renal insufficiency or with a restricted hepatic function (CAMARINI-DAVALOS et al. 1962; CLARKE and DUNCAN 1967). Chlorpropamide, for instance, has a marked antidiuretic effect that may induce symptoms of hydrointoxication with hyponatremia, dizziness, and anorexia (GARCIA et al. 1974).

Cases of hypoglycemia may also occur in the absence of restricted renal function or of overdosage in sulfonyl urea therapy and may in part be of long duration and prove fatal (CLARKE and DUNCAN 1967). Less severe cases occur in 5% of patients treated, according to CLARKE and DUNCAN (1967).

There is an increased incidence of hypoglycemia in maturity onset diabetic patients when meal times cannot be adhered to, owing to concomitant gastrointestinal complaints. A number of drugs frequently prescribed to the maturity onset diabetic for other illnesses display a distinct interaction with the effect of sulfonyl urea derivatives. Phenothiazide, barbiturates, and chlorpromazine weaken the effect; salicylates, phenylbutazone, and dicumarols may intensify the effect substantially, with consequent hypoglycemia (KORP and LENHARDT 1970; KRISTENSEN and CHRISTENSEN 1969). Table 3 lists drugs with an unequivocal influence on the efficiency of sulfonyl urea.

Despite longer-term metabolic consistency in their patients, therapy failure or decreasing sulfonamide efficiency – leading to consecutive deterioration of the metabolism – was observed by MEHNERT and REISNER (1964) in 4% of 500 patients in 10 years, by BERNHARD (1965) in 10.6% of 7,538 patients in 6 years, and by CAMERINI-DAVALOS et al. (1962) in 8% of 2,500 patients in 1 year. Glycosuria with values exceeding 30 g/day was established, despite an unchanged renal threshold. This metabolic situation is termed delayed or secondary failure. The patients concerned here are not those in whom oral diabetic therapy eventually failed on ac-

Table 3. Substances influencing the hypoglycemic effect of sulfonyl urea derivatives

Intensifying effect	Weakening effect
Sulfonamides	
Chloramphenicol	
Salicylates	Nicotinic acid preparations
Phenylbutazone	Corticosteroids
	Estrogen
	Thyroid hormones
Dicumarole	
Beta-receptor blockers	
Alcohol	

Table 4. Sulfonamide derivatives in use today

Generic name	Dosage
Carbutamide	0.5 –1.5 g
Tolbutamide	0.5 –2.0 g
Glycodiazine	0.5 –2.0 g
Chlorpropamide	0.125 –0.5 g
Glibenclamide	0.0025 –0.015 g
Gliburonide	0.00125–0.075 g
Glisoxepide	0.002 –0.0012 g
Gliquidone	0.015 –0.120 g

count of their constantly ignoring the prescribed diet. The reason for this decrease in insulin secretion with increasing sulfonyl urea therapy duration is not unequivocally explained. It may be due to an age-related progressive reduction in the number of β-cells that is connected with the disease itself and not with the therapy (CLARKE and DUNCAN 1967). A survey of sulfonamide derivatives in use today is given in Table 4.

2. Biguanides

The only biguanide derivative still in use is metformin, owing to an increased incidence of lactacidosis following treatment with buformin and phenformin. Therapy based on biguanides alone is feasible only for patients with adult onset or maturity onset (type II) diabetes, as juvenile diabetics cannot be stabilized without additional insulin injections.

The precise therapeutic mechanism has yet to be explained. Direct action on the β-cells of the pancreas has not been verified; the effect is essentially an extrapancreatic hypoglycemic one (BUTTERFIELD and WICHELOW 1962; CREUTZFELDT et al. 1959; MADISON and UNGAR 1960).

According to SCHÄFER (1980), biguanide derivatives react with the phospholipides of cellular and subcellular membranes. As strong bases they induce positive loading of these structures, which inhibits the active transfer of protons. The electron transfer is interrupted at the mitochondria, so that mitochondrial respiration, oxidative phosphorylation, and ATP generation are substantially reduced, resulting in an anaerobic metabolism.

The retardation of intestinal glucose absorption observed by CZYZYK et al. (1968) after phenformin administration is apparently due to the active transfer of glucose being reduced on the one hand by the decreased ATP content (induced by biguanides) of the intestinal wall, and on the other hand by the proton transfer being inhibited. Glucose is known to be actively transferred with sodions via the intestinal wall.

Investigations by DIETZE et al. (1978) suggest that less glucose is excreted by the liver in patients undergoing phenformin therapy than in untreated subjects. The inhibition of the mitochondrial respiration found in vitro by STEINER and WIL-

LIAMS (1958) has been confirmed in vivo by the workgroup DIETZE et al. (1978): the liver of patients undergoing phenformin therapy displays a clearly measurable reduction in lactate utilization. The peripheral muscle absorbs glucose to an increased extent under phenformin medication, according to investigations by WHICHELOW and BUTTERFIELD (1968). The metabolization of this glucose leads, however, to increased lactate concentrations, owing to the anaerobic metabolism under biguanides.

In general, biguanide medication leads to increased lactate concentrations in the blood for the reasons stated. SIRTORI et al. (1978) suggest that it is on account of the shorter half-life period of metformin (1.5 h) that the incidence of lactacidosis may be substantially lower than with other biguanide derivatives. Statistics published by ISNARD and LAVIEUVILLE (1977) show that 76% of all patients undergoing biguanide therapy in France are treated with metformin whereas only 14% of the cases of lactacidosis registered were observed under this therapy. All other cases of lactacidosis were observed under phenformin. BERGER and AMREIN (1978) report that 63% of patients in Switzerland are treated with buformin, 23% with metformin, and 8% with phenformin. Of 31 reported cases of lactacidosis, 84% were observed under buformin, 13% under phenformin, and a mere 3% under metformin.

Among other phenomena, the risk of lactacidosis appears to increase with increasing age (Fig. 7). From more than 300 cases of lactacidosis recorded by various authors after biguanide medication, LUFT et al. (1978) were able to show clearly that the dysbolism occurs primarily in the presence of concomitant diseases that themselves are accompanied by increased lactate concentrations in the blood.

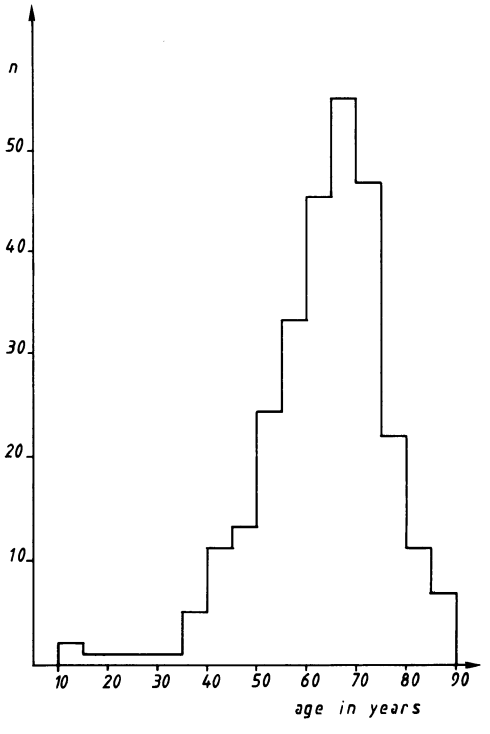

Fig. 7. Age-related distribution of biguanide-treated diabetics suffering from lactacidosis. (LUFT et al. 1978)

These diseases include chronic pulmonary diseases with impaired O_2 exchange, renal dysfunctions with a reduced glomerular filtration rate and proteinuria, hepatic diseases, and – among some 25% of maturity onset diabetics – infections.

The list of concomitant diseases increasing the risk of lactacidosis is headed by cardiovascular complications, such as myocardial infarction and coronary cardiac disease, that have a high incidence in maturity onset diabetics. Statistics published by LUFT et al. (1978) show that a disturbance of this type was present in 44% of all patients. According to ASSAN et al. (1969), lactacidosis under metformin therapy occurs almost exclusively with a concomitant restriction of the renal function.

Lactacidosis in advanced age has a mortality rate of over 50% (LUFT et al. 1978), so that an age of more than 65 years is now regarded as an absolute contraindication for biguanide therapy. The relative and absolute contraindications are as follows:

Patients over 60 years of age

Accompanying illnesses such as:
- Cardiovascular disease
- Renal disease
- Hepatic disorders
- Infectious processes

States which can by themselves result in an accumulation of lactate:
- Schock
- Diabetic acidosis
- Operations
- Pulmonary insufficiency
- Alcoholism
- Weight-reducing diets or fasting

This life-threatening complication has led to the use of these preparations being severely restricted today. Medication with metformin is still indicated, however, in the adipose adult onset (type II) diabetic, according to OBERDISSE (1977). Metformin inhibits the appetite, resulting in patients from this group losing weight.

If diet and sulfonamide treatment fail to produce adequate hypoglycemia, and insulinization is inadvisable, combined therapy – diet, sulfonamides, and biguanides (nowadays only metformin) – can be tried out. The cumulative effect of the two types of substances may still permit the metabolism to be satisfactorily stabilized.

IV. Insulinization of the Maturity Onset Diabetic

Acute metabolic imbalance such as coma or precoma diabeticum, highly feverish diseases with the risk of metabolic imbalance, primary or secondary failure of oral antidiabetic drugs, gastrointestinal complaints accompanied by vomiting and diarrhea, and surgery are all an absolute indication for insulinization of the elderly patient.

In practice, fasting and postprandial blood glucose levels exceeding 200 mg/dl are frequently accepted in patients stabilized by diet and with oral antidiabetic drugs, in order to avoid a changeover to insulinization that might have long been

indicated on the grounds of increasing β-cell insufficiency. This type of hyperglycemia often has a negative clinical effect on the general well-being of the patient. STRAUMANN et al. (1979) report that the decompensated maturity onset diabetic complains of lassitude, increased dizziness, depressions, and neuropathies.

These complaints are frequently accepted by the patient concerned as unpleasant age-related symptoms and are not associated by the patient with the diabetic metabolic situation. It has proved difficult for this reason to convince the elderly diabetic that a changeover to insulinization is necessary, particularly if he then has to fear being restricted to a specific diet or being dependent on others for insulin injections. Patients in need of help can be insulinized only if regular care is assured and the patient himself consents.

In general, elderly diabetics with progressive mental decay and severely impaired sight should not be insulinated even if they have fasting hyperglycemias of 200 mg/dl and more, unless care is available. Nor is this form of therapy justified if the prescribed diet and regular mealtimes cannot be adhered to, as suggested by STRAUMANN et al. (1979). If, on the other hand, a changeover is made from oral stabilization to insulinization in the elderly diabetic, there may be a marked improvement in the subjective symptoms and a much more stable metabolic situation may be attained.

Efficient maturity onset diabetes stabilization can be achieved with two doses of medium-term intermediary insulin (depot insulin). When the metabolic situation is specially stable – a not infrequent occurrence in the maturity onset diabetic – one single injection of long-term insulin each morning is effective, according to WILLMS (1981). Any rapid change in dosage should be avoided when using this type of insulin. The injected dose is absorbed gradually over a period of 24 h so that balanced efficiency and absorption are attained only after 3–4 days, as reported by SAUER (1977). One prerequisite for therapy with long-term insulin is a diet that can be easily adhered to with several small meals per day. This often proves extremely difficult for patients living in a family or in a home for the aged, so that two injections per day of intermediary insulin protect the patient more efficiently from hypoglycemia, despite metabolic stability.

G. Acute Complications

The diabetic coma and hypoglycemic shock are among the life-threatening metabolic imbalances in diabetes mellitus. Both forms of disturbed regulation are a special risk to the maturity onset diabetic and make rapid, pinpointed therapeutic intervention essential.

I. Coma Diabeticum

The diabetic coma is the most serious form of metabolic imbalance and is due to severe insulinopenia. This results in a profound disturbance of the carbohydrate, protein, and fat metabolisms and of the water equilibrium, the electrolyte metabolism, and the acid-base equilibrium.

The lack of effective insulin shifts the physiological glucose equilibrium, the balance between gluconeogenesis and glucose metabolism, in favor of gluconeogenesis. Amino acids are, according to investigations by MANCHESTER (1961), no longer absorbed into the muscles but are metabolized in the same way as pyruvate, lactate, and α-ketoglutaric acid for gluconeogenesis. The increase in contrainsulin hormones such as glucagon, adrenalin, noradrenalin, and TSH results in increased lipolytic activity and in an accumulation of free fatty acids in the blood. In the presence of insulinopenia, these fatty acids infiltrate into the cells for energy production and are metabolized into ketone bodies as no energy can be produced from carbohydrates with intracellular glucopenia. The accumulation of substances of high molecular weight, such as glucose, ketone bodies, free fatty acids, and amino acids, in the blood results in marked intracellular dehydration on account of the extracellular hyperosmolarity. The renal excretion of glucose and ketone bodies leads to a substantial loss of water and electrolytes and consequently to extracellular dehydration. The accumulation of ketone bodies, lactate, and fatty acids may induce metabolic acidosis (DANOWSKI and NABARRO 1965; FLANIGAN et al. 1970; FROESCH and ROSSIER 1971; HURWITZ 1968; KUMAR 1968).

These biochemical changes may not be equally strongly marked, so that a distinction is made between three types of coma. The ketoacidotic coma is associated with blood glucose concentrations of up to approximately 600 mg/dl, metabolic acidosis, and an accumulation of ketone bodies in the serum and urine. This type of coma is observed predominantly in insulin-dependent diabetics. The coma incidence in the diabetic population examined by PANZRAM (1973) is 0.31%, the risk in insulin-dependent patients being much higher at 0.8% than that of noninsulinated patients, to whom most maturity onset or adult onset diabetics belong.

The hyperosmolar coma diabeticum is characterized by severe hyperglycemia with blood glucose concentrations generally exceeding 1,000 mg/dl, marked hyperosmolarity in excess of 350 mosmol/liter, and in general with hypernatremia and hyperurea. Investigations or descriptions of cases by DANOWSKI and NABARRO (1965), ROSSIER et al. (1960), series of observations by JACKSON and FORMAN (1966), ASSAN et al. (1969), GERICH et al. (1971), and SCHMITT and HÖHLER (1971) indicate that this type of coma occurs predominantly in noninsulin-dependent type II adult onset or maturity onset diabetics. The average age in these reports was over 50 years, and in the statistics quoted by SCHMITT and HÖHLER (1971) 70.4 years.

The occurrence of this type of coma in advanced age led JOHNSON et al. (1969) to suspect that the residual insulin secretion maintained in these patients prevents ketoacidosis from occurring.

From the pathogenetic viewpoint, DÜRR (1964) and ANDERSON and WARD (1978) assume that excess dehydration, which may be induced in maturity onset diabetics by diuretic drugs prescribed for cardiac failure or hypertension therapy, leads to hyperosmolar decompensation of the diabetes.

With lactacidosis of the diabetic, a metabolic acidosis has been caused by the blood lactate concentration rising to over 1.5 mmol/liter. Hyperglycemia and ketosis or ketosuria are seldom recorded. The statistics quoted by LUFT et al. (1978) suggest that more than 50% of cases of this type of metabolic imbalance occur in noninsulin-dependent adult onset or maturity onset diabetics over the age of 64.

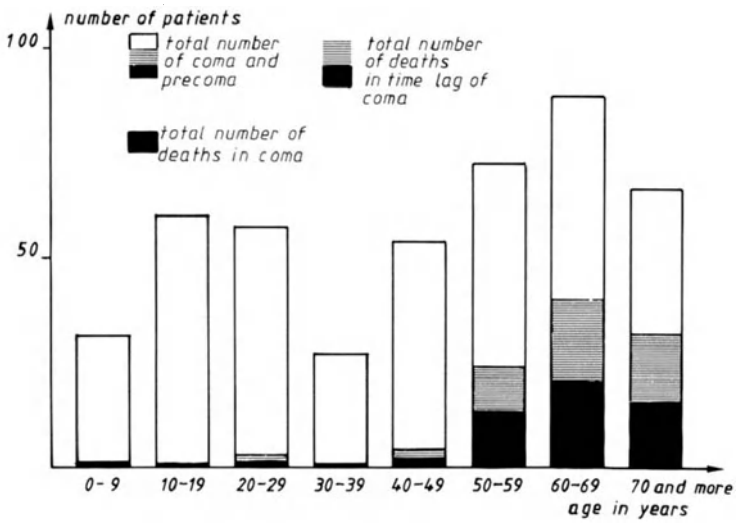

Fig. 8. Age distribution of 472 diabetics with coma and precoma. (PETZOLDT 1981)

The triggering factor is the effect of biguanide therapy on an elderly organism that has been previously damaged by cardiovascular diseases (in some 44% of cases), by nephropathy (35%), or infections (25%) (LUFT et al. 1978).

Precise differentiation between the individual types of coma according to biochemical criteria is not always possible. The absence of acidosis actually distinguishes between a ketoacidotic and a nonketoacidotic hyperosmolar coma. LARCON et al. (1963), KOGUT and LANDING (1967), and ASSAN et al. (1969), however, detected lowered blood pH values with hyperosmolar comas. RICK (1973) describes depressed standard bicarbonate values, so that a compensated metabolic acidosis seems to be present in conjunction with the depressed pH values. FRERICHS and CREUTZFELDT (1971) find this feature in almost half the comas investigated by them. These findings show that the hyperosmolar coma is obviously a variant of the ketoacidotic coma. PAILLE et al. (1970) and NOVAK (1972) observed transitions of ketoacidotic comas into the hyperosmolar type and vice versa.

The mortality rate under the coma diabeticum increases with increasing age. Figure 8 shows the age distribution of 472 diabetics with coma and precoma. According to the so-called Erfurt Study by PANZRAM (1973), one in four coma patients died at the age of 40–59 years, one in three at the age of 60–69 years, and one in two at the age of 70 or more. The mortality rate among patients in initial coma (coma with previously undiagnosed diabetes) is 54% and is thus approximately as high as among patients undergoing only dietary therapy or none at all. Investigations by SCHMITT and HÖHLER (1971) show an increased incidence of manifestation comas with increasing age. Among the different types of coma, the mortality rate in nonketoacidotic hyperosmolar coma is outstandingly high, as is shown by DANOWSKI and NABARRO (1965), HALMOS et al. (1966), PETZOLDT et al. (1971), and SCHMITT and HÖHLER (1971), accounting for between 44% and 70% of fatalities.

A diabetic coma generally occurs in conjunction with a concomitant disease that has induced the metabolic decompensation. These diseases include feverish infections, gastroenterological diseases with diarrhea or vomiting, pancreatitis, and cardiovascular events such as myocardial infarction, pulmonary embolism, or apoplexia cerebri. A coma diabeticum may furthermore occur with infected gangrene, furunculosis, or papillary necrosis with acute renal insufficiency. Feverish infections, particularly of the upper respiratory tract, can induce a coma diabeticum in all age groups (JAHNKE 1977).

When acute metabolic imbalance occurs in the maturity onset diabetic or the elderly insulin-dependent patient, the possibility of a vascular or cardiac event must first be considered. An acute myocardial infarction was registered in 6% of all cases of coma among the patients observed by PENSE and PANZRAM (1962), BRUNS and TAKAC (1965), and PETZOLDT et al. (1971). SCHMITT and HÖHLER (1971) established apoplexy as the cause of the coma in 2.4% of their patients; SCHÖFFLING et al. (1971, 1979) recorded occasional pulmonary embolism.

The clinical symptoms of progressive metabolic decompensation are polydipsia, polyuria, anorexia, and decreased vitality. Nausea, vomiting, occasional diarrhea, and, among elderly patients, frequent cases of abdominal pains (pseudoperitonitis diabetica) and myokinesis occur (coma vigile). In the maturity onset diabetic, the gastrointestinal complaints lead to the intake of water and oral antidiabetic drugs being omitted and to decompensation with dehydration consequently being intensified so that the development of a hyperosmolar coma is promoted. At the precomatose stage, breathing becomes deeper and cardiovascular insufficiency develops, together with signs of disorientation; this leads in the ketoacidotic coma to Kussmaul's respiration, to a cardiovascular shock, and to loss of consciousness and neural dysfunctions.

These coma stages are generally of very short duration in juvenile diabetics so that a coma develops within a matter of hours. With the elderly diabetic, the individual phases are very gradual, frequently covering several days. When the metabolic decompensation is complete, the patient is unconscious, severely dehydrated (hypertonic dehydration), and suffering from cardiovascular insufficiency. JACKSON and FORMAN (1966) observed unilateral symptoms or grand mal seizures or signs of hemiplegia in their patients in hyperosmolar coma, so that apoplexy was originally suspected (FLÜGEL and STOERGER 1966; MANZANO and KOZAK 1969).

Prompt diagnosis by the first doctor attending to the patient is absolutely essential in the life-threatening coma diabeticum. Blood sugar and urine sugar can be determined by means of readily available testing strips as possible confirmation of the tentative diagnosis (JAHNKE 1977). On immediate admission to hospital, the blood and urine sugar levels are checked by enzyme tests, the serum electrolyte count is measured, and the circulatory parameter is measured with determination of the intravenous tension to obtain information on the extent of the dysbolism and dehydration. BERGER and AMREIN (1978) and BERGER et al. (1969) claim that dehydration can be controlled by the central intravenous tension, especially in the elderly patient, in such a way that complications such as cardiac failure and pneumonedema can be prevented. An ECG and an X-ray of the thorax are essential in the case of the maturity onset diabetic, as myocardial infarction with cardiogenic shock may also induce unconsciousness and hyperglycemia.

The top-priority therapeutic measures, particularly for the elderly diabetic patient, include volume substitution under central intravenous pressure control. Rehydration cannot be effected for obvious reasons to the same extent and as rapidly as in the young patient. The fluid intake is substantially limited by cardiac failure, possibly with infarction, or by restricted renal function with the risk of pneumonedema. BRADLEY (1971) infuses one-third of the estimated water requirement within the first 2–6 h. HOCKADAY and ALBERTI (1972) infuse 2 liters in the first hour.

Any previous history of myocardial insufficiency necessitates compensating the losses of sodium and potassium via the kidneys as rapidly as possible and correcting the acidosis with bicarbonate, but only when the pH values are below 7.1 (WALDHÄUSL and KLEINBERGER (1980). Bicarbonate therapy necessitates close control of the serum potassium level as it promotes the flow of potassium into the cells (BERGER et al. 1974; PENSE et al. 1973). Parenteral potassium substitution must be either completely omitted or heavily restricted if chronic nephropathies are present or less than 50–60 ml urine are produced per hour, as the patient with excessively high serum potassium levels is endangered by the occurrence of arrythmia going as far as cardiac arrest.

There are no generally recognized directives for insulin substitution in the diabetic coma. Good recompensation is nowadays attained with small insulin doses of approximately 10–20 IU unmodified insulin i.v. as a bolus and 5–10 IU/h by intravenous drip (BERGER et al. 1974; HEBER et al. 1977; JAHNKE and BURO 1970; LUTTERMANN et al. 1979). This rate of infusion approaches the physiological insulin secretion rate of the healthy subject of approximately one unit per hour. Experience has shown that hyperglycemia, ketosis, and acidosis are normalized within the same period as under the high insulin doses formerly applied.

The former insulin doses of 500–100,000 IU in the first 12 h of treatment were applied by ARKY and HURWITZ (1966) and by TYLER and BEIGELMANN (1960) on the grounds that metabolic imbalance indicates relative insulin hyposensitivity, possibly due to acidosis (WALKER 1963), ketosis, and hyperlipidemia (RANDLE 1969) or in rare instances to genuine antibody binding (YALOW and BERSON 1960). Experience suggests, however, that the elderly patient in particular may be at risk under this form of therapy from severe ileus and respiratory paralysis or, under excessively rapid metabolic adjustment, from cerebral edema (NEUBAUER and ALTHOFF 1980). Life-threatening hypoglycemia has also been not infrequently observed. It is for these reasons that metabolic recompensation by means of small doses of insulin is now recommended.

The serum phosphorus level normally declines in the course of coma therapy; correction of the ketoacidosis often reduces the serum phosphorus concentration to below 1 mg/dl. High-grade phosphopenia, on the other hand, may lead to disturbances of consciousness (BERGER et al. 1974). A 1–2 g phosphorus substitution is therefore advisable in the first 8 h.

In short, large quantities of fluid and smaller doses of insulin are needed for treatment of the hyperosmolar coma than for treatment of the ketoacidotic coma in the elderly patient. Correction of the normally low-grade metabolic acidosis is in many cases unnecessary. Treatment of lactacidosis consists essentially of acidosis correction with bicarbonate of soda and adequate fluid intake. As large quan-

tities of bicarbonate are frequently essential to stabilize the blood pH, hypernatremia may result. Hemodialysis must then be performed with adequate fluid intake to eliminate the excess sodium.

II. Hypoglycemia

From the viewpoint of differential diagnosis, the possibility of hypoglycemic shock must be considered in the unconscious diabetic patient besides the coma, particularly if he is undergoing insulinization or sulfonyl urea therapy. In this event the patient's skin is moist, the pupils dilated, and respiration normal. Differentiation of the symptoms according to SCHWARZ (1971) is reproduced in Table 5.

FRERICHS et al. (1973) and LUFT and EGGSTEIN (1978) distinguish between two forms of hypoglycemia. The acute transitory hypoglycemic shock, induced by i.v. administration of unmodified insulin or a sulfonyl urea derivative (tolbutamide), displays the symptoms described above. In the elderly patient, however, cerebral ischemia or angina pectoris is most likely to be observed. Oral antidiabetic drugs of the sulfonyl urea group or depot insulin lead to insidious hypoglycemia. Depressed blood glucose concentrations can furthermore be observed subsequent to acute hypoglycemia. The symptoms are lassitude, logopathies, and disturbances of consciousness; these may be confused with a cerebrovascular process in the elderly subject. BERGER (1971) reports that 20% of patients display hemiparesis as the primary symptom. These symptoms are closely connected with the cerebral glucose deficiency that is termed neuroglucopenic syndrome by FRERICHS et al. (1973).

The blood glucose levels under hypoglycemic shock or prolonged hypoglycemia are generally below 40 mg/dl (STRIK et al. 1973). The same symptoms are to be observed, however, in patients with previous cerebral damage when the blood glucose level falls below 70 mg/dl, the rate at which the blood glucose level decreases being a substantial factor according to STRIK et al. (1973).

Fatal hypoglycemia has been observed following medication with long-acting sulfonyl ureas such as glibenclamide. Renal insufficiency or interactions with other drugs (Table 3) lead to accumulation or an intensified effect of all sulfonyl urea derivatives and thus to hypoglycemia. This occurs predominantly when meals are omitted. BERGER (1971) observed recurrent hypoglycemia in 1% of maturity onset

Table 5. Symptoms of hypoglycemic shock and diabetic coma. (Adapted from SCHWARZ 1971)

Hypoglycemic shock	Diabetic coma
Anxiety	Polyuria/polydipsia
Hunger	Anorexia, vomiting
Moist skin	Dry skin
Nonhypotonic bulbi	Soft bulbi
Dilated pupils	
Babinski, pyramid signs	Unilateral symptoms, generalized convulsion in hyperosmolar coma
Normal respiration	Kussmaul's respiration
Full pulse	Shallow pulse
Respiratory rate normal–high	Respiratory rate normal – low
Anxiety cramps	Disorientation – coma

diabetics treated with glibenclamide or chlorpropamide after some years' duration of the disease. Whereas hypoglycemia induced by exogenous insulin can be treated quickly and effectively by parenteral or oral glucose application, sulfonamide derivatives lead to recurrent hypoglycemia despite adequate glucose application. According to HASSLACHER and WAHL (1971), relapses occur in the first 3 days in 30%–50% of cases of hypoglycemia due to sulfonyl ureas. Prolonged hypoglycemia has a morbidity rate of up to 10% according to DEVIGAN et al. (1976) and SELTZER (1972). The rate depends on the duration of the hypoglycemia, previous damage, and the previous hypoglycemia incidence in the patient.

H. Chronic Complications

The chronic complications arising with increasing duration of the disturbed metabolism include first and foremost vascular complications such as microangiopathy and macroangiopathy as well as diabetic neuropathy. Lipometabolic disturbances and pyelonephritis are observed with increasing frequency in the course of the disease.

Diabetic microangiopathy is characterized by thickening of the capillary basement membranes, induced by increased synthesis and infiltration of glycoproteins into the intima and media of small arteries (KEEN et al. 1965; KIMMELSTIEL and WILSON 1936; OLSEN et al. 1966; WARREN et al. 1966). From the pathogenetic aspect, insulopenia and consecutive hyperglycemia are regarded as causing the lesions of the organs (SPIRO and SPIRO 1971). SPIRO (1976) demonstrated that glycoprotein components are incorporated more intensively without insulin into basement membranes. CAMERINI-DAVALOS et al. (1977), KIMMELSTIEL and WILSON (1936), and SAMTLEBEN (1972) reported increased glycosyl transferase activity with hyperglycemia as compared with normoglycemia. This enzyme binds glucose to the hydroxylysine galactose. This thickening of basement membranes can be detected in all vascular areas. Manifestation in the eye as diabetic retinopathy and in the kidney as diabetic nephrosclerosis are of clinical relevance.

Lesions of the small vessels certainly play some role in the development of diabetic gangrene and neuropathy. The intercorrelations between the diabetic metabolic situation and the development of diabetic vascular wall lesions are illustrated once again in Table 6.

Table 6. Diabetic vascular wall lesions

Microangiopathy	Macroangiopathy arteriosclerosis
Retinopathy	Coronary arteriosclerosis – myocardial infarction
Glomerulosclerosis Nephropathy (Kimmelstiel-Wilson syndrome)	Nephrosclerosis Cerebral sclerosis – apoplectic seizure
Neuropathy (some cases) Gangrene (additional metabolic factor, not yet clarified)	Peripheral arteries Arterial occlusion
Skin	
Muscles	

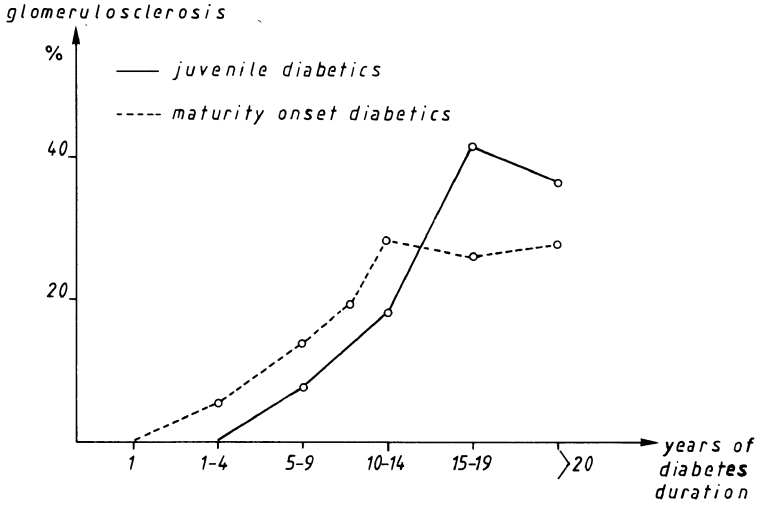

Fig. 9. Percentage incidence of glomerulosclerosis with increasing duration of diabetes, divided into juvenile onset ($n=504$) and maturity onset ($n=1{,}281$) diabetic patients. (IRMSCHER 1977)

Diabetic microangiopathy is observed predominantly in the juvenile onset insulin-dependent type I diabetic. Vascular complications occur most frequently in patients with a manifestation age of less than 20 years and a diabetes duration of 10–30 years. There is as yet no absolute clarity on the pathogenesis of microangiopathic lesions.

The influence of the diabetic metabolic situation with hyperglycemia, leading with increasing duration to vascular lesions, is unchallenged today. Investigations by OBERDISSE and IRMSCHER (1968), SAMTLEBEN (1972), and JOSLIN et al. (1936) established an unequivocal connection between incidence and extent of glomerulosclerosis on material of predominantly autopsy origin.

An influence of manifestation age on the incidence and extent of microangiopathic vascular lesions cannot yet be regarded as certain. IRMSCHER (1977) considers that it may be only an apparently increased incidence due to juvenile onset diabetics having a higher survival rate. Figure 9 shows, however, that it is only after a diabetes duration of 14 years that the incidence of diabetic glomerulosclerosis is unequivocally higher than in the maturity onset diabetic.

The significance of metabolism control in the development of vascular lesions cannot be evaluated unequivocally from the literature available, as the human metabolic situation over an observation period of some years cannot be assessed with certainty. SIPERSTEIN (1975) rejects any possibility of metabolism control influencing the development of microangiopathy. Practical clinical experience by CONSTAM (1965), MARBLE (1971), MEHNERT (1969), and PENSE et al. (1973), on the other hand, suggests that the incidence of glomerulosclerosis is definitely lower under good metabolism control. The survival rate of patients whose metabolism is controlled only at irregular intervals and is not well compensated also undergoes a marked decline. An investigation at the Steno Memorial Hospital on juvenile onset

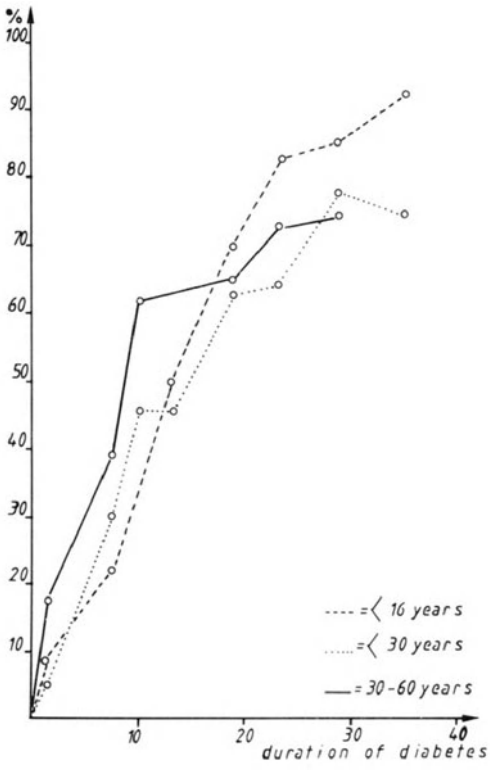

Fig. 10. Frequency of retinopathy in diabetics of different age (at on set of the disease). (BURDITT and CAIRD 1968; JACKSON and GOLDIN 1963; KEIDING et al. 1952; KORNERUP 1955; LARSSON and STERKY 1962; MATTENSON and PALM 1950; WICHELOW and BUTTERFIELD 1968)

(type I) diabetics 40 years after onset of the disease shows that some 28% of uncontrolled but almost 70% of regularly controlled diabetics survived this period (DECKERT et al. 1978).

Retinopathia diabetica occurs in two forms. Nonproliferative retinopathy is characterized by microaneurisms, flecked hemorrhages, and foci of degeneration with exudation and lipomatosis. In the proliferative form, retinal vessels grow into the vitreous body, which may lead to vitreous hemorrhages and eventually to loss of sight. As with glomerulosclerosis, there is also an unequivocal connection here with the duration of the dysbolism in all age groups. Figure 10, based on MATTENSON and PALM (1950); KEIDING et al. (1952); KORNERUP (1955); WHITE (1960); LARSSON and STERKY (1962); JACKSON and GOLDIN (1963), and BURDITT and CAIRD (1968) shows that between 70% and 90% of patients are suffering from retinopathy 30 years after the onset of diabetes.

Diabetic nephroangiopathies are a serious complication of the late diabetic syndrome, owing to the high incidence and the unfavorable prognosis in advanced stages of the disease. Diabetic nephropathy occurs in two forms: as glomerulosclerosis and as nephrosclerosis. In diabetic glomerulosclerosis, nodular, PAS-positive deposits are found at the center of the glomerulus in conjunction with arteriosclerotic lesions of the vasa afferentia and efferentia (DITSCHERLEIN 1969; WEHNER and BOHLE 1974). Pathological changes cannot be detected until 2–5 years after onset of the disease. Age and sex have no influence on the development or

progression of the disease, according to SAMTLEBEN (1972) and SCHLIACK et al. (1964).

The disease is chronically progressive. GELLMAN et al. (1959) and THIEFFRY et al. (1972) report that it rarely occurs as a diabetic nephrotic syndrome, the Kimmelstiel-Wilson syndrome. Juvenile onset insulin-dependent diabetic patients generally suffer from proteinuria and a fully developed nephrotic syndrome with hypalbuminosis, dysproteinemia, hypercholesteremia, edemas, and arterial hypertension after longer duration of the disease. SARRE et al. (1971) diagnosed a Kimmelstiel-Wilson syndrome in only 4.4% of 1,307 patients with some kind of nephrotic syndrome.

Diabetic glomerulosclerosis with the described histological changes and a detectable constant proteinuria is not reversible and is fatal within 3–12 years of the onset of proteinuria according to REUBI (1970). According to CAIRD (1961), 65% of patients with proteinuria survive for 5 years and 28% for 10 years if the symptoms remain constant. The corresponding figures for diabetics without proteinuria are 89% and 59% respectively. According to a report by the Joslin Clinic (MARKS 1965), 49.5% of juvenile onset long-term diabetics with a manifestation age of under 20 years and a diabetes duration of between 10 and 29 years died of diabetic nephropathy. Renal arterioarteriolosclerosis affects the branches of the renal arteries rather than the arcuata vessels, resulting in renovascular hypertension. Arterioarteriolosclerosis is the pathological abnormality most frequently diagnosed in the kidneys of diabetic patients, where the incidence is some 10 times as high as in nondiabetic subjects (DIETZ et al. 1978). It promotes the development and progression of other nephropathies (glomerulosclerosis, pyelonephritis) and accounts for most cases of arterial hypertension in juvenile onset long-term diabetics, especially when proteinuria, restricted renal function, and a diabetic retinopathy are diagnosed.

Cardiac failure is the more frequent cause of proteinuria and edemas in the maturity onset diabetic, according to GELLMAN et al. (1959) and to HATCH et al. (1961). According to SAMTLEBEN (1972), arterial hypertension in the adult onset or maturity onset diabetic is to be regarded either as idiopathic or as a consequence of aortic sclerosis.

I. Diabetic Macroangiopathy

Seventy percent of all diabetics now die from the effects of vascular diseases, the majority – 53% of these – from coronary cardiac diseases, and some 12% from cerebrovascular processes, according to reports from the Joslin Clinic published by MARKS and KRALL (1971).

Diabetic macroangiopathy is a special form of arteriosclerosis affecting essentially medium and large arteries.

Whereas the effects of diabetic nephropathy prove fatal in the juvenile onset insulin-dependent patient, the main cause of death in the maturity onset diabetic is coronary cardiac disease (BERTHOLD and BERGER 1978; KEEN and JARRETT 1973; KIPNIS 1968; MARKS and KRALL 1971; RIFKIN and BERKMAN 1970).

In contrast to arteriosclerosis, where the incidence ratio of nondiabetic men under the age of 50 to women is approximately 4:1, as reported by SCHETTLER and

WOLLENWEBER (1974), macroangiopathy has the same incidence among male and female patients.

According to HARDES (1968), HAUPT and BEYER (1974), and SCHETTLER and WOLLENWEBER (1974), diabetic macroangiopathy has an earlier onset and progresses more rapidly than arteriosclerosis. The incidence of apoplexy is six times higher among diabetic women than among women of the same age with a healthy metabolism (JOHNSON 1970).

Special forms of arteriosclerosis such as Mönckeberg's media sclerosis – a linear calcareous degeneration of the media – have an increased incidence among diabetics (LUNDBAEK 1977).

The etiology of vascular wall lesions has yet to be clarified. Comparative histochemical tests on arteriosclerotic plaques of diabetics and nondiabetics have revealed no distinct differences (HAUPT and BEYER 1974).

Hyperglycemia is regarded as one essential factor in macroangiopathy, with simultaneous hypertension (JOHNSON 1970; KEEN et al. 1965) or lipometabolic disturbances (HAUPT and BEYER 1974; SCHETTLER and WOLLENWEBER 1974) promoting the development and progression of arteriosclerotic vascular wall lesions. Coronary cardiac disease, which occurs as early as the age of 20–40, according to TRAUTWEIN and JULITZ (1967) and HARDERS (1968), with less painful progression than in the nondiabetic or with no subjective symptoms at all, is of primary clinical relevance. MARKS and KRALL (1971) report that adult onset diabetics with a 20-year record of diabetes mellitus are most frequently affected. The paratypical features in conjunction with the relatively low age of the long-term diabetic often give rise to problems in differential diagnosis.

Backache and pain in the abdominal region or only in the chin are reported. Precordial pain that may be due to an infarct event is often unaccompanied by enzymic or electrocardiographic changes (HARDERS 1968). After recovery from an acute event, the risk to the type I diabetic 15 years after diabetes onset and to the maturity onset diabetic, according to MARKS and KRALL (1971), is pulmonary embolism or peripheral embolic occlusions. This complication may induce cardiac failure and a diabetic coma.

BELL (1952) states in his autopsy statistics that fatal myocardial infarction occurs approximately twice as often in diabetics as in subjects with a healthy metabolism. Peripheral ischemic lesions also, located most frequently in the legs, rarely induce painful symptoms in the diabetic patient.

Arterial occlusion in the diabetic leads in only rare cases to intermittent claudication (ANSCHÜTZ 1974; WHITEHOUSE and ROOT 1956; WIDMER and STUDER 1966). Necrotic tissue caused by disturbed microvascular circulation in conjunction with hypesthesia rarely induces severe pain. DAWEKE (1970) established sock-form hypesthesia as an expression of diabetic neuropathy in patients with acral lesions. Minor traumata such as excessively narrow footwear, incorrect pedicure, hyperthermia, or hypothermia are not infrequently the cause of extensive tissue defects that may develop into gangrene. So-called hot gangrene may be induced by superinfections with bacteria coli, *Pseudomonas*, *Staphylococcus aureus haemolyticus*, or streptococci. Despite these ischemic lesions the pulse on the back of the foot, for instance, can generally be felt clearly in the diabetic patient.

Diabetic macroangiopathy of the cerebral vessels is not of clinical relevance in diabetics until after the age of 70, as shown in investigations by ENTMACHER et al. (1964). It occurs in most cases 20–40 years after onset of diabetes. The incidence is the same in male and in female patients. According to this report, the incidence of death from the effects of an apoplectic seizure is twice as high in diabetic patients as in subjects of the same age with a healthy metabolism. While DITSCHERLEIN (1964) quotes an apoplexy incidence of only approximately 6% among diabetics, the figure quoted by JOSLIN et al. (1936) is 12.3%.

The prognosis of all late complications can be positively influenced by good diabetes stabilization, particularly in the early post-diagnosis years (HARDERS 1968; HOWLAND and DRINKARD 1963; PENSE et al. 1973). This hypothesis has been substantiated in experiments on animals (MARQUIÉ 1978) and in clinical studies (BERTHOLD and BERGER 1978; HARDERS 1968; IRSIGLER et al. 1979; JARRETT et al. 1969; MEHNERT 1969; WHITEHOUSE and ROOT 1956). JOSLIN et al. (1959) claim that progression of diabetic retinopathy was successfully inhibited in cases where good metabolism control had been observed in the first 5 years following diagnosis. IRSIGLER et al. (1979) report a reduced incidence of proliferative retinopathy in well-stabilized diabetics. The mortality rate from cardiovascular and cerebral sclerotic complications is also considerably higher with inadequate than with good metabolism control (HARDERS 1968; IRSIGLER et al. 1979).

The question of whether oral antidiabetic drugs, especially sulfonamide derivatives, promote the development of arteriosclerotic vascular wall lesions – as indicated by the UDPG study (TYLER and BEIGELMAN 1960) – has yet to be unequivocally answered. Experiments on animals and clinical investigations both suggest a prophylactic effect with special regard to coronary cardiac disease.

II. Pyelonephritis

A number of autopsy findings and clinical investigations show that the incidence of pyelonephritis is higher in female diabetics between the ages of 40 and 50 and in male diabetics above the age of 60 than in nondiabetic subjects (OSTERBY-HANSEN 1964; O'SULLIVAN et al. 1961; SCHRUB et al. 1973). WARREN et al. (1966) quote the incidence in their autopsies at 36% of all diabetics examined; DITSCHERLEIN (1969) detected the active form of pyelonephritis twice as often in diabetics as in subjects with a healthy metabolism. OBERDISSE and IRMSCHER (1968) found an increase in incidence to as much as 30% in men over the age of 60, to 28% in women aged between 40 and 60, and to as much as 60% of the subjects examined in the 60-plus age group (Fig. 11).

As the course of pyelonephritis in the diabetic patient is frequently chronic and lacking in subjective symptoms, percentage frequency data are low in clinical studies: O'SULLIVAN et al. (1961) quote the rate at 13.3% of 150 subjects examined, SCHRUB et al. (1973) at 14.7% of 650 patients, and BRUNS (1970) at 15.8% of 4,074 diabetics. The extensive investigation by BRUNS, using kidney biopsies and not only significant bacteriuria as evidence, shows that the incidence of pyelonephritis is twice as high in diabetics as in healthy subjects.

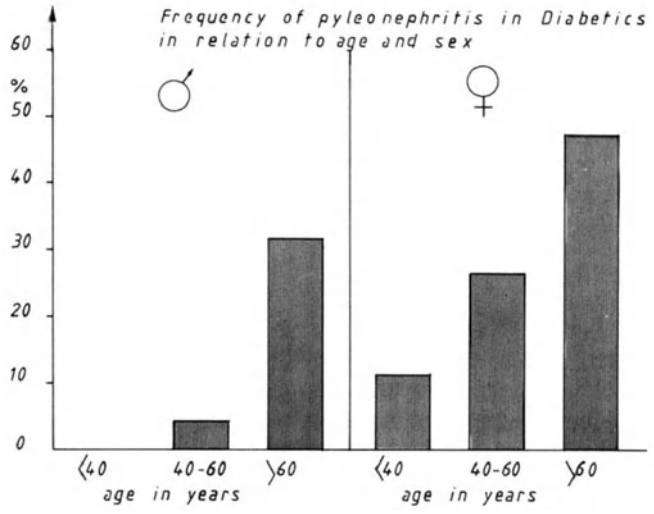

Fig. 11. Dependence of the incidence of pyelonephritis on age and sex in diabetes mellitus. (OBERDISSE and IRMSCHER 1968)

The question of whether saccharomycetes detected by BRUNS (1970) in 10.6% of the diabetics examined are a cause of the increased frequency of pyelonephritis is not answered with certainty in that study either. Glycosuria does appear, however, to promote the growth of these saccharomycetes, according to the study by MEHNERT and MEHNERT (1958): saccharomycetes were found in the urine of 34% of 150 diabetic patients, whereas only 10% of nondiabetic subjects were affected.

The microbial content in urinary tract infections of diabetic and nondiabetic subjects is essentially the same (BRUNS 1970; OSTERBY-HANSEN 1964; O'SULLIVAN et al. 1961; SCHRUB et al. 1973). Antibiotic protection is resistogram based in both groups. Papillary necrosis induced by pyelonephritis is much dreaded by the diabetic patient. Autopsy statistics by WHITEHOUSE and ROOT (1956), ZOLLINGER (1960), and DITSCHERLEIN (1969) quote this complication in 3.4%–11.5% of diabetics and in only 0.13–0.7% of nondiabetics.

III. Diabetic Neuropathy

Neurological disturbances occur in all age groups in conjunction with the diabetic metabolism. BISCHOFF (1977) demonstrated, however, that these disturbances have their peak incidence in the second half of life, generally in the 6th decade. According to DAWEKE (1970), this observation results from the higher diabetes morbidity rate in that age group. Clinical studies by BROCH and KLÖVESTADT (1947), MATTHEWS (1955), FEUDELL (1963), and MALINS (1968) indicate, on the other hand, that neurological disturbances among maturity onset diabetics occur more frequently than would correspond to the percentage increase in diabetes morbidity.

MALINS (1968) diagnosed polyneuropathic symptoms in 44% of his patients under the age of 30 but in 83% of those aged between 50 and 70. GAMPSTORP et al. (1966) found peripheroneurological failures in 20%–30% of diabetics under the

age of 30 and in 70% of those over 60, taking account of the statistical increase in diabetes in advancing age.

These studies collectively indicate that neuropathy undergoes a distinct increase in advanced age. In contrast, GREGERSON (1967) and HIRSON et al. (1953) found no unequivocal substantiation for this observation.

CONSTAM (1965), PIRAT (1970), FEUDELL (1969), and MATTHEWS (1955) showed in their statistics that the incidence of diabetic polyneuropathy is connected essentially with the duration of the disease and with the quality of metabolic stabilization. With insidious progression, as is frequently observed in the maturity onset diabetic, POMERANZE (1959) diagnosed polyneuropathies in 10% of his patients and JARRETT et al. (1969) in 19.5% of those examined, despite the absence of clinical diabetes symptoms. Pathogenetic examination gives above all indications of the vascular cause of neuropathic complaints; this is substantiated by histological examinations carried out by FAGERBERG (1959) and by RAFF and ASBURY (1968). From the clinical aspect there was frequently a discrepancy between neuropathy and localization of circulatory disturbances in those patients examined by CHRISTENSEN (1967) and GREENBAUM (1964). It is obviously not only circulatory disturbances but the dysbolism itself that is responsible for the nervous lesions.

Whereas classical, bilateral-distal sensomotor polyneuropathy occurs at any age, the predominantly motor-amyotrophic, asymmetric-proximal polyneuropathy is found almost exclusively in the adult onset or maturity onset diabetic. Vegetative neuropathies are predominantly a disease of the younger adult onset diabetic. Ophthalmoplegia, in contrast, occurs almost exclusively in the elderly maturity onset diabetic, as described by BISCHOFF (1974, 1977).

The motor-amyotrophic asymmetric polyneuropathy of the adult onset and the maturity onset diabetic prevents most patients affected from climbing stairs or makes it difficult for them to rise from an armchair (BISCHOFF 1974, 1977). GREGERSON (1969) states that the levators of the foot may be paralyzed. BLOODWORTH and EPPSTEIN (1967) report that the paralytic symptoms are often preceded by myalgia.

Vegetative neuropathy affects predominantly the autonomous nervous system. It is expressed as a diabetic bladder that becomes clinically manifest as vesical atonia in 10% of patients affected (ELLENBERG 1966; PIRAT 1970). HALMOS et al. (1970) and HOWLAND and DRINKARD (1963) found X-ray evidence of delayed evacuation of the stomach that becomes manifest as matutinal nausea and a sensation of repletion. The disturbed intestinal motility may be expressed in a similar way to a genuine malabsorption syndrome with diarrhea and steatorrhea, as observed by WHALEN et al. (1969) and by VINNIK et al. (1962). SCHÖFFLING et al. (1963) and MARTIN (1953) established disturbances of potency in 30%–55% of their male diabetic patients; these disturbances may be induced, according to SPRAGUE (1963), by dysuria.

The diabetic foot is characterized by cutaneous lesions and atrophy of the subcutaneous fatty tissue, by trophedema and trophic ulcers. These pathological changes are described in particular by ELLENBERG (1968), GREENBAUM (1964), and MARTIN (1953).

Paresis of the cerebral nerves in elderly patients usually occurs unilaterally as ophthalmoplegia with ptosis and diplopia (BISCHOFF 1974). According to LINQUET-

TE et al. (1968) and to MAN et al. (1968) the most frequent pupillary abnormality was low-grade anisocoria; reflex iridoplegia was recorded in rare cases only.

Relevant literature fails to show unequivocally to what extent the individual neurological symptoms are reversible. According to BISCHOFF (1974, 1977), regular-asymmetric amyotrophic and motor pareses of the cerebral nerves are remittant. PIRAT (1970) describes an equally high remission rate with sensomotor paralyses. MÜNZENMAYER (1971) established a substantially higher remission tendency among younger than among elderly diabetic patients examined by him.

Observations of the development of neurophysiological diseases by GREGERSON (1967) and by WARD et al. (1971) suggest that the best therapeutic results in all types of diabetic polyneuropathy are obtained by optimum metabolism control.

I. Prognosis

Whereas the diabetic had a mean survival time of 5–6 years in the "pre-insulin era" and the coma diabeticum was the most frequent cause of death, the prognosis for the diabetic today is influenced by a large number of factors. Apart from the age of the patient at the time of manifestation, these factors include the quality of metabolism control (Fig. 12) and above all the long-term complications resulting from diabetes. The average survival time has now risen to some 18 years in all age

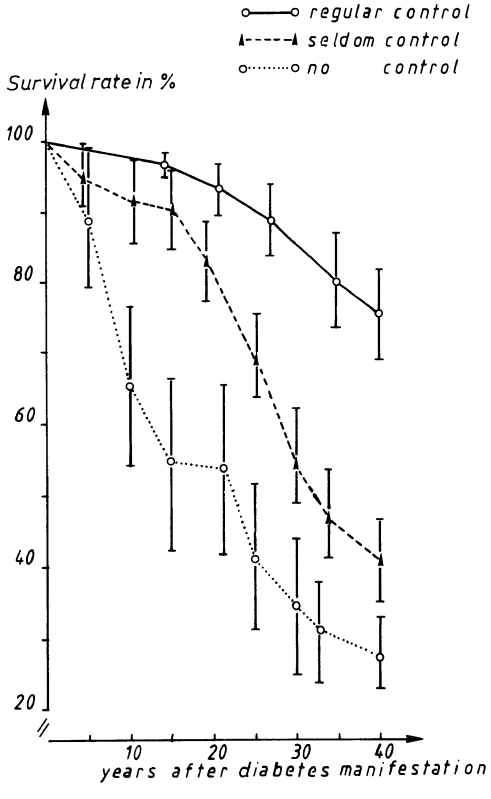

Fig. 12. Survival rate of type I diabetics under different stages of metabolism control. (DECKERT et al. 1978)

groups. That of infantile and juvenile onset diabetics is especially high; observations made over a period of some decades in the Joslin Clinic (MARBLE 1971) show that it is now some 30 years. The type I diabetic thus has the absolutely higher expectation of life.

Fifty-five-year-old diabetic patients, for instance, survive for an average of 13.8 years, whereas the mean survival time for the overall population of that age is 20.8 years, as can be seen in KRALL's analysis (1971). This investigation shows that a 10-year-old diabetic can be expected statistically to live to the age of approximately 54.3 years but a 10-year-old healthy subject to the age of 71.5 years. The discrepancy between healthy subjects and diabetics diminishes with increasing age: 35- or 40-year-old diabetics can expect to live only 10 years less than healthy persons.

As already stated, it is first and foremost the long-term complications that have a decisive influence on the prognosis for a patient suffering from diabetes mellitus. These complications include diabetic microangiopathy and macroangiopathy. The incidence of vascular diseases increases with increasing duration of diabetes (HAUPT and BEYER 1974). Arteriosclerotic vascular wall lesions in the sense of macroangiopathy occur more frequently with increasing age. According to HAUPT and BEYER (1974), BRADLEY (1971) and SCHETTLER and WOLLENWEBER (1974), arteriosclerotic vascular wall lesions can be detected earlier in the diabetic and tend to progress faster than in the subject with a healthy metabolism. Figure 13, based on a report by GENSLER et al. (1965), shows that approximately 10% of diabetics suffer from advanced vascular wall damage at the age of 40–50 years, and over 40% at the age of 60–70 years.

The connection between the extent of the macroangiopathic changes and the duration of the dysbolism has yet to be unequivocally explained. SCHOOP et al. (1967) found an absolutely positive correlation among their patients, whereas PENSE et al. (1973) and ALEXANDER (1967) were unable to establish any influence of the duration of the dysbolism on the development of the vascular lesions. Men and wo-

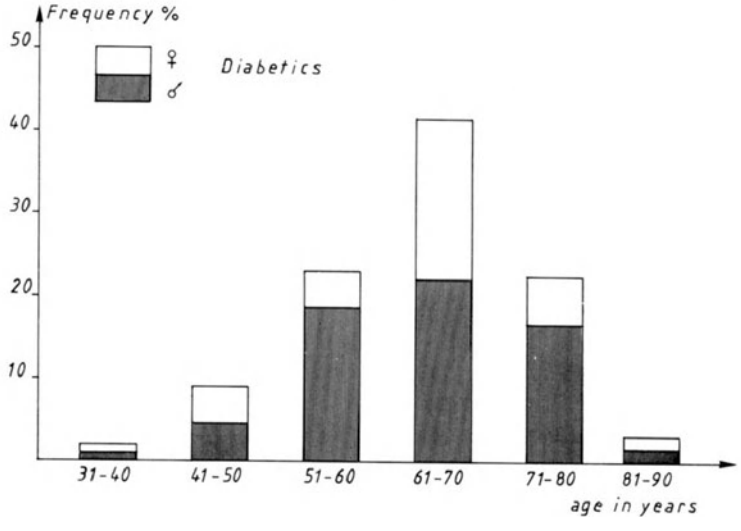

Fig. 13. Frequency of vascular disease in diabetics of different age. (GENSLER et al. 1965)

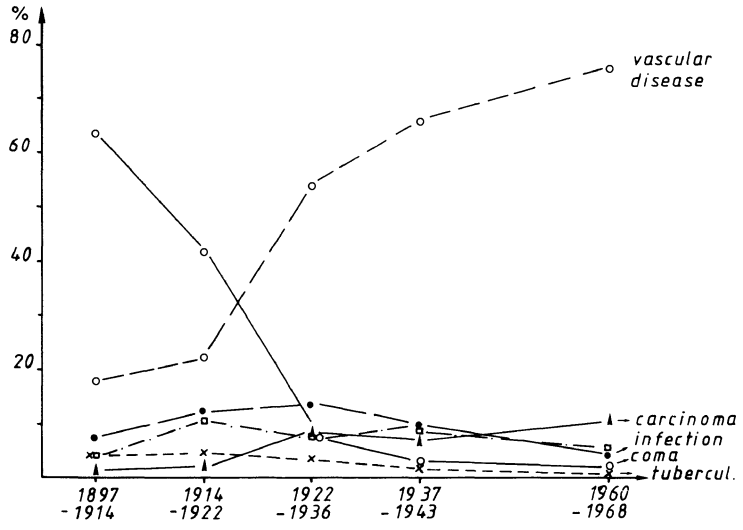

Fig. 14. Causes of death in different decades among diabetics at the Joslin Clinic. Adapted from MARBLE (1971)

men are equally affected by diabetic macroangiopathy, according to JAROSCH and SCHWEDER et al. (1975), whereas the male: female incidence ratio of general arteriosclerosis is 4: 1. ROOT et al., for instance established a fatal coronary occlusion in autopsy material 5 times more frequently among diabetics than among nondiabetics. Diabetic macroangiopathy apparently occurs sooner after the onset of diabetes in maturity onset (type II) than in younger diabetic patients. BINDING (1971) quotes the incidence of glomerulosclerosis at 53% in patients over the age of 50 and at 14% in patients under the age of 40, 6–10 years after onset of diabetes.

The main causes of death among diabetics have also undergone a radical change in the past few decades. Prior to insulin being introduced into diabetes therapy, almost 50% of diabetic patients in all age groups died in coma. The current coma mortality rate is a mere 1%, whereas vascular diseases prove fatal among almost 80% of diabetics, as shown by Joslin Clinic statistics up to 1968 (MARBLE 1971, Fig. 14).

Impaired glucose tolerance is characterized by low-grade insulin deficiency (JARRETT et al. 1979). The incidence of manifest diabetes mellitus is higher in persons with impaired glucose tolerance than in others. Relevant literature quotes the diabetes incidence at 1%–6% per annum (JARRETT and KEEN 1975b, 1976; JARRETT et al. 1979). According to an investigation by SARTOR et al. (1980), manifest diabetes mellitus had developed after 10 years in 17% of subjects with impaired glucose tolerance. The diabetic incidence in those patients observed by FITZGERALD and MALINS (1976) was 8.5% (45 patients) after 10 years. O'SULLIVAN and MAHAN (1968) established a manifest carbohydrate metabolism disturbance after 10 years in 52.5% of their patients.

The reduced glucose metabolization obviously promotes the development of vascular wall lesions, according to FLORA (1966), HAGENFELD and WAHLBERG

1967), and ALEXANDER (1967). Experiments on animals by MARQUIÉ et al. (1978) and clinical reports by JARRETT and KEEN (1976) and SARTOR (1980) indicate that sulfonyl urea therapy in conjunction with a diabetic diet may reduce the incidence of diabetes and the development of arteriosclerotic vascular wall lesions in persons with impaired glucose tolerance. A number of other authors such as STOWERS (1973), GUTSCHE (1979), and O'SULLIVAN and MAHAN (1968) were unable to establish any influence at all of sulfonamide derivatives on the diabetes morbidity rate. Forty-five to seventy-five percent of adipose diabetics displayed pathological glucose tolerance, according to publications by KARAM et al. (1965), DUNCAN et al. (1968), and SCHILLING et al. (1965); this was particularly marked in advanced age.

The question of whether consistent reduction in weight can prevent later manifestation of diabetes mellitus in these patients has yet to be answered. Studies by BERGER et al. (1976) and NEWBURGH (1939) indicate that glucose tolerance can be improved and manifestation of diabetes prevented by weight reduction.

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Sexual Function During Advancing Age

A. L. FINKLE

Among the interests of aging people is sexual contact. This presupposes an available, willing partner. It does not necessarily involve sexual intercourse, since interpersonal warmth, companionship, and association with the opposite sex suffice for many elderly people, married or not. For women in particular, a history of a satisfactory sex life, generally within the context of marriage, is usually a prerequiste for entering into a total relationship with another man in later life, when she may be widowed or divorced (FINKLE 1977).

A. Anatomic and Physiologic Considerations

Advancing age brings about physical changes of the genitourinary tract. The symptom of nocturia is most commonly noted, in both men and women. There may also be associated urinary incontinence, again more common in women (FINKLE 1978). Hormonal changes are associated with the menopause: local lack of estrogen may account for vaginitis and, in turn, dyspareunia. Despite the lack of definitive proof, benign prostatic hypertrophy probably has a hormonal etiology. In any event, alterations in urinary and sexual function occur with advancing age. In men, there is no change as to sexual desire and competency on the basis of benign prostatic hypertrophy – or, for that matter, prostatic cancer (although this malignancy is a highly common cause of death in aging men, second only to gastrointestinal cancer) (PETERSON and KENNEDY 1975). In other words, there is no biologic end point to sexual desire and competency, in male or female. It is true that sexual activity declines in frequency beyond the 60–70 year age range (FINKLE et al. 1959). The reasons for diminished sexual activity in advancing age are highly variable – but, for the most part, they reflect the experiential history of individuals and of couples.

Specifically, while it has been suggested and, more recently, even demonstrated (KARACAN 1978; BLAIVAS et al. 1980) that vascular changes occur in the major blood supply to the male genitalia, these changes are not of themselves the unequivocal basis for altered sexual competency. Otherwise stated, some men maintain sexual competency despite genital arteriosclerosis, while others do not. According to our present state of knowledge, the life experience of the individual and the availability of a willing partner are far more pertinent to his continuing sexual function than are neural or vascular factors.

Atrophic vaginitis in aging women is a well-documented postmenopausal condition (FINKLE 1978). Just as for men, the previous sexual patterns of a given woman are more important for continued sexual activity, with or without local discom-

fort, than the hormonal changes (FINKLE 1978). For example, diabetes has little influence upon sexual desire or competency of women (ELLENBERG 1977), whereas approximately one-third of diabetic men may suffer impotency, presumably on the basis of their illness (RENSHAW 1978).

B. Totality of Factors in Human Sexuality

My definition of human male sexuality, used for 20 years, refers to "... psychologic desire for coitus, manifested by penile erection suitable for intromission and pleasurable climax – although not necessarily ejaculation" (FINKLE et al. 1959). Furthermore, for purposes of correlating studies, it is required that the subject have participated in sexual intercourse within 1 year prior to or 1 year following a given point of reference, such as a surgical operation.

This definition involves a number of significant factors. For one thing, it presupposes a healthy person, irrespective of age, who has had prior sexual experience. The partner may be of the same sex or of the opposite sex. Simply developing penile erection is inadequate under the terms of this definition: thus, if an aging man were physiologically potent but, out of deference for a crippled arthritic wife, abstained from sexual intercourse, he would not fall within the limits of this definition.

It is presumed that, in human sexuality research, the interviewers ask questions about sexual activity in such a manner as to elicit forthright, accurate answers (MARTIN 1975). There is generally a large gap in age between an interviewer and an elderly person. This difference, per se, may cause inaccuracy to develop, truly due to a generation gap (SOLOMON and VICKERS 1979). Lastly, the manner in which the questions are voiced, as well as the morals of the era in which the subject grew up, have distinct quantitative and qualitative bearing on the reply (SNYDER and SPRITZER 1976). Perhaps it would be as significant as statistical analysis of data to note the attitude, atmosphere, and other related circumstances of the interview in order to draw accurate conclusions.

In brief, at an interview fixed in time, any person represents the continuum of activities, attitudes, religious training, education, sexual experience, and self-consciousness of a lifetime.

C. Male Psychogenic Impotency

Any man who has spontaneous penile erection (such as morning erection) or can stimulate himself to erection adequate for masturbation has an intact neurovascular mechanism. A man who has never had sexual intercourse and is incapable of developing erection in suitable circumstances with a willing partner may be identified as suffering from *primary impotency*. By contrast, any man who has had sexual experience and later becomes incapable of developing erection and of maintaining it to completion of the sexual act, or who has ejaculatory difficulties, is properly identified as suffering from *secondary impotency*.

Although more elaborate classifications are available in the literature, it is clear that these categories suffice for our present purposes.

This chapter considers mainly secondary impotency and later includes detailed description of my method of encouraging preservation of sexual potency in aging men.

D. Organic Basis of Impotency

Just as for any classification of organic or psychologic illness, disease, trauma, and neoplasm constitute the primary groups.

I. Systemic Illness

Diabetes mellitus is commonly recognized as contributing to, if not causing directly, a substantial incidence of male impotency (ELLENBERG 1977; RENSHAW 1978). Although it is estimated that 30%–40% of men with diabetes are impotent – and that the impotency is sometimes the first sign from which a diagnosis of diabetes is subsequently established – I am far more concerned with the 60%–70% of diabetic men who *retain* sexual potency (FINKLE and FINKLE 1977). Because the sex drive is not completely understood and is so forceful, and because there is no apparent relationship between good or poor control of the diabetes and preservation of potency, it is possible by urologic counseling to encourage a diabetic to successfully resume sexual intercourse despite continuation of his illness (FINKLE and FINKLE 1977). Drug therapy or dietary regulation need not be modified. A similar evaluation as to nonorganic basis for impotency in diabetic men was reported by WAXBERG (1978).

Numerous other illnesses may cause temporary or long-term impotency, mild or severe. Thyrotoxicosis, adrenal neoplasms, and Addison's disease are endocrine disorders that may be primarily or secondarily related to impotency, whereas chronic pulmonary obstructive disease would indirectly but significantly diminish, if not terminate, sexual activity (TRIMMER 1978).

II. Neurologic Deficit

In diabetes mellitus, it is the neuropathy, presumably at L_4, L_5, and S_1 levels, which interferes with erectile and ejaculatory potency. Disease of the central nervous system, such as multiple sclerosis or paresis, can impair potency, although prediction as to who will become the victim is beyond our current knowledge.

III. Vascular Problems

Certain partial occlusions of major vessels, as in Leriche's syndrome, can adversely affect sexual potency; and, of course, larger impediments to neurovascular flow, such as abdominal aneurysms, can be involved (News Reports 1979; VELCEK et al. 1980).

IV. Chronic Hemodialysis

Chronic hemodialysis is becoming increasingly important in survival of patients with kidney failure. For many reasons, some of which are poorly understood, patients who require long-term hemodialysis have a high incidence of sexual impotency. This subject and proposed treatments have been summarized in a recent article by CARRION et al. (1980).

V. Malignancy

While genitourinary neoplasms, per se, do not deter sexual activity until advanced cachexia, it is significant that chemotherapy interferes with normal sexual libido and potentia. Recently, CHAPMAN et al. (1979) described this effect in young women who were undergoing cytotoxic therapy of Hodgkin's disease.

VI. Cosmetic Factors

Facial disfigurement or direct deformity of the male genitalia impede sexual activity, the former because of emotional distress and the latter because of pain (as in Peyronie's disease). Shame that visible abnormalities of the genitalia may induce revulsion or rejection by a sexual partner is a deterrent to sexual activity. It is well known to every clinician that many men believe that their penis is too small; this belief is not only a source of embarrassment to the subjects but also of the erroneous conclusion that it is functionally deficient. The size of a penis has, of course, nothing to do with sexual prowess.

VII. Postoperative Impact

Direct effect on sexual function of abdominoperineal resection is well known (BABB and KIERALDO 1977). The incidence of impotency after such an operation for bowel cancer is greater than for a colitis operation, varying from 33% in one series to 95% in another, including in the latter both erectile and ejaculatory problems (BABB and KIERALDO 1977).

Parasympathectomy for peripheral vascular disease, and lymphadenectomy in diagnosis and treatment of primary genitourinary neoplasms, are also known to produce sexual impotency.

VIII. Drugs

There is increasing use of medication in the United States for all types of ailments. Tranquilizers, in particular, are widely prescribed. The most commonly abused self-prescribed drug is alcohol. Recent use of some antihypertensive agents has produced impotency of variable degree as an untoward side effect.

Drug usage in the elderly should be carefully evaluated and the generally greater impact of any drug in people of advanced age should be recognized. Catabolism and excretion of drugs are much influenced by impaired liver and kidney functions (FINKLE 1978). Judicious choice and prescription of medication for aging

individuals is urged. In the event that some drugs show unanticipated side effects, including adverse impact on sexual potency, suitable preparations with comparable pharmacodynamic effect but without the undesired side reactions can often be substituted.

Perhaps it is unwise and unnecessary to forewarn patients of potential side effects of drugs on sexual potency. Many people are highly suggestible. The very intimation from a physician that sexual function might be impaired can bring about that complication.

It is hoped that most patients will bring to the attention of the physician any diminution of sexual ability. Some are sufficiently sophisticated to notice the relationship of medication to potency. Others are aggressive enough to call a physician's attention to the problem. Many patients do not know for sure whether diminished potency is drug induced. Others are too timorous to discuss it. Therefore, when his patients take such medication, a physician can tactfully and subtly inquire whether side effects have occurred – with the aim of taking appropriate remedial steps.

It is my conviction, forged from long experience, that male sex hormones are administered much too casually in the treatment of diminished sexual potency. Specifically, when a patient complains of some sexual problem to a busy physician or to a clinician who is not secure in his own sexuality, all too commonly the latter will elect hormonal treatment. Some physicians believe such treatment appropriate (CHAPMAN et al. 1979). Others, perhaps following a scientific bent, may order rather elaborate, expensive blood and urine hormone tests before instituting male hormone therapy (New Reports 1979). There is no definitive evidence that lack of male hormone is involved in secondary sexual impotency. Quite to the contrary, RENSHAW (1978) has pointed out that it is seriously debated whether diminished serum or urine testosterone levels follow or result from sexual inactivity.

I believe that when sex hormones are given to a man who complains of secondary impotency, any improvement of his condition is the result of a triple interaction, namely, the desire of an *expectant patient* to be helped by a *purportedly useful* medicine given by an *ostensibly knowledgeable physician.* If favorable response ensues, it is generally short lived – lasting only for a period of several weeks. The patient may then return to the physician, who will give a larger dose, thereby starting a vicious cycle. Before long the patient has a recurrent problem. Having lost confidence in his original physician, he may see another. When he tells the second therapist that he has received hormone therapy, further treatment may be started with a large dose. All of this is generally unnecessary and can be avoided by taking a careful history, showing active interest in the problem, and offering moral support. If this listening-and-supportive method fails, other forms of therapy can be investigated and conducted.

E. Methods of Diagnosis of Sexual Impotency

Owing mainly to the work of KARACAN (1978) and SCOTT et al. (1979), both psychologic and laboratory investigations of impotency by means of mechanical aids have recently come into prominence.

I. Clinical Acuity of Interviewer

First and foremost, the interests and clinical acuity of an interviewer are essential to put a patient at ease and to acquire information about sexual problems, preferences, and approach to therapy.

Certain fundamental tenets have become part of my diagnostic and therapeutic armamentarium during the past 25 years. When a patient is referred by a colleague, by the physician of the patient's spouse, or by a former patient, he is usually ill at ease. It is the responsibility of the interviewer to enable the man to specify his problem. As questions are directed to the patient, it is important to ascertain whether the sexual problem concerns only himself, himself and his wife, or a lover. Situational impotency has to be considered: for instance, a man may not perform well sexually with his wife but may perform very well in an extramarital situation. While a man may feel that his quality or frequency of sexual intercourse is inadequate to satisfy his wife, that perception may not reflect reality. TRIMMER (1978) believes that all sexual counseling should be conjoint. I and many others disagree. It is sometimes desirable to interview a wife or friend, separately, to establish whether she is interested in intercourse at all, whether she will cooperate only to accommodate her lover, or whether the frequency or quality of sexual encounter that her partner believes is lacking is truly a problem (FINKLE 1978).

A patient may develop a semierection of the penis during sexual excitement. Out of fear that the penis may not become fully turgid, he may seek intromission prematurely. This may serve only to end the erection. Thus, a clever or experienced woman may find that manual stimulation will enable the penis to become and remain erect, and adequate for climax for one or both partners. A therapist may suggest to the patient that if lubrication of the vaginal lips with a water-soluble jelly is done just before intromission, the warmth and moisture of the vagina may suffice to induce full erection. Therefore, extensive psychotherapy of one or both partners, extensive "sensate education" as developed by MASTERS and JOHNSON (1976) and advocated widely by KAPLAN (1974), may not be required for everybody. Indeed no particular approach to therapy should be regarded as competitive with or superior to any other, but part of the total endeavor to help – a concept succinctly and gently broached by BOYARSKY and BOYARSKY (1978).

II. Testing Techniques: Mechanical Aids

Thorough clinical evaluations and mechanical studies (including penile plethysmography, cavernosograms, and even determination of serum hormone levels) have been promulgated recently (BARRY and HODGES 1978; KARACAN et al. 1978; SHROM et al. 1979). My approach for many years has underscored *clinical judgement* as a fundamental first step (FINKLE et al. 1959; FINKLE and FINKLE 1977; FINKLE 1978). The overall appraisal of the patient by an interested clinician is essential. Accessory data may support a primary clinical diagnosis, but rarely do they refute it. In other words, help may be given a patient despite what appears to be overwhelming organic illness or laboratory and radiographic evidence of overwhelming organic disease (FINKLE and FINKLE 1977; BABB and KIERALDO

1977; BOYARSKY and BOYARSKY 1978; SHROM et al. 1979; FINKLE 1980). This philosophy has been most effectively exemplified by the long-term longitudinal studies directed by PFEIFFER (1974).

F. Therapy of Male Impotency

I. Counseling

Rather than detail the techniques of urologic counseling advocated and developed by the author (FINKLE 1977, 1978, 1980; FINKLE and FINKLE 1977), it suffices to say that attentive listening and rendering emotional support – for suitable patients – constitute the most salient features. If it is clear early in the interview that a sexual problem is only the tip of the psychological iceberg, the urologist (or whoever the counselor may be) should at once refer the patient to appropriate, specialized psychotherapeutic facilities.

Reinstatement of self-esteem is the primary purpose of urologic counseling for the psychogenically impotent male.

Most cases of secondary impotency are psychogenic (KAPLAN 1974; FINKLE 1977; WAXBERG 1978; TRIMMER 1978; SHROM et al. 1979). This author has been able to help, in three sessions at weekly intervals, more than 75% of over 400 patients in the past 25 years (FINKLE 1979). This is not to say organic aspects are to be neglected – or to be treated entirely by surgical insertion of prostheses (CARRION et al. 1980; SCOTT et al. 1979). For example, with reference to the impact of hormones on impotency with advancing years, DAVIS (1977) has stated clearly that "... loss of sexual potency is so complex a process that it is unjustified to attribute it primarily to decreased androgen production." Although some advocate testosterone therapy, KOLODNY et al. (1978) are emphatic in pointing out, with particular reference to diabetic impotency, that "... results of testosterone therapy alone, or with chorionic gonadotrophin, have not been successful in our experience, or in the experience of Ellenberg" (ELLENBERG 1971). Finally, as noted previously in this chapter, urologic counseling can help overcome sexual impotency in the presence of serious, continuing organic problems.

II. Prosthetic Devices

During the past several years, men with irreversible organic impotency have been afforded an opportunity to have sexual intercourse. Semirigid plastic rods were used in a gradually perfected surgical technique by SMALL and CARRION (1980). In addition, since 1973 SCOTT et al. (1979) performed 245 operations wherein a reservoir of fluid is implanted in the suprapubic area. Pumps to propel a radiopaque fluid into channels surgically inserted in the penis and valves to empty those penile channels at will serve to simulate erection and detumescence. As previously noted, KARACAN and his colleagues working in conjunction with SCOTT (1978), sought to eliminate unsuitable patients, essentially by differentiating those with psychogenic and those with organic impotency. A few patients with psychogenic impotency have received the surgically implanted mechanism just described with good results.

In brief, patients offered penile prostheses are to be carefully selected. While this answer to organic impotency is not for everyone, it has helped a large number of people and is being applied in ever-increasing instances for growing numbers of men (FINKLE and TAYLOR 1981). As time goes on, it is probable that consensus will support urologic or other counseling techniques before a decision is made to insert any type of penile prosthesis. A surgical procedure can always be carried out, and only a short time is lost in an effort to accomplish reinstatement of sexual functioning by urologic counseling.

G. Therapy of Female Sexual Dysfunction

Abbreviated discussion in this chapter of sexual dysfunction in women is influenced by the fact that the author has had limited therapeutic experience with the sexual problems of aging women. Furthermore, hormonal treatment, primarily topical, is far more efficacious in the female than in the male – and is given more often by a gynecologist than a urologist.

Local application of estrogens to the vaginal mucosa generally improves local vascularization. This, in turn, leads to better natural lubrication of the tissues during precoital excitement and intercourse. After favorable response to topical estrogen therapy, the atrophic tissue becomes less susceptible to mechanical injury. A foreshortened atrophic vagina is not significantly improved by local estrogen therapy, but that is generally not a common or major problem. As noted previously, coitus can be substantially facilitated by local application of a water soluble jelly just before sexual intercourse. This, too, eases local discomfort. Suppression of dyspareunia is likely when there is a loving relationship, when the woman has had a past history of satisfactory sexual expression, and when her partner is tender and gentle (FINKLE 1981). It goes without saying that the complex psychological factors that influence sexual interest and activity in women are extremely important.

As noted previously, I have on occasion, during my years of urologic counseling, invited the female sexual partner to a separate interview. If her attitude toward maintaining or resuming sexual intercourse was not positive, I would usually prefer that the effort be discontinued. However, women are often quite willing to help overcome the declining sexual interest of a spouse when invited to do so by the urologist. In my urging the cooperation of the woman I generally point out that, as she aids the flagging efforts of her husband, both turn out to be winners. As the husband is taught by the counselor that his sexual efforts are not a contest, he understands that mutual love and exchange of sexual pleasure is the important achievement – often a concept in sharp contrast with the "hit and run" sexual activity of his younger years, whether with his wife or someone else. Most women who love their husbands can readily comprehend the embarrassment of the male. His sense of impaired masculinity can often be reversed by her tender attentions, both in the bedroom and out. Contrariwise, if a woman demeans an already self-humiliated male, chances for mutual satisfaction are extremely limited.

Althoug TRIMMER (1978) insists that all marital counseling to improve sexual relationships should be done *conjointly*, his opinion can be challenged. Whether

therapy is rendered individually, to the husband alone, to the wife alone, or to both together, on a one-to-one basis, as I prefer it, or whether the couple enters into some form of concurrent or group therapy, is not of definitive importance. What works for one individual or for one couple need not serve satisfactorily to others. Whatever path leads to favorable results is commendable.

H. Concluding Remarks

Sexual intercourse is not the end-all nor the be-all of human relationships, in young or old participants. It is but one facet of a sharing, caring exchange, and of the ability to provide gratification and pleasure to a loved one. In the opinion of the author, the discussion of sexual relationships is, without lofty phraseology, to be conducted within the framework of loving.

The psychodynamics of human relationships are far too complex a subject even to be touched upon in this chapter. It might in any case seem strange to hear a urologist expound on psychological mechanisms. Nonetheless, a human being must be studied as a total entity by all therapists, whether his presenting problem is urologic or other.

It is of prime interest to me that urologists be in the forefront of dealing with sexual problems (FINKLE 1980). Indeed, the urologist is often a primary physician in these areas – as well he should be. However, psychosexual problems have not been regularly taught to urologists during their training period. If these problems are not encountered and dealt with during a formal residency, it is not likely that the urologist will, de novo, undertake to confront them once in practice. Among other things, it is necessary that any therapist be secure in his own sexuality. He may not recognize his sense of security or the lack of it until he begins to witness such problems in his patients. Whatever the situation, it is only by investing one's time and only by being a careful listener that one emerges as a true physician.

The key issues of this chapter have been the evaluation of the patient as a total personality and the willingness of a therapist to invest time, to offer attentive listening, and to give moral support to his patient. Skill in dealing with psychogenic problems may be developed by any clinician, provided he honestly faces his limitations. If the patient's difficulty is so massive that the psychiatrically untrained attendant cannot capably deal with it, prompt referral to a specialized individual or facility should be made. On the other hand, not every patient requires extensive psychological study and treatment for every emotional problem.

It is my strong belief that a patient with recent secondary sexual impotency seeks mainly to reinstate his sexual competency. Time-counsuming and expensive thoroughgoing evaluations are generally not necessary. In my experience, supportive therapy, such as urologic counseling, suffices for most patients. For men with irreversible organic impotency, or for the few with psychogenic problems who would appear likely to benefit from surgically implanted penile prostheses, these modalities should be made available. The surgical complications are now minimal and the overall emotional benefits to the patient appear to justify the effort and expense of these operative procedures.

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Kidney and Urogenital System

The Kidney

L. SOURANDER

A. Characteristic Features of Geriatric Nephrology

Kidney diseases in the aged are the same as in younger age groups, but the process of aging modifies their clinical presentation. Clinical signs of kidney disease in the aged often differ from signs of these diseases in younger patients, depending on an altered somatic response to disease in advanced age and the simultaneous occurrence of age-induced changes in the kidneys.

The aging process per se is not only difficult to define but also to discriminate from changes induced by diseases. This is obvious in the kidneys, where structural and functional changes are present in the majority of the elderly. BROCKLEHURST (1971) studied the findings of 100 consecutive autopsies on geriatric patients at Farnborough Hospital in England and found only three cases showing a normal histology of the kidneys.

There are considerable difficulties in establishing defined clinical diagnoses of kidney diseases in aged patients. Kidney function tests and urinary sediment and bacteriological findings must always be interpreted taking the age factor into consideration. There is, however, a lack of basic information about what should be considered normal and what pathological in the aged.

The treatment of renal diseases in the aged follows the same principles as in younger subjects but the response to treatment in the aged is often different from that in younger subjects. The outlook for the aged patient with renal failure has recently been better, with hemodialysis and even renal transplantation available for more patients in higher age groups.

An important practical question in geriatric medicine is the clinical significance of bacteriuria, asymptomatic and symptomatic, and the need for treatment of this condition. Attitudes have varied from total neglect to a generous prescription of antimicrobial agents. The benefits and hazards of various therapeutic regimens have not been thoroughly assessed. Although a majority of cases of bacteriuria are due to lower urinary tract infections, chronic pyelonephritis is one of the commonest renal diseases in the aged.

Clinical examination of an elderly patient must always be made taking into account the possibility of renal disease, regardless of the fact that the actual symptoms and complaints are not pointing in this direction. The checking of renal function is also of importance for the control of treatment with drugs like digitalis, antibiotics and psychopharmaca. Some clinical examinations are informative in the aged, some are of a limited value and some must be practically abandoned. Noninvasive methods must be preferred; for example, echorenography is well suited to the aged.

Good geriatric practice requires routine checking of the renal status of an elderly patient and early detection of renal disease and deteriorated function of the kidneys. The treatment policy must take into consideration the special needs of the elderly both from the biological and psychosocial points of view.

B. Aging of the Kidney

I. Structural Changes

1. Loss of Nephrons

There is a considerable loss of nephrons with increasing age. This loss of nephrons is reflected in a decrease in kidney weight and in a loss of parenchymal mass. ROESSLE and ROULET (1932) showed a decrease of kidney weight after the age of 30, which is accentuated after 70. OLIVER (1952) reported an average weight of both kidneys of 250 g at 60 years of age, 230 g at 70 and 190 g at 80. MOORE (1931) counted the glomeruli and reported a decrease with advancing age. From about one million glomeruli at birth the number decreases to about 700,000 in the elderly, which is in accordance with the decrease of the weight of the kidneys. The changes start in the glomeruli and result in atrophy of the afferent arterioles. There is also an increasing number of aglomerular arterioles with age as has been shown by TAKAZURA et al. (1972). As a compensation for the loss and shrinking of the nephrons there is an enlargement of the residual nephrons.

2. Glomerular Changes

There is an increasing thickening and reduplication of basement membranes surrounding Bowmans capsule and the capillary tuft. HOWELL and PIGGOT (1948) and SHIMADA (1960) described hyalinization of the glomeruli. According to ZOLLINGER (1966), this change is, however, not induced by the aging process alone.

3. Tubular Changes

DARMADY et al. (1973) made a very extensive study using histological, electron microscopic and microdissection techniques on human cases from birth to 101 years. They showed that there is a steady thickening of the basement membrane of the convoluted tubules. When the mean length of the proximal convoluted tubules in the various age groups was plotted against the weight of the kidney it was seen that the apparent shrinkage of the tubules is a gradual process and cannot account for the somewhat sharp reduction in weight after 60 years as has been suggested. DARMADY et al. (1973) observed diverticula on the distal convoluted tubule and the numbers were shown to increase with age. They thought that these diverticula may play a part in the production of pyelonephritis and in causing recurrence of renal infections.

4. Vascular Changes

The progressive nature of the aging process is very obvious in the arterial tree. The changes start in the small arteries and arterioles and progress in a centripetal pat-

tern. The main arterial stems are affected later. LJUNGQVIST and LAGERGREN (1962), using microangiography after injection of contrast material, showed that after the age of 50, the renal afferent arterioles undergo changes, with spiralling and shortening of the vessels. The cortical aglomerular arteries increase with age. According to REYNES et al. (1968) and DAVIDSON et al. (1969), medullary blood is supplied by branches of the juxtamedullary cortical capillary plexus.

5. Renal Hypertrophy

In the young animal or man, unilateral nephrectomy is followed by renal hyperplasia and compensatory hypertrophy. There is a reduction in the degree of compensatory change in the aged kidney. The older kidney is also less able to respond to the stress of transplantation (DARMADY 1974).

II. Functional Changes

1. Renal Plasma Flow

As was shown by SHOCK (1952), using Diodrast clearance studies, there is a marked reduction in renal plasma flow with advancing age. HOLLENBERG et al. (1974) used the xenon washout technique and showed that the flow per gram of renal mass decreases and that this is especially marked in the cortical region. The reduction of renal plasma flow is partly dependent on a decrease in cardiac output and partly on the reduction of the renovascular bed (BROD 1968).

2. Glomerular Filtration

Many studies have confirmed the observation made by SHOCK in 1946 and DAVIES and SHOCK in 1950 that there is a decrease in glomerular filtration rate with advancing age. These studies of the glomerular filtration rate were performed using inulin clearance and endogenous creatinine clearance (BINET et al. 1952; DEROT and FAYE 1956; HERBEUVALL 1961). In a longitudinal study of renal function SHOCK et al. (1979) reported interesting observations. They stated that even though there is, on average, a decrement in clearance decade by decade even in early adult life, the longitudinal technique shows that there are some individuals who show a remarkable maintenance of their renal function. Some individuals show improvement in renal function with age. Subjects who died after the age of 55 had lower clearance values and showed a greater rate of decline in renal function than did those who were still living.

3. Tubular Function

The proximal tubular function has been studied by maximal excretion of paraamino hippurate and with Diodrast. There is a clear decrease in the tubular function with advancing age, and the decline is parallel with the decline of the glomerular filtration rate, indicating a dropout of nephrons with advancing age.

4. Fluid and Electrolyte Balance

The regulation of volume and composition of extracellular fluid is impaired in the elderly. A decrease in kidney function will affect the ability to maintain homeostasis. There is an age-related decrease in concentrating ability and a decline in water-conserving capacity. Under normal conditions this has no significance, but during limited fluid intake or loss of water aged patients develop volume depletion. Under salt loads the elderly are also at risk from volume expansion. The lowered glomerular filtration rate is responsible for the lack of ability to excrete an excessive salt load.

Renal response to acute reduction in salt intake has been studied by EPSTEIN and HOLLENBERG (1976), who showed that the half-time for reduction of urinary sodium after salt restriction was 17.6 h in the young and prolonged to 30.9 h in old subjects. This salt-losing tendency can lead to depletion of the extracellular fluid volume when salt intake is reduced.

C. Disease of the Kidney – Geriatric Aspects

I. Renovascular Disease

Arteriosclerotic changes in the kidneys are very common and obviously responsible for a great number of cases of chronic renal failure in the elderly. It is, however, difficult to differentiate histologically between pyelonephritis and nephrosclerosis. The glomeruli are destroyed as a result of changes in the afferent glomerular arterioles. Renal ischaemia is induced by narrowing of the interlobular arteries. It is surprising that malignant hypertension is not more common in the elderly in spite of the frequent vascular changes found in autopsies.

Urinary findings are often without diagnostic significance even in cases showing a chronic renal failure. Coexisting pyelonephritis is very common.

In vascular disease, examination of the scars (DARMADY and MACIVER 1980) shows that they consist almost entirely of shrunken and atrophic nephrons. The glomeruli are completely obliterated and are closely packed together with some intervening areas of fibrosis. In places, lymphocytic infiltration is seen, particularly near the capsule. The lesions tend to be wedge shaped, and are not scattered indiscriminately throughout the kidney.

Macroscopic examination of the kidney reveals the presence of scars on the surface. The capsule is firmly adherent to the underlying tissue. The changes are similar in chronic pyelonephritis and are difficult to differentiate.

II. Pyelonephritis and Urinary Tract Infection

Acute pyelonephritis in the aged is not very common and presents with symptoms which are not different from those in younger age groups. The diagnosis of chronic pyelonephritis in the aged is often beset with difficulties. Autopsies reveal a higher prevalence of chronic pyelonephritis than clinical examinations. The prevalence of chronic pyelonephritis in the aged ranges in different autopsy studies between 20%

and 28% (BAUMANNIS and RUSSEL 1959; BRUCKEL and WINCKLER 1963). According to KASS (1955) pyelonephritis is clinically diagnosed in only one-fifth of those cases detected at autopsy. As has been pointed out by FREEDMAN (1967) the non-specificity of the pathological features of chronic pyelonephritis is most likely to be partly responsible for this discrepancy. On the other hand, the interpretation of clinical findings is difficult in the aged. The best clinical evidence of chronic pyelonephritis is obtained by radiological examination. Intravenous urography cannot, however, be considered indicated in the great number of patients showing abnormal urinary sediment and bacteriuria. In clinical practice, most cases of chronic pyelonephritis are diagnosed by means of the interpretation of the urinary sediment, bacteriological urinary findings and serum creatinine values in close connection with a follow-up of the patient. In more advanced cases of pyelonephritis with uraemia the clinical diagnosis has a high reliability, as has been shown by SOURANDER et al. (1979) in an epidemiological study of uraemia. In this study of patients with a serum creatinine value exceeding 230 μmol/litre the previous clinical diagnosis changed in only 2% of the autopsies.

In cases with a normal serum creatinine value and no radiological changes indicating renal parenchymal damage the occurrence of significant bacteriuria is obviously at least in some cases due to an infection in the renal parenchyma.

1. Bacteriuria and Pyelonephritis

Significant bacteriuria is one of the most common findings in elderly patients. The occurrence of bacteriuria in the aged population has been studied by SOURANDER (1966) and BROCKLEHURST et al. (1968), and the findings were very similar. In about 20% of the aged and in even higher percentages in hospitalized patients bacteriuria is present. There are many questions which have been answered in different ways. Why are women affected more often than men? What is the renal involvement? What is the correlation between bacteriuria, decrease of renal function and development of arterial hypertension in the aged? What is the prognostic significance of bacteriuria? When and how should it be treated?

Bacteriuria in the aged is usually asymptomatic. In the epidemiological study of SOURANDER (1966) 94% of the subjects with significant bacteriuria were asymptomatic. The most common pathogen is *E. coli*, which, like many other pathogens producing urinary tract infection, is mostly derived from the patients own faecal flora. The most common pathway of the bowel organisms is through the perineum to the periurethral area. In women the Enterobacteriaceae which colonize the vagina are frequently identical to those isolated from the urine in patients with recurrent urinary tract infections (STAMEY and SEXTON 1975). Certainly incontinence and poor hygiene are factors increasing the risk of urinary tract infection in the aged. An interesting observation is the role the pili of the micro-organism play in attaching it to the periurethral epithelial cells. The attachment depends, on one hand, on the degree of piliation (SVANBORG-EDEN 1978) and, on the other hand, on the number of "receptor" sites of the periurethral cells for *E. coli* (Fig. 1) (KÄLLENIUS and WINBERG 1978).

Obviously the most common mechanism which promotes infection of the renal pelvis and parenchyma is ascending infection. In the aged there is not only a good

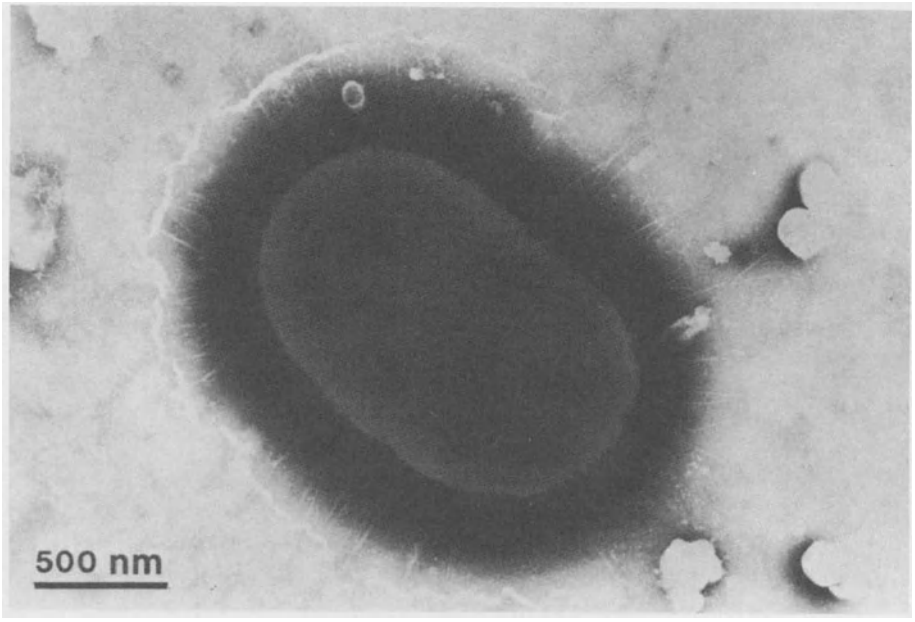

Fig. 1. *E. coli* strain, isolated from a patient with pyelonephritis. The whole cell is covered with pili, thickness about 7 nm and length about 0.5–1.0 μm. (Courtesy of Dr. T. KORHONEN)

chance of the bowel organisms being present in the peri-urethral area but also of entering the bladder. The defensive mechanisms, the hydrokinetic and mucosal (COX and HINMAN 1965), are obviously weakened in the aged.

There are several direct and indirect methods available for the assessment of the site of the bacterial infection. Urinary tract infections are usually divided into lower and upper urinary tract infections. Discrimination between these has also been called "level diagnosis". Among the direct methods the bladder wash-out described by FAIRLEY et al. (1971) seems to be beneficial in geriatric practice. The method is briefly the following: A catheter is introduced into the bladder, which is filled with 50 ml of a solution containing 0.1% neomycin. The neomycin sterilizes the bladder contents. Fibrinolysin is also added to the solution with the aim of removing the fibrinous exudate. The bladder is then washed out with sterile water. After the bladder wash-out several urine specimens are collected. Patients with renal infection will have bacteria in the post-wash-out samples.

Of the indirect methods of level diagnosis the fluorescent antibody method seems promising. Organisms deriving from the renal parenchyma are coated with antibody which can be detected with the use of fluorescein-labelled anti-IgG^{10} and which probably represents antibody produced in the kidney. The method is, however, not yet clinically useful.

An interesting but still unsolved question is what role the L-forms of the bacteria play in causing recurrent pyelonephritis. GUTTMANN et al. (1965) and CONNER et al. (1968) have reported that L-forms have been isolated in most cases in old patients with chronic urinary infections, often with severe underlying diseases.

2. Predisposing Factors

Hydrokinetic mechanisms are weakened by anatomical changes in the bladder and by disturbed neuromuscular function of the bladder. The presence of obstruction is very clearly a leading cause in the development of renal infection in men. Prostatic hypertrophy and carcinoma account for the vast majority of infections in men. Obstruction can also be promoted by changes in the bladder neck, malformations, nephro- and ureterolithiasis and neoplasms. In women prolapse conditions and even slight descensus of the vagina increase the possibility of urinary tract infection (SOURANDER et al. 1965). In both sexes neurological disorders and diabetes are important factors in the development of urinary tract infection. An atonic bladder is at risk of infection.

The role of ureteral reflux seems to be of no significance in the aged in the promoting of infection, but it can be a mechanism which enhances the risk of renal involvement (PARVINEN et al. 1965).

The protective effect of prostatic secretion against bacterial infection might partly explain the great difference in the occurrence of non-obstructive infection in males and females. Other protective mechanisms are localized to the bladder mucosa. These are, however, not clear. Postmenopausal changes in women with estrogen deficiency are probably factors which decrease the mucosal resistance to infection in elderly women.

A weakened immunological response to infections in the aged can also be of importance in the development of urinary tract infections.

An important factor promoting urinary tract infection is the application of indwelling catheters in the aged. In 100 consecutive autopsies performed on geriatric patients in the University Hospital of South Manchester CARTY et al. (1981) found chronic pyelonephritis in 22 patients and acute pyelonephritis in four patients. In 14 of these 22 patients with chronic pyelonephritis there had also been significant bacteriuria in life; in seven cases of the autopsied pyelonephritis patients no significant bacteriuria obtained. There was a clear correlation between infected renal pathology and indwelling catheter in life. The findings showed that in 30% of the clinically manifest urinary tract infection cases there were patho-anatomical changes of renal infection. This is in good concordance with estimations that in one-third of the elderly with bacteriuria pyelonephritis changes can be expected (SOURANDER et al. 1965).

3. Urosepsis

Urosepsis is a sepsis originating from the kidneys or the urinary tract. It is caused by Gram-negative pathogens and is considered a grave disorder with a high mortality.

ESPOSITO et al. (1980) reported a retrospective analysis of 100 consecutive geriatric patients with community acquired bacteremia. In 34% the bacteremia originated from the urinary tract. Out of these 34 patients only six had symptoms suggestive of urinary tract infection and eight had an indwelling catheter. SOURANDER and SAARIMAA (to be published) studied 40 consecutive cases of septicaemia in patients over 65 years of age admitted to a community hospital and in two cases

considered the source of infection an indwelling catheter and in 16 cases the urinary tract. In both studies the temperatures ranged from 37.2 °C to 42.2 °C. Urosepsis usually presented with symptoms like nausea, diarrhoea, skin rush and confusion. Mortality is high but can be decreased when the detection of the condition is early and the treatment started immediately. In various reports the mortality rate is between 20% and 40%. Out of the 34 cases reported by ESPOSITO et al. (1980) five died. In fatal cases urosepsis is usually complicated by shock. According to SENECA and GRANT (1976) older patients are susceptible to the consequences of instrumentation and surgical operations involving the genito-urinary tract. A decreased resistance towards infections in aged patients with grave diseases renders them susceptible to septicaemia.

4. Treatment of Urinary Tract Infection in the Aged

As a general rule, asymptomatic urinary tract infection in the elderly should not be treated. Therapy is only indicated when the patient has distressing symptoms. In some cases a foul smell of the urine in incontinent patients can be considered as an indication for treatment. This attitude has been widely accepted among geriatricians since it has been stated that asymptomatic bacteriuria in the aged is a benign condition with very slight or no impact on renal function (BROCKLEHURST 1977).

Although the estimation of the level of infection is without doubt of diagnostic interest, it does not greatly influence the decision to treat the patient, nor does it have predictive value for the success of treatment (CATTELL et al. 1973).

A more active attitude has been proposed by DONTAS and his group, who claim that urinary tract infection in the aged is correlated with a deterioration of renal function and also with the development of arterial hypertension (DONTAS et al. 1966; DONTAS et al. 1968; MARKETOS et al. 1969; MARKETOS et al. 1970).

There are some groups of patients which can be considered at risk, namely those with already existing renal disease. Patients with obstructive nephropathy, diabetic nephropathy and patients with adult polycystic renal disease should be treated when bacteriuria is present.

Proteus infections must be considered more dangerous than *E. coli* infections because *Proteus* is mobile. According to ASSCHER (1980), in urinary tract infections caused by a *Proteus* strain, ascending infection involving the kidneys is almost invariably established. The vast majority of bacteriuria cases are caused by *E. coli*, *Proteus* being present in only about 6% (SOURANDER 1966).

When the decision to treat the elderly patient with urinary tract infection has been made, the following facts must be remembered: the antimicrobial agents affect not only the patient and patient's microbes but also the microbiological environment. Benefits and hazards including the possibility of creating bacterial resistance must be evaluated before the treatment decision is made (Table 1).

In short-term treatment of urinary tract infection sulphonamides, nitrofurantoin, co-trimoxazole and plain trimethoprim are suitable chemotherapeutic agents as are also amoxicillin and cephalexin in the group of antibiotics. Sulphonamides and plain trimethoprim should be avoided in the hospital routine because of the disadvantage of creating resistant bacterial strains. As a general rule those antimi-

Table 1. Recommendations for use of drugs in urinary tract infections. KASANEN (1982)

Drug	Out-patients	Hospital	Degree of clinical severity			Renal insufficiency		
			Mild	Mode-rate	Severe	Mild	Mode-rate	Severe
Nitrofurantoin	+++	+++	+++	+	−	−	−	−
Sulphonamides	++	+	++	+	−	++	+	−
Trimethoprim	+++	+	+++	++	−	+	+	−
Trimethoprim/ Sulphonamides	+++	++	+++	+	+	+	+	−
Methenamine hippurate	++	++	++	+	−	+++	+++	+++
Amoxicillin	++	+++	−	++	+++	+++	+++	+++
Cephalexin	++	+++	−	++	+++	+++	+++	+++

+++ = recommended; ++ = suitable; + = usable; − = not recommended

crobial agents which do not have a considerable effect on the bowel flora are preferable. Nitrofurantoin and cephalexin are favourable in this respect; sulphonamides have the disadvantage of producing bacterial resistance quite readily. Trimethoprim should also be avoided in geriatric hospital patients for the same reason. Tetracyclines are not acceptable in the treatment of urinary tract infections in the aged because they can deteriorate an already impaired renal function. Gentamycin and tobramycin are used in the treatment of *Pseudomonas* infections.

There have been different opinions on the duration of the treatment, beginning with recommendations for treatments which last for only 1 day. In the aged it seems clear, however, that treatment should last 5–7 days, and there is no convincing evidence that a shorter treatment could be recommended. Renal function must be checked before onset of treatment, and a correction of the dosage should be carried out in cases with an impaired renal function. Normal serum creatinine values can be misleading in this respect. Clearance estimations should be performed if possible. Long-term treatment must be restricted to the few cases where the indications for this treatment have been carefully evaluated.

5. Resistance Problems in Geriatric Wards

Bacterial resistance to antimicrobials is a problem in geriatric hospital wards. Since urinary tract infections are derived from the faecal flora, the development of resistance of the bowel flora is of utmost importance. Long-term suppressive treatment with antibiotics and chemotherapeutics can alter the sensitivity pattern. The transferable resistence is of special interest. In this case molecules of DNA, R-plasmids, carry genes that determine resistance to antibacterial agents. These R-plasmids are transferable between bacteria and can also be transferred between different Enterobacteriaceae. In long-term treatment of urinary tract infections nitrofurantoin is suitable because R-plasmid resistance is unknown for nitrofurantoin.

HUOVINEN et al. (1982) reported that trimethoprim resistance in urinary tract pathogens was found in 38.3% of strains from a hospital with predominantly psy-

chiatric and geriatric departments and in only 12.2% of the strains from the university hospital situated in the same city, Turku. One-third of the strains showed transferable resistance. There was no difference between the two hospitals in this regard. The drawback of the widespread use of trimethoprim in the region is the development of resistant strains, which are especially found in long-stay wards. This is partly explained by the fact that many patients have been transferred from the university hospital, where the treatment with trimethoprim in many patients had previously been started.

SOURANDER et al. (to be published) performed a 2-year follow-up study on the changes of the resistance patterns in the City Hospital of Turku. All patients in three geriatric long-stay wards were checked for bacteria in the urine initially and every 6th month. The use of antimicrobial agents in urinary tract infections in two wards was limited to only those patients who presented an infection with fever or with distressing symptoms. All cases with asymptomatic bacteriuria or cases with mild urinary symptoms were left untreated. No long-term treatment was performed. In the third ward the previous treatment policy was unchanged. Patients presenting significant bacteriuria were treated with antimicrobials, and after the urine was rendered sterile many of the patients received prophylactic long-term treatment mainly with methenamine hippurate. The results of the 2-year follow-up were the following: In the wards with restricted treatment policy the number of bacterial strains went up considerably. These were, however, dominated by *E. coli* and *Streptococcus faecalis*. The number of *Proteus* strains was unchanged. In the wards with restricted treatment there were initially six *Pseudomonas* strains and at the end of the follow-up two. In the ward with unrestricted treatment there were initially two pseudomonas strains, and after 2 years four. Even when the *E. coli* strains increased in number there was a favourable change in the antimicrobial resistance patterns. Initially resistant strains decreased in number in favour of sensitive strains.

There is obviously a great need for a critical attitude and a restrictive treatment policy for the use of antibiotics especially in hospitals. GRÜNEBERG and BENDALL (1979) reported a hospital outbreak of plasmid-borne trimethoprim resistance in pathogenic coliform bacteria which was associated with heavy use of co-trimoxazole, sulphonamides and ampicillin, but was controlled by isolation of the patients and restriction of antibiotic use.

6. Treatment of Patients with Indwelling Catheters

A urinary catheter left in place for more than a few days will invariably give rise to bacteriuria (BROCKLEHURST 1977; BROCKLEHURST and BROCKLEHURST 1978). The most obvious danger is the development of symptomatic infection, often associated with fever or in some cases life-threatening urosepsis. The development of renal infection in patients with indwelling catheter is very much a question of time and in this respect the elderly with a reduced life expectancy are in a favourable situation.

The treatment of bacteriuria with antibiotics in patients with indwelling catheter should be restricted to those who have symptoms – in the asymptomatic cases antibiotic treatment should be avoided (BROCKLEHURST and BROCKLEHURST 1978).

BROCKLEHURST and BROCKLEHURST (1978) studied the effect of preventing infection using continuous hexamine hippurate or wash-outs with noxythiolin and considered this kind of treatment useless. Wash-outs did, however, diminish leakage.

The disadvantage with the use of short-course antibiotics or long-term antimicrobial treatment of patients with indwelling catheters is obviously not only the development of resistant bacterial strains. If an *E. coli*-infection is repeatedly treated with antibiotics there is good chance of the next infection being produced by a *Proteus* strain and finally by a *Pseudomonas* strain. A generous antibiotic treatment policy in patients with indwelling catheters is not only useless but harmful both for the patients and their environments – especially the geriatric long-stay ward.

NORBERG et al. (1979) studied the effect of short-term high-dose treatment with methenamine hippurate on urinary infection in geriatric patients with an indwelling catheter. The duration of the treatment was 34 days. The patients were administered 2 g methenamine hippurate 3 times daily. The authors claimed that during the treatment the number of catheter changes was halved, and complications associated with indwelling catheters, bacteriuria and pyuria, reduced.

7. Prognostic Significance of Bacteriuria

The problem of the significance of covert urinary tract infection has been studied by means of the determination of survival. SOURANDER and KASANEN (1972) showed in a 5-year follow-up of bacteriuria in the aged that the infection was often intermittent and that the great majority of significant bacteriuria disappeared during the 5-year follow-up period. In a smaller proportion of cases the bacteriuria persisted. The female patients with bacteriuria had an increased mortality rate (Table 2), but this was not caused by renal failure. The authors concluded that the

Table 2. Mortality in 5 years in different age groups. Subjects without and with significant bacteriuria. Light sector: subjects still living in 1968; dark sector: subjects deceased between 1963 and 1968 (SOURANDER and KASANEN 1972)

	Age group, years (1963)				Total
	65–69	70–74	75–79	80–	
Men					
No bacterial growth or <100,000 bacteria/ml	40 14	35 16	20 21	9 27	182
>100,000 bacteria/ml		2 1	3 3	2 8	19
Women					
No bacterial growth or <100,000 bacteria/ml	35 5	34 6 $X^2=2.2$	21 14 $X^2=8.2$	7 15 $X^2=2.1$	137
>100,000 bacteria/ml	9 1	13 5	7 10	4 18	67

increased mortality rate could be explained by the fact that bacteriuria is more common among subjects in poor health and among inmates of institutions. The patients with significant bacteriuria often suffer from other concurrent disease, such as cerebrovascular disease, senile dementia, or cardiovascular disease.

MARKETOS et al. reported in 1969 that bacteriuria in the aged is often coincidental with arterial hypertension. Patients in institutions are more susceptible to hospital infections, and catheterizations increase the rate of infection.

DONTAS et al. (1981) studied the effect of asymptomatic bacteriuria on survival in 342 healthy residents of a home for the aged in Athens. Out of these 76 subjects (22%) had bacteriuria. The authors found a reduction in survival of 30% to 50% among subjects with bacteriuria. There were no differences in age distribution, blood pressure, hematocrit, smoking habits, cholesterol, or myocardial changes between bacteriuric and non-bacteriuric subjects. Bacteriuric subjects had a median survival of 30 to 34 months regardless of sex of age at entry, in contrast to non-bacteriuric subjects, who survived for 20 to 41 months longer than bacteriuric subjects. The authors claimed that bacteriuria is an important factor associated with a statistically significant reduction of survival in both sexes, that the effect of bacteriuria overrides that of age and sex, and that in contrast to bacteriuria, extremes of blood pressure do not appear to influence survival.

The conclusions made by DONTAS et al. have been criticized by KIRKLAND and ROBINSON (1981), who draw attention to the fact that diseases of the central nervous system, cerebrovascular accidents and senile dementia could account for both reduced life expectancy and bacteriuria. They stressed that it may be premature to consider treating elderly patients with asymptomatic bacteriuria in the expectation that treatment will improve their survival. According to DONTAS even if the relation between bacteriuria and shortened survival is shown to be non-causal, well-controlled trials of long-term treatment should be carried out to test the potential reversibility of this condition.

III. Acute Glomerulonephritis

Presentation of acute glomerulonephritis in the aged differs considerably from that in younger subjects. The disease has previously not been taken in account practically in geriatric medicine and considered non-existent. The aetiology of the disease is diverse in the higher age groups and is not limited to streptococcal infection. The correct diagnosis is often difficult to establish because the clinical picture does not always point in the direction of renal disease. The initial impression is usually that of worsening of some pre-existing illness, congestive heart failure or infection. The most common manifestations are those of oedema, dyspnoea, circulatory congestion, infection and non-specific symptoms such as anorexia, nausea, vomiting, diarrhoea and muscular pain. Hypertension is less common. In 1971 and 1973 ARIEFF et al. summarized the principle facts about acute glomeulonephritis in old people. The first to draw attention to these facts were NESSON and ROBBINS (1960), BERLYNE et al. (1964) and BOSWELL and EKNOVAN (1968).

The diagnosis appears to need a needle biopsy (LEE et al. 1966, BERLYNE et al. 1964). Laboratory findings are often non-specific. Protein and red blood cells are variably present in the urine. Azotaemia, anaemia, elevated erythrocyte sedimen-

tation rate and hypoalbuminaemia are also variable. Hypertension or oedema usually indicates a post-streptococcal aetiology and favourable prognosis. The prognosis of acute glomerulonephritis in the elderly is not as grave as previously believed. Pulmonary oedema secondary to circulatory congestion and pulmonary infection are the most common causes of death. Corticosteroids in combination with immunosuppressive agents can give a favorable response. In good geriatric medicine this entity should be considered in old patients in the presence of urinary abnormalities of unknown aetiology especially after streptococcal and non-specific skin infections. Rapidly progressive glomerular nephritis in the aged has been reviewed by MONTOLIU et al. (1981). They consider it to be the most common primary glomerular disorder in adults over 60 years of age. The dominant histological feature of this disorder is extracapillary proliferation affecting the glomeruli and formation of crescents. The prognosis is generally poor.

IV. Nephrotic Syndrome

Nephrotic syndrome in the elderly is often associated with a systemic disease, especially diabetes mellitus but also renal amyloidosis, malignancies, systemic lupus erythematosus, polyarteritis, renal vein thrombosis and heart failure (FINKELSTEIN and HAYSLETT 1976). FAWCETT et al. (1971) reviewed 100 consecutive adult cases of nephrotic syndrome, 25 of whom were over 60 years of age. Excluded were patients with a preceding chronic glomerulonephritis and patients with diabetes. They compared the histology of the glomeruli of these elderly patients with that of younger patients and concluded that the incidence of membranous glomerulonephritis was similar in the two groups, but that proliferative glomerulonephritis was more common in the younger. Minimal-change disease and amyloidosis were seen with equal frequency in both age groups. Five of the elderly patients with minimal change lesion were treated with prednisone and complete remission occurred in at least four. As is the case with acute glomerulonephritis, the correct diagnosis usually requires a needle biopsy. The right choice of treatment requires diagnosis of the renal condition. The treatment of nephrosis due to amyloidosis with steroids is contraindicated. The same can also be stated in diabetic nephropathy. The nephrotic syndrome secondary to lipid nephrosis without focal glomerulosclerosis responds to steroid treatment with a complete resolution of proteinuria. FINKELSTEIN and HAYSLETT also recommend cyclophosphamide as an alternative treatment in elderly patients. Immunosuppressive therapy and steroids have not been beneficial in membraneous nephropathy.

V. Other Renal Diseases

Nephropathy caused by urinary obstruction is usually a disease in men with prostatic hypertrophy. When obstruction is corrected the renal function is usually restored if the renal trauma is not irreversible. Urinary infections must be treated because there is a risk of ascending infection and renal damage. Adult polycystic disease is occasionally found in elderly patients with recurrent urinary infections, haematuria and azotaemia. The treatment of infection and hypertension is important (RALSTON 1975). Papillary necrosis occurs in the aged with diabetes, obstruction or analgesic abuse.

D. Uraemia

I. Acute Renal Failure

The aetiological factors leading to acute renal failure in the elderly are the same as in younger individuals. KUMAR et al. (1973) reviewed acute renal failure in the elderly (Table 3). In the majority of cases renal failure was attributed to ischaemic renal damage. Dehydration and electrolyte imbalance were important factors as well as major surgery and hypotension in connection with various severe diseases like myocardial infarction. Acute renal failure was caused by primary renal disease in 10 out of 122 cases. Dialysis was required in 24.6%, in most cases carried out by the peritoneal route. The mortality was 57.3%.

KASSIRER (1969) has reviewed athero-embolic renal disease and claims that it is a disease which in elderly patients promotes acute renal failure and that athero-embolism to the kidney and acute renal failure is a geriatric entity.

Table 3. Causes of acute renal failure (KUMAR et al. 1973)

Aetiology	Males	Females	Total
Multifactorial acute renal failure		29	
Dehydration and electrolyte imbalance	30	29	59
Major surgery	17	21	38
Hypotension	13	20	33
Bronchopneumonia	7	6	13
Antibiotics	5	4	9
Jaundice	2	4	6
Septicaemia	2	4	6
Diuretics	3	1	4
Contrast media	2	0	2
Primary renal disease			
Pyelonephritis	1	5	6
Acute glomerulonephritis	0	1	1
Acute polyarteritis	0	1	1
Focal embolic nephritis	1	0	1
Renal-vein thrombosis	1	0	1
Obstructive renal failure			
Enlarged prostate	18	–	18
Bladder retention[a]	4	5	9
Acute fulminating obstructive pyelonephritis	2	5	7
Calculus anuria	1	3	4
Carcinoma bladder	1	3	4
Carcinomatosis (ureteric obstruction)	0	2	2
Carcinoma ovary	–	2	2
Fibroid	–	1	1

[a] Due to causes other than prostatic hypertrophy. This includes one patient who could not micturate while forced to be supine because of bilateral retinal detachment

II. Chronic Renal Failure

Chronic renal failure in the elderly is mainly due to chronic pyelonephritis, renovascular disease or chronic glomerulonephritis. The aetiology is the same as

in younger individuals but diseases like myeloma and amyloidosis are more frequent in the older age groups. The geriatric aspects of chronic renal failure are the clinical presentation and the treatment policy and response to treatment in the elderly. In cases of azotaemia the condition can be due to renal disease or it can be pre- or postrenal. The most common causes of prerenal azotaemia are dehydration, congestive heart failure and negative nitrogen balance and increased catabolism. Postrenal azotaemia is associated with obstruction caused by a variety of diseases.

An epidemiological study of uraemia in the aged was performed in south-west Finland by SOURANDER et al. (1979), and 668 cases of uraemia – a serum creatinine value exceeding 230 μmol/litre = 2.6 mg-% – were detected in the region. Out of these 372 were 65 years or older. In other words this means that more than half

Table 4. Clinical diagnoses in 112 subjects with prerenal uraemia (SOURANDER et al. 1979)

Myocardial infarction		24
Infections		18
Pneumonia	10	
Sepsis	5	
Other infections	3	
Diabetes		13
Cerebral thrombosis		11
Malignancy		8
Congestive heart failure		6
Drug therapy		6
Other thromb. emb.		5
Other causes		16

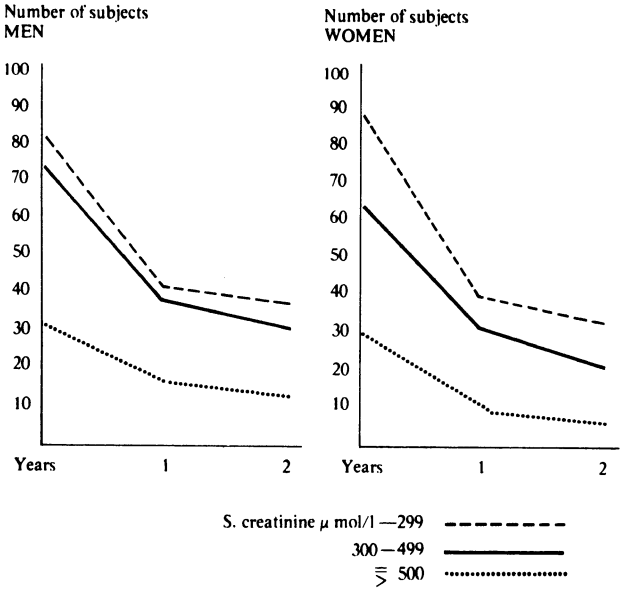

Fig. 2. Patients with uraemia alive after 1 and 2 years. (SOURANDER et al. 1979)

of the uraemic subjects in the region concerned were aged. Compared with younger age groups both prevalence and incidence rates of uraemia were about ten-fold in the aged. Fifty-one percent of the women suffered from chronic pyelonephritis, which was more common in women than in men. The most common cause of uraemia in men was postrenal obstruction, which occurred in 35%. In the majority of these cases there was also pyelonephritis. Prerenal uraemia was present in 31% of the women and in 29% of the men (Table 4). Among other diagnoses the following were the most frequent: nephrosclerosis, diabetic nephropathy, amyloidosis and myeloma.

Figure 2 shows the number of subjects alive after 1 and 2 years. Eighty-two percent of the deceased had congestive heart failure. Out of the 157 subjects with pyelonephritis 64% had received long-term treatment for infection. The death rates in the group of patients which had received long-term treatment did not differ significantly from the death rate in the group of patients who had not received this treatment. Obviously long-term treatment in advanced cases of uraemia caused by chronic pyelonephritis has no or very little effect on death rates and prognosis.

III. Treatment of the Uraemic Elderly Patient

In acute renal failure the principles of treatment are the same as in younger individuals. In chronic renal failure the principles are also basically the same with some adaptations for the elderly. The deranged metabolism can be improved by a low protein diet, restriction of movement and exercise and the administration of anabolic steroids.

The control and correction of fluid and electrolyte balance follows the following principles: correction of acidosis, control and correction of hyperkalaemia and reversal of dehydration with a sufficient supply of fluid. The danger of excessive fluid administration is hyponatraemia, which must be controlled and corrected. The condition develops readily in the aged and is dangerous (BAEHLER and GALLA 1976).

In the treatment of oedema, frusemide in high dosages is a very useful diuretic, working even at very low clearance levels. Early detection of congestive heart failure and its appropriate treatment are of the utmost importance. Digitalis must be administered with reduced clearance in mind. Serum digoxin estimation are valuable.

The treatment of end stage renal failure in the aged is in many instances a question of local possibilities. Haemodialysis is often complicated by cardiovascular problems. Peritoneal lavage is useful, and benefits from the use of this method have been reported (BARTECCHI 1975). TENCKHOFF and SCHECHTER (1968) introduced a silicone rubber peritoneal dialysis catheter which made chronic peritoneal dialyses a feasible procedure. In 1978 POPOVICH et al. outlined the principle of continuous ambulatory peritoneal dialysis (CAPD). This procedure seems to be very suitable for elderly patients with end stage renal failure. PRICE and MORIARTY (1980) stated that age and sex are not a factor as far as selection criteria are concerned; the same was reported by FENTON et al. (1980), who claimed that older patients adapted well to CAPD.

Mental deterioration and intellectual impairment as well as disseminated neoplasms are contraindications whereas ischemic heart disease and hypertension are not contraindications according to FENTON et al. (1980). Patients who live alone often fail with CAPD and do best on intermittent peritoneal dialysis (IPD) in hospital, where they enjoy the social contact with staff and other patients on 2–3 times per week basis.

CAPD has a dramatic effect of hemoglobin and hematocrit; an initial increase during the first 3 months is followed by a late decline, and then the hemoglobin seems to stabilize (OREOPOULOS 1980). The disadvantage of CAPD is the frequent occurrence of peritonitis, requiring hospital admission and immediate treatment, KAYE et al. (1982) compared the complications in two groups of patients – one under the age of 65 and the other over the age of 65 – and reported that the average interval between episodes of peritonitis in the younger group was 5.6 months and in the older group 6.5 months. The results of KAYE et al. showed that the elderly behaved no differently from younger patients when maintained on CAPD for as long as 4 years.

Kidney transplants have been performed successfully in aged patients, and recent reports have shown that strict age limits are not justified. Results with cadaver kidneys are not encouraging because of infections. Related donor kidney transplants are very much a practical and an ethical problem. There have, however, been reports of good success with relative donor kidney transplants in the aged (KJELLSTRAND et al. 1976).

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Bladder and Prostate

W. FERGUSON ANDERSON

A. Bladder

The bladder is a waterproof container through which no exchange of electrolytes or other substances occurs.

I. Embryological Origins

Entodermal tissue forms most of the bladder, the detrusor muscle, the female urethra, the male posterior urethra, the prostate, the paraurethral glands, the vagina, the uterus, and the Fallopian tubes. On the base of the bladder extending from the ureteric orifices to the urethra there is an island of mesoderm which becomes the trigone. The external meatus of the urethra, the vulva and the distal urethra in the male are ectodermal. It is probable that there is an invasion of the mesenchymal tissue in the trigone by entoderm and of the entodermal tissues of the urethra by ectoderm (ZUCKERMAN 1940). The clinical relevance of this is that because the trigone may be a mixture of varied origin sensitive to oestrogen levels this may be an aetiological factor in dysuria in elderly women (BROCKLEHURST 1978 a).

II. Anatomy

The longitudinal fibres of the detrusor muscle are continued into the urethra and form a major part of the urethral wall. When these contract, the urethra in both male and female is shortened. The trigone and the detrusor muscle are intimately linked to each other but the trigone muscle fibres, which rise as a continuation of the fibres of the ureter and which extend medially to form the interureteric bar, also run down into the bladder outlet to be inserted into the verumontanum urethrae in the male and in the terminal part of the urethra in the female. The muscles of the urogenital diaphragm, including the external sphincter (the peri-urethral sphincter), and the pelvic muscles are under voluntary control. They maintain continence and initiate micturition. The mechanics of bladder emptying begin with contraction of the trigone muscle, which opens the bladder outlet and shortens the urethra. Contraction of the detrusor muscles follows, which further opens the bladder outlet and increases the intravesical pressure. This is accompanied by reflex relaxation of the external sphincter. When micturition is consciously willed there is a voluntary relaxation of the muscles of the perineum and frequently there is a superadded increase in abdominal pressure by the contraction of other striated muscles. The bladder muscle is best regarded as a single meshwork contracting in

unison and thus hypertrophy of the muscle of the bladder occurs in obstructive conditions of the urethra. This is recognised cystoscopically as trabeculation of the bladder wall. The muscle bundles of the detrusor pass down the urethra in continuity and are arranged so that they open the neck of the bladder on contraction. Micturition is not caused by relaxation of the "internal sphincter," which probably does not exist but is produced by active contraction of the detrusor muscle with associated relaxation of the striated muscle of the external sphincter. HUTCH (1972) had views based on mechanical action where the base plate of the bladder consists of trigone and of circular detrusor fibres and when the base plate is flat the bladder outlet is closed. If the base plate is broken, the same muscle bands then form a diminishing cone, which contributes to bladder emptying.

III. Nerve Supply

The detrusor muscle is supplied mainly by the nerve fibres of the sacral outflow passing from the anterior roots of the 2, 3, and 4 sacral segments. Bladder detrusor contractions are mediated by cholinergic neurotransmission. Afferent fibres travel by the posterior roots of the same segments from sensory nerve endings in the bladder wall and the mucosa. These fibres carrying sensations of pain in the bladder and urethra and desire to micturate travel up the spinal cord in the spinothalamic tract of the lateral columns and those conveying touch, pressure or tension in the urethra pass in the posterior columns (NATHAN and SMITH 1951). These pathways pass by way of the reticular substance in the medulla where excitatory and inhibitory centres have been described and continue via the mid-brain to cerebral levels (SMITH 1976). The highest centres with the power of inhibition over those beneath them lie in the superior medial part of the middle of the frontal lobe, in the anterior end of the cingulate gyrus and in the white matter between these areas and the genu of the corpus callosum. Sympathetic nerve supply travels from the bladder via the hypogastric nerve to the lumbar sympathetic chain and thoracolumbar sympathetic outflow. These fibres probably carry some pain sensation from the bladder and exert control over the blood vessels of the bladder and possibly the urethra; an intact sympathetic nerve supply is essential for the achievement of ejaculation. The striated muscle of the pelvic diaphragm and the external sphincter plays little part in the maintenance of continence but reinforces the passive mechanism when the intra-abdominal pressure is raised in coughing or straining. Somatic nerves pass from the 2, 3, and 4 sacral segments by way of the pudendal nerve to the striated external sphincter muscle and carry motor fibres and sensory fibres from that muscle. The nervous control of micturition has been complicated by the discovery of adrenergic nerve endings throughout the bladder but predominantly situated in the bladder fundus and proximal urethra (HARRISON 1976). Ganglion cells in the bladder wall have been found to be not only parasympathetic but also sympathetic. In the bladder neck region alpha-adrenergic receptors predominate and there is evidence that alpha activity increases bladder neck and urethral closure. Pharmacological experiments have shown that alpha-adrenergic block by pentolamine leads to a drop in urethral pressure (WHITEFIELD et al. 1976). Beta-adrenergic receptors have been demonstrated in the fundus of the bladder, bladder neck region and the urethra. The functional effect of beta stimulation is to raise bladder volume, reduce

voiding pressure and increase residual urine. The main element, however, in contraction of the bladder is cholinergic as demonstrated by pelvic nerve stimulation (DIOKNO et al. 1973).

IV. The Functioning Bladder

The urinary bladder accommodates approximately 600 ml urine and fills slowly without much increase of intravesical pressure. It is capable of emptying itself completely and can hold as much as 2,000 ml urine, but when filled to this capacity there is usually pain except in some very elderly people or if this volume has been reached over a long period of time. Old women in particular who are cared for by relatives who leave them alone in bed for many hours, toileting them only morning and evening, may gradually develop a very large thin-walled bladder with a huge capacity. This may be impossible to feel by abdominal palpation. Standing the patient up may reveal the condition because the floor is flooded.

Additional pressure may be placed on a full bladder by increased intra-abdominal pressure, e.g. coughing or laughing. Awareness of distension reaches consciousness at about 250 ml, but no intrinsic contractions of the bladder occur then unless they are consciously allowed by the individual in order to empty the bladder. When the bladder is full to capacity there is an urge to micturate with a rapid rise in intravesical pressure, but this desire can be suppressed if socially inconvenient by cortical inhibition of the spinal reflex arc. If bladder filling continues, a point is reached where further cortical inhibitory control is impossible and voiding occurs. When micturition is desired, contraction of the detrusor muscle and funnelling of the bladder outlet takes place, the bladder neck and the urethra are opened, the pelvic floor muscles relax and voiding occurs. The rising intravesical pressure is conveyed by afferent impulses via the parasympathetic nerves and the detrusor muscle continues to contract smoothly and urine is expelled at a steady rate until the bladder is empty. Detrusor muscle contraction that cannot be suppressed is called unstable or an uninhibited contraction. BATES (1971) showed that detrusor instability may be provoked by events such as rapid bladder filling (quicker than 100 ml/min), changes in posture, removal of a catheter or coughing but that this did not occur in most people without urinary symptoms.

Closure of the urethra takes place first in the male at the external sphincter and in the female about the midurethra. The external sphincter in males, and in females the proximal urethra, maintains continence when intra-abdominal pressure is raised in coughing or straining. In normal subjects, straining during micturition increases the rate of urine flow but in some males with enlargement of the prostate such action decreases the urine flow. Continence after prostatectomy is maintained by the passive elastic properties of the membranous and supramembranous urethra. Voluntary interruption of micturition is achieved by contraction of striated muscle of the pelvic floor and the distal sphincter, which elevates the bladder and closes off the urethra (CAINE and EDWARDS 1958). Detrusor relaxation is a slower process but is usually completed as striated muscle activity declines. Any urine proximal to the region of the external sphincter empties back into the bladder. Backflow into the ureters is normally prevented by a non-return valve at the junction of each ureter with the bladder.

With advancing age there is a gradual decline in the tone of voluntary muscle, which is reflected in the genito-urinary tract by the diminished strength of the pelvic floor and the external sphincter (WILLINGTON 1976). Trabeculation and diverticula are seen with increasing frequency in old age due partly to hypertrophy of the detrusor muscle and partly to loss of supporting elastic tissue (BROCKLEHURST 1978 b). This is reported to be associated with reflex or uninhibited neurogenic bladders in which case the obstruction is functional rather than organic and is the result of bladder contractions occurring with an unrelaxed outlet producing a high intravesical pressure. Mucosal prolapse of the external urethra has also been described and this may restrict the urinary flow. Incompetence of the pelvic floor associated with varying degrees of uterine prolapse has been studied by BROCKLEHURST and DILLANE (1967). Declining levels of oestrogen result in atrophic changes which produce not only senile vaginitis but also marked thinning of the tissues of the external genitalia and of the lower urinary epithelium.

V. Symptoms Associated with Bladder Dysfunction

Nocturnal frequency (nocturia) is usually the first symptom of increased frequency of micturition. It may be caused by irritation or inflammation of the bladder wall, which makes the stretch receptors more sensitive. Frequency is a symptom of bacterial or chemical cystitis, bladder stone, tumour or a neurological lesion. When retention of urine with a large residual volume of urine in the bladder at the end of micturition is present, frequency may occur. Frequency of micturition in prostatic hypertrophy is not always due to a large amount of residual urine but may be caused by the inversion into the bladder of the sensitive urethral mucosa by the enlarging prostate (HODKINSON 1980).

Urgency of micturition is a common symptom in the elderly and while it is stated that the signal denoting the sensation of fullness of the bladder presumably declines over a lengthy period, little is known about the mechanism of its fading (WILLINGTON 1976). YEATES (1976) described hypaesthetic urgency where partial deficiencies of sensation may exist so that the patient is unaware of the usual rise of tension in the central excitatory state denoting bladder fullness. He then has the desire to micturate only when the stimulation from the bladder is greatly increased by the actual bladder contraction just before the onset of micturition. According to EXTON-SMITH and OVERSTALL (1979), with increasing age the higher centre control weakens so that instead of being able to postpone micturition for an hour or more after the sensation of fullness has been experienced, an older person may be able to delay micturition only for a matter of minutes. The combination of frequency and urgency in the absence of infection, mechanical or neurological abnormalities may be due to overactivity of the detrusor muscle and this may be called detrusor instability, resulting in the unstable bladder. This is a bladder showing uninhibited contractions which occur at any capacity and these may take place during normal filling or following any rise in intra-abdominal pressure such as coughing or change of posture. This is common in men with enlarged prostate showing obstruction; such patients will often be incontinent and this fact must be known before operation as surgery may fail to cure the incontinence. Painful micturition (dysuria) is characteristic of lower urinary infection while hesitancy, i.e. a

delay between voluntary initiation of micturition and the occurrence, if associated with diminution in the urinary stream, is usual in patients with prostatic obstruction. Occasionally dysuria will be complained of in patients who have a sterile urine and an enlarged prostate. Dysuria may also be used to describe difficulty in passing urine.

B. Special Diagnostic Methods

I. The Cystometrogram

A cystometer is a manometer attached to a catheter in the bladder which reveals pressure changes within the bladder as the bladder fills. It is linked to a recording device and a reservoir is also used to fill the bladder as desired, i.e. continuously or by increments of 25–100 ml fluid at a time. The pressure in the rectum is also measured and thus the intravesical and the intra-abdominal pressures are recorded simultaneously. When the intra-abdominal pressure is subtracted from the intravesical pressure a true recording of the pressure in the bladder (the pure detrusor pressure) is obtained. It excludes all pressure changes taking place as a result of changes in posture or coughing. By this method the bladder's reaction to increasing distension can be obtained and information can be recorded regarding residual urine, the capacity of the bladder and the presence or absence of uninhibited bladder contractions. A complete voiding cycle is now studied as well and the cystometrogram is divided into a filling and a voiding phase. The rate of the bladder filling by saline solution or contrast medium should be stated as fast filling may reveal detrusor abnormalities which would otherwise be missed. The International Continence Society (1976) suggested the following definitions:

Slow fill cystometry	Up to 10 ml/min
Medium fill cystometry	10–100 ml/min
Rapid fill cystometry	Over 100 ml/min

In present practice a separate fine catheter (1 mm in diameter) is passed alongside the filling catheter and connected to a strain gauge pressure transducer which is connected to a chart recorder. The rectal pressure is measured by a fine fluid-filled catheter introduced into the rectum. The rectal pressure can be electronically subtracted from the total bladder pressure to give the detrusor pressure. The filling phase of the cystometrogram is performed with the patient lying or sitting and continues until a strong desire to void is stated. The filling catheter is removed but the fine pressure catheter remains in place while the patient is asked to cough and strain and then to void. During voiding the urine flow rate and the volume voided are recorded. Cystometry is performed with the patient awake to obtain information regarding the sensory aspects. By this investigation the types of neurogenic bladder can be identified and the unstable bladder discovered.

II. Peak Flow Rate

Peak flow rate (maximum flow rate) is a most useful measurement to record but the volume voided must be known as flow rates are related to bladder volume. Values above 15 ml/s in the male and 20 ml/s in the female are unlikely to be as-

sociated with obstruction. Mathematical calculations can give many other measurements. High voiding pressures with low flow rates suggest outflow obstruction. High voiding pressures with normal flow rates are probably due to detrusor hypertrophy in response to increased resistance while low flow rates with low detrusor pressure indicate a deficient detrusor (HARRISON 1976). An isolated measurement of flow is of doubtful value.

III. Micturating Cystogram

The micturating cystogram is useful and the pressure recordings of the cystometrogram can be taken simultaneously with X-ray screening of the bladder filled with a radio-opaque fluid. This technique has been made possible by the use of the image intensifier. Videotapes can be made and BATES (1971) described this development. By this method, differentiation can be made between neurogenic and non-neurogenic causes of incontinence. Bladder neck obstruction will be revealed by the presence of trabeculation and eventually by diverticula.

IV. Urethral Pressure Profile

Urethral pressure profile is a graphic record of intraluminal pressure exerted by the urethral wall on a recording catheter as it is withdrawn from the bladder to the external sphincter. A modification by HARRISON and CONSTABLE (1970) using a catheter position transducer has the advantages that profiles can be superimposed. The International Continence Society (1976) defines maximum urethral closure pressure as the difference between the maximum point on the profile and the bladder pressure. Functional urethral length is the length of the urethra over which profile pressure exceeds bladder pressure. The maximum urethral closure pressure declines with age. The shape of the profile may be characteristic and changes in response to various methods of stimulation, e.g. drugs can be studied. This procedure has not found universal acceptance but indicates a shortened urethra in genuine stress incontinence and a low maximal closing pressure in this condition while a high closing pressure is found in spasticity of the external sphincter and in urethral strictures (BROCKLEHURST 1978c).

V. Cystoscopy

Cystoscopy will reveal the presence of inflammation, hypertrophy as trabeculation or diverticula and other abnormalities such as stone, papilloma and carcinoma of bladder.

Non-traumatic information about the bladder will be revealed by the use of ultrasound or less commonly of the whole body scan.

EASTWOOD (1978) considered that the best results from cystometry were obtained by continuous filling and found that the interpretation of the urethral pressure closing profile is difficult in the elderly, confirming the view that normal values for men and women decrease with age and thus there is a diminishing difference between normal and abnormal results.

The importance of physical and mental assessment before resorting to the use of urodynamic studies must be stressed. Unfortunately in many places the elderly do not have access to such specialised facilities. Cystometry is not difficult to perform and could be introduced by co-operation between physicians practising geriatric medicine and urologists. There is every advantage to the elderly patient in a team approach. Unsuitable patients should not be referred for elaborate investigations and on the other hand curable people should not be neglected for lack of expert advice and scientific examinations. Reference is made to the accurate assessment of the elderly in the section on incontinence. EASTWOOD (1978) defined groups of those who might benefit from urodynamic studies:

a) Where urinary incontinence is the sole symptom or following surgery.
b) Those with stress incontinence where clinical doubt exists concerning the mechanism.
c) Those with nocturnal incontinence or nocturnal frequency.
d) Those with neuropathic bladder excluding those with chronic brain failure.
e) Men with postprostatectomy incontinence or possible outflow obstruction.
f) Women with retention, overflow or palpable bladder.

The following generally showed no benefit from such studies:

a) Very disabled elderly whose incontinence is just one feature of their dependency.
b) Those with chronic brain failure.

Combined pressure flow studies with micturition cystography can be tiring and possibly micturating cystography is the least valuable component.

C. Prostate Gland

I. Anatomy

The prostate gland lies around the urethra and is situated behind the symphysis pubis, to which it is attached by a strong fascia containing large veins. The prostate is separated from the rectum by two layers of peritoneum attached to one another called the fascia of Denonvillier's. In the adult male the healthy prostate is composed of acini and ducts, each of which is surrounded by a sleeve of smooth muscle fibres running radially from prostate to urethra. These acini secrete a prostatic fluid and contraction of the smooth muscle empties the duct and the secretion enters the urethra. The detrusor muscles of the bladder continue down through the entire gland and there is a condensation of the smooth muscle fibres at the periphery of the gland merging with the thin connective tissue capsule. Most of the detrusor muscle fibres pass down between the radially arranged acini and ducts and are inserted into the urethra just beyond the entry of the ejaculatory duct. The entire volume of the prostatic fluid, estimated at 0.5 ml, is secreted with the semen during ejaculation. The prostate is pierced obliquely from behind forwards by the common ejaculatory ducts, which emerge from either side of the verumontanum. At the neck of the bladder there is a circular ring of smooth muscle made up of loops of detrusor muscle fibres coming around the bladder neck. This tissue is closely mixed with the acini of the prostate gland. The external sphincter lies below

the prostate gland and the verumontanum is always situated approximately 1 cm above it.

As the individual ages, the pattern of the muscle fibres changes and in the gland the vertically running fibres begin to form a septum which defines an inner and outer zone of acini. The inner zone is the common site of development of nodular hyperplasia and corresponds to the surgical middle and lateral lobes of the elderly subject. The outer zone is the more usual site for cancer and is very thin anteriorly but is much thicker posteriorly and is called the posterior lobe.

II. Benign Enlargement of the Prostate

The cause of this common condition is unknown and the resulting obstruction if it occurs bears little relationship to the size of the prostate. Large adenomata can be found with no residual urine, while severe urinary obstruction may occur with a small fibrous contracted prostate. The basic lesion is the nodule, which may be predominantly stromal, muscular or adenomatous or a mixture of these. Nodules can occur diffusely or aggregated together in a large nodule. The small fibrous prostate represents a diffuse change while the "adenoma" is a large aggregation. In prostatic adenomas removed surgically, infarcts are often found, raising the question of how often acute retention may be precipitated by oedema round an infarct.

ASHLEY (1966) quoted a figure of 89.4 cases per 10,000 men over 65 years of age admitted to hospital in England and Wales with prostatic hypertrophy each year.

III. The Pathology of Prostatic Obstruction

When pathological changes in the prostate lead to obstruction of the output of urine, the detrusor muscle of the bladder hypertrophies with resultant herniation of vesical epithelium through gaps between the thickened bundles of detrusor muscle fibres. Saccules are now formed, which may enlarge and form diverticula. When the bladder empties, urine tends to remain in the saccules or diverticula so that infection is almost certain to occur. Sometimes this phase of detrusor hypertrophy with diverticular formation is followed by weakness and thinning of the bladder wall and this results in the development of large amounts of residual urine. Progressive increase in outflow obstruction will cause this and then infection is likely to take place, which may lead to stone formation, epididymitis or ascending infection in the renal tract. Kidney function may also be affected by dilatation of the upper urinary tract. Impairment of the concentrating power of the kidney results in diuresis, which aggravates the desire to pass urine more frequently. Ultimately the clinical signs of uraemia follow and unfortunately this process of upper renal tract failure is rapidly worsened by infection, which can occur at any time.

IV. Symptoms

In the age group below 65 years of age the presenting symptom is usually increasing difficulty in passing urine. In the elderly the first symptom may be haematuria or

acute retention precipitated by diuretic therapy or anti-cholinergic drugs. The old man with chronic retention and overflow, especially if mentally confused, may not complain of pain so that dribbling incontinence with restlessness may be the initial signs. An unexpected finding of uraemia requires the exclusion of prostatic obstruction as a cause. Older patients often do not report their symptoms until a late stage and direct enquiry about the function of micturition is an essential part of history taking. Progressive urinary frequency, hesitancy and intermittency of the urinary flow, decreasing size and force of the urinary stream, sensations of incomplete emptying and nocturia are other common symptoms. This grouping of symptoms is referred to as prostatism.

Haematuria is caused by the congestion of the superficial veins of the prostatic urethra and trigone, which rupture when the patient is straining to void. Burning sensation on micturition, which may be accompanied by chills and fever, indicate urinary infection. Episodes of acute urinary retention may follow prolonged attempts to retain urine, exposure to cold, immobilisation, the ingestion of diuretics or the taking of alcohol. Nocturnal enuresis may be the only symptom of retention.

V. Diagnosis

The symptoms of prostatism may be produced by cancer of the prostate or of the bladder as both of these diseases may produce outflow obstruction. Depression can present with somatic symptoms and one common complaint is of frequency of micturition. The side-effects of anticholinergic drugs may cause dysuria and can occasionally precipitate an acute episode of retention. Diabetes mellitus may present for the first time as prostatism.

The importance of an accurate history with careful detailing of the urinary symptoms cannot be overstressed and in the pre-operative assessment is more important than any one scientific investigation. No one symptom is diagnostic of prostatic enlargement as frequency of micturition may be due to polyuria from excessive fluid intake, to pathological changes in the kidney or to the action of diuretic drugs, to anxiety or to an irritative as well as an obstructive lesion.

Nocturia may be found in prostatic hypertrophy, in urinary infections and in the uninhibited neurogenic bladder. The triad of frequency, hesitancy, and dribbling, when found in association with a poor stream of urine, are pointers to prostatic obstruction in contrast to urinary infection, where frequency is associated with scalding or burning dysuria. Dysuria and frequency may rarely be found in patients with a bladder calculus, which can also cause incontinence. The possibility of prostatic carcinoma must always be kept in mind and therefore rectal examination should be part of the routine examination of every elderly patient. This investigation provides the initial clinical sign of prostatic enlargement.

Necessary investigations include culture of urine, estimation of blood sugar, urea, creatinine, and electrolytes. An intravenous pyelogram is usually performed but some surgeons do not recommend this as a routine procedure in patients with urinary retention, provided they have a sterile urine and there is no history of haematuria . Urodynamic studies are recommended irrespective of the patient's age if there is reasonable doubt as to the diagnosis. It is found that the results of these are helpful in patients who presented with incontinence not due to overflow and

in cases of chronic retention of urine due to a neurogenic bladder. Patients are thus found who are diagnosed as suffering from prostatic hypertrophy but have an uninhibited bladder (SHALDON 1979a).

FITZPATRICK et al. (1979) noted a group of patients with complaints of frequency, nocturia, and urgency before prostatectomy who were later found to have detrusor instability. They recommend that patients with this triad of symptoms should have a urodynamic assessment before operation; otherwise they may remain incontinent afterwards. In total only a small number of men require urodynamic investigation and it must be noted that uninhibited contraction may result from prostatic obstruction to flow. Results are often poor in patients with parkinsonism, and after full investigation prostatectomy should be avoided if possible.

VI. Treatment

The treatment of prostatic hypertrophy, which causes symptoms rendering life unpleasant, is prostatectomy. Age itself is not a contra-indication to operation and the causes of postoperative deaths are concomitant medical and surgical problems. Contra-indications to operation are intractable cardiac failure, heart pain at rest, gross respiratory disease limiting mobility and a recent cerebrovascular accident. Most surgeons would postpone the operation for 3 months if the patient had sustained a myocardial infarction. If the pacemaker is in the pectoral region, patients with implanted pacemakers are considered suitable for operation.

The operation of transurethral prostatectomy, when this is possible, is most popular, but when the prostate is considered to be very large, retropubic prostatectomy is the usual operation. The aim of surgery is to remove all the adenenomatous tissue. The mortality rate increases with age, being very low under 80 years of age, less than 1%, but rising to approximately 5% in those over 80. A complete knowledge of the patient's medical and surgical status before operation is essential. Epidural anaesthesia is of value for both open and transurethral prostatectomy in patients with cardiovascular and respiratory problems. The main indications for operation are the symptoms of bladder obstruction, acute retention and chronic retention, and whenever possible it is safer to undergo a planned elective operation before urinary retention takes place. Many surgeons do not routinely catheterise patients even with chronic retention before operation. This procedure is reserved for those with severe biochemical disturbances or who are in renal failure or distressed by overflow incontinence or requiring diuretic treatment before operation. In the care of such patients, the closest co-operation between physician and surgeon is essential.

D. Prostatic Carcinoma

This is a common disease of old men and according to KLEIN (1979) 42,000 new cases of prostatic cancer are discovered every year in the United States, with 17,000 deaths. Some 95% of these cases are in those aged over 60 years and the disease is rare before 50 years and increases rapidly in occurrence with age until 80 years. This illness is more commonly found in urban than in rural areas and is not related

to economic class or occupation. There is no relationship to benign prostatic enlargement, which usually affects the lateral lobe, whereas malignant disease commonly starts in the atrophic glandular epithelium of the posterior lobe. Almost all prostatic cancers are subcapsular adenocarcinomas, either the fast-growing invasive small-cell variety or well-differentiated and slower-growing types. Because of the subcapsular site of origin, early invasion of the nerve and venous plexuses communicating with the veins in the pelvis and vertebral column may be found. Lymphatic involvement is often early and widespread and local spread takes place in the vesicles and the bladder base. Bony metastases occur in the pelvis, lumbar spine, and femora with the next most frequent sites being the lungs, the liver, and the aortic nodes.

I. Symptoms

In the case of potentially curable carcinoma, diagnosis depends on rectal examination. Most patients appear for the first time with symptoms of urinary obstruction or of metastatic lesions. The younger patients frequently present with symptoms of prostatism, i.e., decreased force of urinary stream, frequency of micturition, nocturia or urgency. The incidence of retention increases with age while haematuria, symptoms of anaemia or pain from metastases may be presenting symptoms. Oedema of lower limbs with lymphadenopathy may be discovered while unexplained malaise with deteriorating social behaviour may be noted.

II. Diagnosis

Diagnosis depends on digital rectal examination and the lesion is recognisable because elderly patients usually present with locally advanced disease; needle biopsy is now being used more frequently to make this diagnosis. Biochemical changes do not indicate early pathology; an elevation of acid phosphatase beyond the upper limit of 5 King-Armstrong units/dl is found most commonly in men with prostatic carcinoma, especially in the presence of metastases. Acid phosphatase of prostatic origin is biochemically different from that derived from other tissues and is estimated as the formol stable fraction and is normally less than 1 King-Armstrong unit/dl. In the presence of metastases the alkaline phosphatase may also be elevated. A raised plasma calcium may be found where there are secondary bone deposits. In the future, radio-immuno-assay for acid phosphatase may be useful in detecting early cases, and KLEIN (1979) adds that the use of ultrasound or computerised tomography might be of value (RESNICK et al. 1980).

III. Treatment

Immediate consultation with a urological surgeon is indicated, and where there are any problems a team approach with radiotherapist and physician specialising in the care of the elderly is recommended. The current principles of therapy used and classification on which they are based can be outlined as follows:

Clinical stage A is unsuspected clinically and many such tumours are discovered at routine post-mortems or by examination of prostate gland removed at

operation for what was considered to be benign enlargement of the prostate gland. Most stage A tumours do not become clinically important. According to JEWETT (1975) there may be two groups within group A which cannot be distinguished early: group A_1 and group A_2. A_1 shows well-differentiated cells histologically while A_2 reveals a poorly differentiated pattern. Repeated transurethral biopsies may distinguish between the two. The treatment of group A_1 is by reassurance and annual digital rectal examination. If there is any obstruction, a transurethral resection is indicated. Oestrogens are not advised; they may shorten life. If stage A_2 is diagnosed, Cobalt teletherapy high-energy X-rays produced by a linear accelerator should be directed to the centre of the prostate (KLEIN 1979).

At stage B the tumour is detectable on rectal examination and is usually about 1.5 cm in diameter or involving one lobe. There is a histological differentiation as above into groups B_1 and B_2. While in both groups some advise the patient to undergo a radical prostatectomy, others use oestrogens. Prostatectomy for this condition is an awesome procedure in the elderly and postoperative incontinence is common. Stage C is present when rectal examination reveals a carcinoma which has spread beyond the prostatic capsule usually into the seminal vesicles. The untreated survival rate is now 2–3 years. External beam irradiation is claimed to achieve a local control rate. Many believe that hormonal treatment is not indicated and feel that there is little advantage in this therapy prior to onset of bone pain and evidence of active progression, e.g. anaemia, weakness, and outflow obstruction.

Included in stage D are all tumours which have spread beyond the prostate to lymph nodes, bones or viscera, regardless of size or histology. This stage responds equally well to oestrogen administration or bilateral orchidectomy. The dose of diethylstilboestrol recommended is 1–3 mg per mouth per day. As a general rule those more likely to die from cardiovascular disease should not be treated with diethylstilboestrol. There is no advantage and considerable danger in giving larger doses. The complications of diethylstilboestrol therapy are gynaecomastia, and fluid retention with dependent oedema; diuretics will control the oedema.

In spite of these problems SHALDON (1979 b) has recommended, when a very quick therapeutic response is required, the use of intravenous phosphorylated stilboestrol (Honvan) over a period of 7–10 days in a dose of 1,000 mg/day. This treatment has not been used for retention of urine for which a transurethral resection has been the routine. Despite initial response to hormone treatment, stage D tumours usually show signs of reactivation within 2–3 years. Bilateral orchidectomy has also only a temporary effect and has little value if performed after long-term oestrogen therapy. Chemotherapy, e.g. estramustine phosphate has been used in those tumours unresponsive to stilboestrol. The diagnosis and treatment of prostatic carcinoma has been reviewed (SKINNER and DE KERNION 1978).

E. Prostatitis

Potentially pathogenic organisms, e.g. *Escherichia coli* and *Streptococcus faecalis* live almost certainly in the glands in the distal part of the urethral mucosa of the normal male. A variety of organisms and yeasts can be found in the prostatic se-

cretions of apparently healthy men (AMBROSE et al. 1961). Infection may reach the prostate from the urethra (trauma from instrumentation), from the blood stream, and from infection of the upper urinary tract, and possibly from the lymphatic system.

I. Acute Prostatitis

Acute inflammation of the ducts and acini is commonly due to infection with *Escherichia coli*, *Streptococcus faecalis* or Staphylococci and may be found in gonorrhoea. The condition can resolve by itself or as a result of therapy, or become chronic. It is reported to be commoner in diabetics (YOUGEN et al. 1967). Brucellosis can affect the prostate and should be suspected in those working with animals, e.g. veterinary surgeons. The initial symptoms are fever, rigors, and a feeling of weakness. Then frequency of micturition, pain on passing urine, and pain in the perineum or groin may be noted. Rectal pain and painful defaecation may occur while haematuria appearing at the end of micturition may be present. Perineal pain of great intensity gives an indication that a prostatic abscess may have occurred and this condition can also be associated with retention of urine. Prostatitis can be present without pain and then may be the cause of general malaise with mild febrile episodes and no localising features. Diagnosis depends on rectal examination and the gland is painful to touch, swollen, and may feel nodular. Confirmation rests on the culture of the causative organism. Only direct examination of the expressed prostatic secretion can provide evidence of the exact localization of the infection. There is a raised pH greater than 7 and increased leucocyte count of more than 10 per high-power field in the expressed prostatic fluid.

Treatment is initially to reduce the patient to bed, and co-trimoxazole and erythromycin are the drugs of choice but the result of the bacteriological culture may reveal the need for a change of antibiotic. The fundamental problem is that few antibiotics penetrate into the prostatic fluid. Gonococcal infection will require the appropriate antibiotic and surgical drainage of abscess may be necessary.

II. Chronic Prostatitis

This is a condition whose cause is not clearly understood and asymptomatic prostatitis is described in ankylosing spondylitis, Reiter's disease, and anterior uveitis. Rarely cases have been attributed to infection with *Trichomonas vaginalis* and *Entamoeba histolytica* (OATES 1976). Introspective patients and those with psychosexual problems may describe symptoms similar to prostatitis.

F. Carcinoma of the Bladder

Carcinoma of the bladder is diagnosed most commonly in the 7th decade with a male to female ratio of 3 to 1 and in women it occurs more frequently as age increases. The whole lining of the urinary tract is exposed to urine-borne carcinogens and this subject was reviewed by WALLACE (1976). In countries free from *Schistosoma* infestations this disease occurs more commonly in industrialised areas. Aetio-

logical factors are exposure to various chemicals, e.g. 2-naphthylamine and benzidine and their use in industry and in the laboratory. Heavy smoking was incriminated and the part played by it was discussed by KIPLING (1976). The role of coffee drinking is doubtful and urinary stasis and chronic infections are other possible factors (SKINNER and DE KERNION 1978). Newer aetiological factors may yet be discovered and cyclophosphamide was regarded as a possible cause by WALL and CLAUSEN (1975). They found that the haemorrhagic cystitis sometimes noted was on rare occasions due to carcinoma of the bladder and suggested immediate cessation of the drug if this complication arose, as well as a most careful follow-up by cystoscopy even if the haemorrhage stopped and the patient appeared better. In countries where *Schistosoma haematobium* is endemic, e.g. rural areas of Egypt, squamous cell carcinomas of the bladder are common in contrast to the more usual transitional cell lesion. This latter lesion varies widely in appearance and behaviour. The tumours may be solid or ulcerated, single or multiple and infiltrating or non-infiltrating and while many remain confined to the mucosa for a long time, some will invade early and form metastases by way of blood vessels or lymph glands to bones, liver, and lungs. Rate of growth tends to be slow in the elderly.

I. Pathological Staging

Pathological staging is essential and the one commonly used is as follows: $T_1{}^S$ denotes a carcinoma in situ, one type being called flat in situ. It has the appearance of inflamed mucosa and urinary cytology is usually positive, biopsy being necessary for diagnosis. T_1 indicates infiltration of subepithelial tissue, T_2, involvement of superficial muscle, T_3, involvement of deep muscle, and T_4, infiltration of adjoining tissues.

The number of solid high-grade undifferentiated and invasive tumours increases with age.

II. Diagnosis

Diagnosis is based mainly on presenting symptoms and the commonest one is painless haematuria usually throughout the flow but on occasion noted at the beginning and end of micturition. Frequency with or without painful micturition is less commonly reported and a urinary infection occurring for the first time in old age should be regarded as suspicious while rarely episodes of urinary difficulty and even acute retention arise in the male (RIDDLE 1976). Pain from varying degrees of ureteric obstruction from locally invasive disease or from secondary deposits are rare presenting symptoms. Bladder carcinoma may be an incidental finding in a routine preprostatectomy cystoscopy and the symptoms of frequency, urgency, and perineal pain may be noted in flat in situ carcinoma. After a careful clinical history, examination of the patient including a rectal examination and X-ray of chest is routine and the urine is always tested for albumen, glucose, and blood and a specimen is sent for culture. If *Schistosoma* infection is suspected, an early morning specimen of urine should be examined for ova. A normal urine test does not exclude carcinoma of bladder.

The blood should be tested for haemoglobin level, for white blood cells and erythrocyte sedimentation rate, and biochemical checks for urea, creatinine, and electrolytes should be carried out. In addition to the chest X-ray, an intravenous pyelogram is essential to exclude upper urinary tract damage from extension of tumour or obstruction to ureters; and if there is any bone pain, a skeletal survey and if necessary a bone scan are required. Rarely a pubic mass will be felt but in all cases a bimanual examination under an anaesthetic should be performed where possible. In right-handed individuals this is done by using the left hand suprapubically and with the right forefinger in the rectum or vagina. Special examinations include cysto-urethroscopy with biopsy of the bladder tumour.

III. Treatment

Treatment is planned as the result of consultation with the urological surgeon and help may be required from a team including the radiotherapist and a physician specialising in the care of the elderly. An outline of present methods of therapy is given.

The use of intracavity radiations for T_1 lesions is contraindicated as it is unsatisfactory because of local recurrences and because of the development of a contracted bladder. SHALDON (1979c) recommends transurethral resection and diathermy of the tumour where possible. Where a solitary lesion of superficial nature is found in a difficult site for operation, RIDDLE (1976) advises treatment by open excision and partial cystectomy, but because of improved instrumentation this is now seldom required. In the circumstances where the tumour is so large that initial resection is difficult, treatment with the Helmstein balloon (ENGLAND et al. 1973; HELMSTEIN 1972) may cause the majority of lesions to slough, leaving remnants to be destroyed by resection. Recurrences of T_1 type are treated by diathermy. Open cystodiathermy is not now commonly used. T_2 lesions are usually treated by external radiotherapy (RIDDLE 1976).

In patients over 65, T_3 tumours are probably best treated by radiotherapy of the bladder using telecobalt. In the very elderly, if a T_3 or T_4 lesion is discovered without symptoms, it may be wise to consider giving no treatment. For T_4 lesions palliative radiotherapy may cause regression of the tumour, while the Helmstein balloon may be useful in the treatment of intractable bleeding.

Follow-up is essential after therapy and in younger patients 3-monthly cystoscopy for 1 year and every 6 months for 2 years and then every year is advised.

For those unable to undergo operation the use of cytotoxic drugs may be tried. Epodyl is a tumour inhibitor of the bisepoxide group and may be used for intracavity instillation and can produce temporary regression and cessation of haemorrhage from multiple T_1 and T_2 papilliform recurrent tumours in the very elderly where cystectomy is not considered justifiable. Further research is required before systemic chemotherapy can be recommended.

From bimanual examination superficial lesions that have been resected or otherwise destroyed should be impalpable. A lesion just penetrating into bladder muscle may be felt as an ulcerated area and tumour in deep muscle or through bladder should be felt as a mass of variable size movable in all directions. If the lesion has extended beyond the bladder and become attached to adjacent structures, al-

though it may be movable in one direction, it will not be freely movable in all directions and should be regarded as fixed.

Common associated conditions in the elderly, including chronic chest disease, anaemia, and heart or renal failure, must be treated.

Transurethral prostatectomy may be of value in relieving symptoms of bladder outlet obstruction and also in reducing the incidence of retention of urine from bleeding and clot as a result of recurrent tumor (SHALDON 1979c).

Prognosis in carcinoma of the bladder depends on the degree of anaplasia of the tumour and the pathological stage of the tumour at the time of presentation. The elderly tend to have anaplastic tumours with high local recurrence rates. Papillary tumours not invading muscle do well and more than half of the patients are clear after 5 years. GROSSMAN (1979) concluded that transurethral resection was adequate treatment for low-grade low-stage bladder carcinoma of bladder and gave the patient good quality and length of life. A multidisciplinary approach in the early stage of bladder carcinoma offered hope that cure was possible in the great majority of patients. This subject was reviewed by SKINNER and DE KERNION (1978).

G. Retention of Urine

Retention of urine is commonly found in the elderly, especially in men, and the main problem is an accurate diagnosis. There may be no complaint of urinary retention by the patient and a distended bladder is recognised as one of the most frequent causes of restlessness. Uraemia from prostatic obstruction with a dry brown furred tongue and a full bladder may be discovered without the patient complaining of any urinary disturbance. Faecal impaction must be excluded as an underlying cause and in all cases of retention of urine a rectal examination must be performed. Extra care must be taken in the care of those who are mentally confused.

I. Causes

This condition can be found as a transitory phenomenon in patients after an abdominal operation, or a stroke or any illness where the supine position has to be adopted as some patients are incapable of passing urine while lying down and thus might develop retention. Retention may also occur in alcoholics or following the use of diuretic or bronchodilator drugs. This condition, however, is more frequently seen in patients with true outflow obstruction. Urethral stricture is now rare and almost never found in women and the history is frequently of an elderly male with increasing frequency and a deteriorating stream, ending up with acute retention. This may be precipitated by the old person becoming cold, being tired, getting drunk or being given a diuretic. Occasionally the patient will be seen with a long history of gross outflow obstruction, distended bladder, dilatation of upper urinary tract, and obvious anaemia and uraemia. This emphasises the necessity of an accurate assessment of the clinical state of the patient.

II. Treatment

Treatment will depend not only on the diagnosis and the relevant pathological condition but on the availability of immediate skilled aid. If the retention is acute and the patient is near a hospital, immediate admission is the best policy and if the cause is thought to be prostatic enlargement, a urologist should be consulted at once. In fact most patients with acute retention will require admission to hospital and a subsequent operation. If the elderly patient has developed painful retention and lives far from a hospital he should be given an effective dose of morphine and then placed in a warm bath. If urine is passed the emergency is over. The newer alpha-adrenergic-blocking agents may be tried, e.g. phenoxybenzamine, which has the disadvantage of producing hypotension especially of postural type (CAINE et al. 1976). Even the successfully relieved patient will almost certainly require further diagnostic assessment in hospital in the immediate future. If drug therapy fails, hospital admission becomes essential unless catheterisation is possible in the patient's house. For patients who can be sent immediately to hospital, BLANDY (1978) recommended that direct admission to a surgical ward be arranged as a casaulty department was not a suitable place to pass a catheter because of the risk of infection. Catheterisation is just as essentially an aseptic procedure as lumbar puncture.

The patient with the transient cause of retention will probably be able to pass urine once the acute retention is relieved and in hospital it is likely that the routine of morphine injection and a warm bath will be followed out before a catheter is passed. Any attack of acute retention with a history of prostatism is an absolute indication for a prostatectomy. The patient requiring a prostatectomy or immobilized in bed for some other reason may benefit from the insertion of a Foley's catheter. In a rational and co-operative patient a Gibbon's flexible catheter is easy to insert and comfortable for the patient (BLANDY 1978). If it is impossible to pass a catheter, skilled assistance is required and eventually it may be necessary to use a suprapubic catheter (RICHES 1979).

If the patient is being considered for a prostatectomy a careful history must be obtained and a full clinical examination performed with a check on cardiac status, haemoglobin, urea, and electrolytes, bacteriology of the urine and ideally an intravenous pyelogram. MARSHALL et al. (1975) have shown that there is no need to postpone operation for this investigation as it can be done later. Some patients will require long-term catheterisation in the management of chronic retention and incontinence when they are unfit for surgery (FERRIE et al. 1979).

H. Cystitis

Cystitis in older men is usually found with urinary stasis either from prostatic disease or rarely urethral stricture, and in women this disease is frequently associated with a cystocoele. In both sexes, when the cystitis does not yield to appropriate treatment, the complications of bladder stone or of bladder tumour must be considered. Cystitis may occur when the patient has been in bed for some time or is

suffering from disease of the nervous system with bladder dysfunction, and the infection may be introduced into the bladder by catheterisation. This infection must be distinguished from the urethral syndrome, which causes similar symptoms but without detectable bacterial infection of the urine. In elderly women this is commonly associated with senile vaginitis but may also be found after gynaecological surgery. Abacterial urethritis is common in senile vaginitis.

I. Causes

In cystitis, bacterial infection is usually due to *Escherichia coli* but coagulase-negative *Staphylococci*, *Proteus*, *Klebsiella*, *Pseudomonas*, and *Streptococcus faecalis* may be discovered. The symptoms found in acute cystitis are frequency of micturition, a scalding feeling on passing urine and sometimes severe pain in the lower abdomen. Haematuria may be noted in cystitis in elderly people. The diagnosis is made by examination of the urine and a mid-stream specimen should be submitted promptly for bacteriological examination. Cells should be looked for and the urine should be tested for protein and sugar. It is common practice to commence treatment without cystoscopy and radiological examination, and it is often necessary to start treatment before the results of the sensitivity tests to antibiotics are available. Carcinoma of the bladder may present as a cystitis which has occurred for the first time in an elderly person. In very old people very elaborate searches for the underlying cause are only performed if the cystitis fails to respond promptly to treatment or recurs. Some recommend cystoscopy in cases of recent onset in older people. Macroscopic haematuria is common in uncomplicated cystitis but in the older fit person would render cystoscopy mandatory.

II. Treatment

Treatment consists in advising the patients to drink plenty of fluids and in severe infections co-trimoxazole tablets two three times per day are given with amoxycillin as an alternative drug. In this condition, therapy should continue for 7–10 days. The choice of antibiotic may have to be changed as a result of the bacteriologist's report or failure of clinical response to treatment. After an interval of 10 days a mid-stream specimen should be repeated for test of bacteriological cure.

I. Incontinence of Urine

Incontinence is present when urine is passed repeatedly other than into a suitable container and when this occurrence is out of the patient's control (Anderson 1976). The International Continence Society (1976) defined it as a condition in which involuntary loss of urine is a social or hygienic problem and is objectively demonstrable. The prevalence of this symptom varies, depending on the criteria used, from 13% to 48% of older patients in hospital and between 1.6% and 42% in the community. Thomas et al. (1978) found by postal survey that the incidence

of incontinence occurring twice or more per week was 7.6% for males and 12.5% for women 65 years and over living in the community. If severe incontinence alone is considered, the figure in the community over the age of 65 years does not exceed 7% (WILLINGTON 1976). If stress incontinence is excluded, this symptom probably occurs with equal frequency in both sexes. While the prevalence of incontinence does not increase with age, opinions vary as to the importance of urinary infection as a cause. WALKEY et al. (1967) concluded that chronic urinary infection did not exert a major influence in the production of incontinence. Acute urinary infections may be related to incontinence. WILSON (1948) and SOURANDER (1966) found an association between infection and incontinence. It is generally agreed that old people who are confined to bed are more likely to be incontinent. ISAACS and WALKEY (1964) found that incontinence was not related to age, sex or duration of stay in hospital but to the presence of brain damage and whether the patient was able to dress, feed or walk independently.

I. Causes

Causes of urinary incontinence include disorders of the nervous system, intrinsic lesions of the bladder neck, obstruction of the urethra, extrinsic pelvic disease, fistulae, stress incontinence, and the uninhibited neurogenic bladder, and these are all found in old people.

Transient incontinence may be noted due to acute urinary infection, acute confusional states, acute cerebrovascular disease, retention with overflow due to faecal impaction, drugs or psychological causes. This type of incontinence may occur in almost any acute medical condition, e.g. pneumonia and in the last days of life. Where increasing amounts of urine are passed by elderly individuals with small bladders, incontinence has been described, e.g. in diabetes mellitus, chronic nephritis or following the administration of a diuretic. Loss of mobility associated with diminished bladder volume and urgency may increase the risk of incontinence and this may be found in patients with parkinsonism, arthritis, stroke or fractures. A distant toilet, decreased mobility and urgency add up to incontinence. False incontinence may be induced on admission to hospital by a combination of lack of knowledge as to the situation of the toilet with oversedation. It may be necessary to rouse the patient during the first night in hospital and take her to the W.C. in order to prevent incontinence. It is likely that any old person will have been getting out of bed at home at least once a night for many years to micturate. The combination of strange surroundings, night sedation and urgency mean that many older patients are wrongly labelled as incontinent. Hospitals should have clear directions as to where the toilets are and a kindly welcome should be given to the patients trying to overcome the strangeness and fear associated with hospital admission. The rheumatoid hand of the old man may not be able to maintain a tight grip on a urinal which may spill and the patient may be thought to be incontinent. Communication problems in the dysphasic and the blind must be overcome.

Established incontinence is most commonly due to the uninhibited neurogenic bladder, prostatism, prostatic obstruction with overflow, atonic neurogenic bladder, atrophic trigovaginitis, and stricture.

Before considering these in detail it must be stated that as people age, there is a diminished time interval between their awareness of bladder fullness and their ability to delay the act of micturition. The higher centre control weakens so that postponement of micturition may only be possible for a matter of minutes. In chronic brain failure (dementia) at the onset of the illness inability to control the flow of urine may be nocturnal but as awareness diminishes incontinence occurs during the day as well. Prolonged urinary incontinence without recognisable disease suggests brain damage.

Disorders of the nervous system cause urinary dysfunction in older people and may be considered under the different types of neuropathic bladders with sensory and motor loss (McGuire 1980).

An autonomous bladder may result from loss of bladder sensation due to destruction of 2–4 sacral segments of the cauda equina from tumours or other causes of compression. Emptying of the bladder occurs from time to time due to intrinsic contractions. Painless bladder distension leads to overflow incontinence. The bulbocavernous reflexes are absent and the patient micturates by straining or with the help of manual compression.

An atonic bladder is found when loss of bladder sensation takes place in lesions of the posterior nerve roots or posterior horn cells, e.g. in diabetes mellitus, tabes dorsalis or alcoholic peripheral neuropathy. Increase in bladder volume occurs with retention, and overflow results. The bladder is not trabeculated and the patient can be helped by intermittent catheterisation. Diabetic patients are reputed to tolerate a Foley's catheter poorly.

A flaccid decompensated bladder may also be associated with obstruction of the bladder outlet in, e.g. prostatic enlargement or in women with a large cystocoele.

A reflex bladder is due to loss of bladder sensation in lesions occurring between the sacral segments of the cord and the higher centres, e.g. in spinal injury or tumours, and in this type the bulbocavernous and anal reflexes are present. The bladder empties reflexly and is unstable; the external sphincter response may fail to relax and high intravesical pressures may occur. If frank detrusor-sphincter dyssynergia is present the hyperreflexic sphincter response may be depressed by small doses of skeletal muscle relaxants, e.g. dantrolene sodium (Dantrium), baclofen (Lioresal) or diazepam (Valium) and thereafter anticholinergic therapy given in small doses.

Another type of autonomous bladder is produced by loss of motor preganglionic nerves to the bladder and on this occasion the bladder tone is maintained. Intravesical pressure generated by filling ultimately equals intraurethral pressure and urine is forced out of the urethra. Areflexic voiding takes place with a large residual urine. Vesico-ureteral reflux is common and the bladder usually becomes trabeculated and hypertonic. The use of anticholinergic agents with intermittent catheterisation is helpful. Radical pelvic surgery for malignant disease of rectum, uterus or prostate may be associated with motor and sensory denervation.

The uninhibited bladder is found when there is damage to the brain, i.e. in the higher centre or its cortical connections, e.g. in chronic brain failure (dementia) or following a cerebrovascular accident or in frontoparietal tumour. Sensation is retained but ability to inhibit reflex contractions is lost and the bladder becomes un-

stable. The unstable bladder shows uninhibited contractions at any capacity and this can happen during normal filling or following a rise in intra-abdominal pressure and in association with coughing or laughing or standing up. There is often a history of childhood bed-wetting. This is one cause of urge incontinence and is common in old people whose desire to micturate is so strong that control is lost before the toilet is reached. Frequently the same type is associated with urinary infection and may also be found where there is bladder calculi or neoplasm. Outflow obstruction in men with enlarged prostate or stricture may cause instability and the persistence of incontinence or urgency after prostatectomy is usually due to unrecognised instability. Symptoms of unstable bladder include frequency, nocturia, urgency, urge incontinence, stress incontinence, and enuresis. It appears that the motor limbs of the volitional pathway for suppression of detrusor events are intact but subconscious recognition of detrusor reflex events is lacking. Afferent information either never reaches the cortical centres or reaches them too late. For the treatment of this condition some recommend a rigid programme of timed voiding every 2 h and the use of anticholinergic drugs such as Imipramine or Propantheline. Sometimes an indwelling Foley's catheter makes the condition worse because the patient feels the need to void the residual urine and the urine leaks round the catheter. Long-term catheter management is discussed by FERRIE et al. (1979).

Intrinsic lesions of the bladder neck such as tumours of the bladder or bladder stone may cause incontinence, while obstruction of the urethra from prostatic enlargement may present with a retention overflow and little past history.

Extrinsic pelvic lesions such as disease of adjoining organs, e.g. uterus, rectum or sigmoid may be responsible for incontinence. Where there is a fistula the patient is always wet, and a ureteric or bladder fistula may be found.

Stress incontinence is defined as an involuntary loss of urine through an intact sphincter as a result of sudden increase of intra-abdominal pressure with the patient in the upright position. 95% of significant stress incontinence occurs in multiparous women and is probably the result of the supports of the urethrovesical junction being either stretched or torn during child birth. The low incidence in those who have had a Caesarian section is the same as for nulliparous women. While it is agreed that the basic problem is inadequate support of the bladder base, the vesical neck and the proximal urethra, one theory is that when the bladder neck and the urethra are displaced downwards they are no longer intra-abdominal and thus outside this field of force. When then the intravesical pressure rises without a concomitant increase in intraurethral pressure, stress incontinence occurs. Stress incontinence takes place during coughing or straining, and the absence of other symptoms distinguishes it from an unstable bladder. When instructed to cough about one-half of patients with genuine stress incontinence actually leak during coughing. There is often deficiency of the striated muscle of the pelvic floor. GRABER (1977) in a comprehensive review described iatrogenic stress incontinence following gynaecological surgery. He emphasised the need for a complete pre-operative assessment including adequate history, physical examination, and careful evaluation of the urogenital area and commended the use of urodynamic studies. Cystometry is essential to differentiate detrusor dyssynergia, urge incontinence, neurogenic dysfunction and change due to disease or irradiation. Determination of residual urine after voiding is a most important parameter. A significant amount

of urine indicates neurogenic deficiency or urethral obstruction. Surgery performed on a contracted, very dilated or dyssynergic bladder is doomed to failure.

II. Clinical Examination of the Incontinent Patient

The clinical examination commences with a full history of the present complaint with a complete review of the patient's past illnesses in consultation with a relative or friend. This is time-consuming but essential. Knowledge must be obtained about the duration of the incontinence, the time of day or night it occurs and the presence of any associated symptoms. Incontinence that takes place only on coughing or with other causes of raised intra-abdominal pressure unassociated with other symptoms is stress incontinence. Most patients will have a stable bladder; the amount of urine loss is small. Frequency and urgency with urge incontinence giving evidence of flooding suggest detrusor instability (FENELEY 1980).

A comprehensive physical examination should be accompanied by the completion of a mental test score. As well as the physical assessment of the patient's condition it is essential to make a judgement on the patient's mental state. The amount of highly specialised investigation and the use of complicated apparatus will depend on the mental ability of the patient. Thus this appreciation of the patient's brain capacity is necessary not only for diagnosis but for the overall plan of care. A simple classification of the mental disorders of the elderly is as follows:
Brain failure: acute or chronic
Disorders of mood: depression
Other disorders: anxiety states, paranoid states, personality disorders

In assessment of the mental state a scoring card can be very helpful. This is based on the function of certain mental activities, e.g. to test immediate memory by seeking the recall of a simple statement; remote memory is checked by asking the place and date of birth and similar questions; other tests are orientation in time and in place, e.g. what is the date? where are you? what place is this? and general information, e.g. name the prime minister. A simple test of memory and intellectual function was described by CAIRD and JUDGE (1974). It is wise to make some value judgement of the patient's ability to co-operate in the diagnostic routine and in the future planned therapy.

Inspection of the perineal area is essential and ascertainment of bladder size by palpitation should always be followed by a rectal examination and in women by an examination per vagina. Where indicated a bimanual examination of the bladder should be performed. The testing of the bulbocavernous reflex and the search for peri-anal anaesthesia should be routine. Urine analysis, a mid-stream urine for culture and examination of the urine by microscope should be untertaken. Blood screening, biochemistry and erythrocyte sedimentation rate test with a chest X-ray and plain X-ray of abdomen are necessary. Further investigation should be performed in consultation with a urologist. If there is one lesson from recent advances it is the importance of urodynamic studies in the appropriate case. An intravenous pyelogram will often be necessary as will cystoscopy, while retrograde pyelography, renal or bladder ultrasound and micturating cystometrography all have their place. The more accurate the diagnosis, the more likely the cure. Diagnostic techniques were reviewed by GLEN (1979).

III. Treatment

A complete reorientation of planning of home accommodation and of hospital is essential in dealing with incontinent patients. The term designing towards continence was used by HOOD (1976), who pointed out how frequently older people were in accommodation where the toilet was an unreasonable distance from the sleeping space and reminded us that many old people are unable to walk more than 10 metres before becoming incontinent. The implications for design are obvious; hospital beds must be low enough for the old person to rise at night and this requirement can be met by the use of adjustable height beds, and there must always be a toilet, or in domiciliary practice a commode, a short distance from the patient. The advantages for incontinent patients of clothes which can be removed quickly are apparent and MANDELSTAM (1977) has demonstrated what can be done in this respect. In modern hospitals where incontinent patients are being cared for, it is essential to provide the most up-to-date labour-saving equipment for bathing, lifting, and handling overweight disabled people. Modern methods of foul linen disposal, disposable bedpans and an abundant supply of disposable appropriate pads, pants, and suitable clothing are required (ADAMS 1977).

The treatment of incontinence will depend on the diagnosis and certain basic decisions must be made. Is the incontinence of urine true or false? Is it transient or established? The incontinence chart must be inspected to discover when the incontinence is taking place, i.e. during the day or night or throughout the 24 h. Is there also incontinence of faeces? This may increase the likliehood of chronic brain failure being considered. The incontinence record is invaluable also in determining the progress or otherwise of the individual and of great help when the time comes for discharging the patient, e.g. to an old person's home as evidence of complete continence. It also ensures regular attention to the patient by the nursing staff and without doubt has a stimulating effect on the patient's morale, especially if reinforced by active encouragement.

The unconditional need for kindness in the treatment of incontinence was stressed by ADAMS (1977), who condemned the occasional inconsiderate behaviour or open rudeness to incontinent patients. Difficulties common to most elderly patients and sometimes not understood, especially by untrained staff include: lack of awareness of those with clouded consciousness, the frequent impairment of sensory perception, difficulty of communication with deaf or dysphasic patients, self-consciousness of those with insight and postural difficulties of those who have to contend with arthritis when using a bedpan and the aggravation caused by apprehension and neglect of efficient routine management.

By means of physical and mental assessment it is possible to distinguish those who are mentally clear and can co-operate. From the very start of treatment it is a great advantage if the physician has knowledge of the social background and the home conditions of his patient. He then has foreknowledge of how fit the patient has to be to return to that particular environment. Plans can be laid for necessary alterations to the house to suit the residual disability of the patient.

Simple ideas like improving the mobility of the patient can transform the situation, e.g. from the use of levodopa in parkinsonism and imipramine in depression or adjustment of the physical environment. While the diagnosis is being made the

patient where possible should be out of bed and have a careful chart taken of his incontinence habits. These patients with chronic brain failure (dementia) must have an accurate assessment of their incontinence and then a well-planned pattern of management. It must be ascertained that no curable condition has been overlooked and if the diagnosis is one of intractable incontinence that suitable appliances or other therapy are given.

Transient incontinence demands initially a correct diagnosis and then the treatment is essentially that of the underlying condition. It is important to avoid the use of a catheter if possible. It must be noted that the patient may not complain of having a distended bladder and that this condition is one of the commonest causes of restlessness in the older patient, especially following a stroke or after an operation. Change of environment and lack of awareness of the new situation may produce a temporary phase of incontinence, which will pass after a few days. If the patient is male and immobile in this type of incontinence, a sheath-type appliance may be useful. In many elderly men with a recent stroke, incontinence may be noted during the night only, and a urinal placed between the legs may keep the individual dry at night. If the patient is conscious, every effort should be made to sit the patient out of bed and on to a commode. If an indwelling catheter is required, the insertion should be regarded as requiring the same standard of asepsis as any surgical procedure.

Intractable incontinence is treated with the objective of keeping the incontinent patient independent and dry with dignity; some form of protection must be provided. Therapy of this condition demands the need for a management scheme and this in turn depends on the availability of an incontinence chart to give clear indications of the pattern of the incontinence. MANDELSTAM (1980) gave a full description of the types of appliances available. She stressed the importance of encouraging the patients to talk about incontinence and to reveal their worries. Patients in conversation may give valuable clues, which may help to solve their own problems. The physician must be prepared to give ample time to these patients. When urgency or frequency is the main difficulty a commode may be of great assistance and many elderly cardiac patients given powerful diuretics are not truly incontinent but will become so unless the toilet is very near or a commode is provided. This may prevent the need for hospital admission. Small urinals are available now for females which can be slipped under the buttocks and can be handled by the patient herself. If this is impossible the help of one person only is needed as the buttocks do not require to be elevated from the bed or chair. The old woman who is living alone will need a commode beside her bed if she is using a small urinal to empty the contents.

One such urinal is the Subseal and another is called St. Peter's boat, which consists of a pointed plastic dish with a handle and can be slipped between the legs and used in a standing position. These devices were described by MANDELSTAM (1980) and information was given as to suppliers. For intractable incontinence where the patients have no control over the bladder, protection can be given using pants with a replaceable absorbent pad. One such type is called the Kanga pants (WILLINGTON 1976) and consists of pants which fit tightly and have a pouch containing a pad which absorbs urine. This pocket can be opened from the outside and the pants do not require to be changed to insert another absorbent pad. The patient has to

be measured so that the pants fit firmly like a bathing suit. Both men and women can wear the pants but it is essential to be aware of how often the pads become saturated or the urine leaks back towards the patient. It is wise to encourage the patient to go to the toilet every 2 h as the pad cannod absorb all the contents of a full bladder. For patients who have to live with an indwelling catheter, devices like the Shepheard sporran, which has an adjustable waist belt supporting a drainage bag, can be worn by both sexes (MANDELSTAM 1980). Underpads are useful particularly for an old person living at home with no one to care for him or her during the night. The Kylie bedsheet combines a draw sheet and an underpad. It is made of an absorbent material which is quilted and allows the urine to spread across the sheet and not gather under the patient (MANDELSTAM 1980).

Treatment of stress incontinence depends on an accurate diagnosis, confirmed where possible by cystometry and urethrocystoscopy. In older women in whom an operation may be inappropriate, the use of pessaries to elevate the bladder neck may be tried and this course of action would be taken in consultation with a gynaecologist whose advice would also be sought regarding any operative procedure. Some benefit may arise from oestrogen by mouth or applied locally as a cream. Dilatation of the urethra may be of help, and if there is urgency, drugs such as Probanthine may improve control. The treatment of choice is operative and demands that the patient be referred to a gynaecologist. The different operations were reviewed by GRABER (1977). The use of faradism (intermittent) and pelvic floor exercises may improve the pelvic floor tone (KEGEL 1951). The exercises can help women with stress incontinence and can diminish frequency of micturition and nocturia (SHEPHERD 1980). Electrical stimulation of the pelvic floor by electrodes worn either intravaginally or intra-anally may be tried (GLEN 1979). These devices and the implantation of electrodes in the levator muscles have less application to elderly patients (SHEPHERD et al. 1980). Useful general advice on incontinence was given by WILLINGTON (1978).

J. Drug Therapy in Incontinence

The use of drugs in the treatment of incontinence has been in general unsatisfactory. Anticholinergic drugs are of value in the treatment of unstable bladder contractions in uninhibited neurogenic and irritable bladders, e.g. in urge incontinence. Such drugs should not be given where there is a possibility of glaucoma or prostatic obstruction. The most useful drug of this type is emepronium bromide. The side effects are mucosal ulceration of the mouth and occasionally of the oesophagus, and patients should be warned not to keep the tablet in the mouth but to swallow it immediately with plenty of fluid.

Propantheline bromide (Probanthine) also produces increase in bladder capacity and reduction in uninhibited contractions and like flavoxate hydrochloride, which has a relaxant effect on the bladder, and imipramine, which has anticholinergic properties, has been of use in similar conditions.

The alpha-adrenergic antagonist phenoxybenzamine is worthy of trial in patients with voiding difficulties due to neurogenic disorders of bladder function,

e.g. spinal cord injuries. It is of use where there is a spastic external sphincter. In patients with bladder instability the beta-adrenergic agonists orciprenaline and salbutamol have been tried (FENELEY 1980). Uninhibited detrusor contractions are also diminished by newer drugs including prostaglandin-synthetase inhibitors, e.g. indomethacin or flurbiprofen (STANTON 1980), while phenylpropanolamine stimulates alpha-adrenergic receptors and increases urethral resistance (AWAD et al. 1979). Cholinergic drugs have been used with caution to re-establish voiding after surgery or in selected patients with the atonic type of neurogenic bladder, e.g. bethanecol subcutaneously initially then later orally. Cholinergic drugs can cause severe side-effects, e.g. sweating and abdominal colic. The anticholinerase preparation, distigmine bromide is an alternative choice and can be used orally. Skeletal muscle relaxants, e.g. dantrolene sodium (Dantrium) may be tried where detrusor-sphincter dyssynergia is present. Finally oestrogen preparations must be kept in mind where atrophic (senile) vaginitis is a component in causing the urinary incontinence.

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Haematological System

Blood in the Aged

P. DE NICOLA and G. CASALE

A. Ageing of Bone Marrow

Bone marrow gradually diminishes in volume, starting after adolescence. Its involution is particularly marked in the presenile (45–60) and senile age (over 60). The haemopoietic tissue is reduced and replaced by fat and connective tissue, which is increased also in order to compensate the enlargement of the bone inner space, due to osteoporosis.

The *total volume of bone marrow* is about 1,500 ml in the adult and is progressively reduced during ageing, above all in the tibia, ribs, and vertebrae. Fatty marrow was not found in the vertebrae below 60, but was present in 42% in the 6th decade, 61% inthe 7th decade, 76% in the 8th decade, and 100% in the 9th decade (TANAKA and INOUE 1976).

In the sternum the *cellular density* in the 7th decade is reduced by half in 50% of subjects and is lower than 20,000/mm^3 in 3% of elderly subjects (GINGOLD et al. 1958). The accumulation of fat begins in areas adjacent to larger veins, while the subcortical areas remain active as primary sites of marrow haemopoiesis. Due to the progressive accumulation of fat in the bone marrow, there is a decrease of the haemopoietic activity with ageing. While in the adult there are about 100,000 haemopoietic cells/mm^3, after the age of 60 there is a reduction of more than 50%. A significant correlation was found between the amount of haemopoietic bone marrow and the haemoglobin concentration in peripheral blood (SCHRODER and TOUGAARD 1977).

In adddition to the influence of ageing on the deterioration of the bone marrow, the following factors may play a role in this respect: (1) vascular alterations, with reduction of blood flow and local hypoxia (alteration of bone marrow micro-environment); (2) decrease of factors enhancing proliferation (e.g. hormones); and (3) an actual proliferative impairment and exhaustion in the course of life.

Erythropoiesis is more affected than leucopoiesis, with a reduction of the leucoblastic/erythroblastic ratio. The mitotic indexes are decreased in all haemopoietic series. Erythropoiesis may often show a maturation arrest in the prehaemoglobin phases, probably related to a decreased iron utilization.

In the bone marrow of elderly subjects there are several *cytological alterations*, such as:

1. Increase of the cytoplasmatic acidophilia
2. Frequent occurrence of nuclear picnosis
3. Decrease in the number of specific granules in granuloblasts
4. Sometimes, alterations of cellular maturation, with arrest of cytoplasmatic division and presence of polyploid elements

A characteristic of ageing is the loss of the Y chromosome in phenotypically normal old persons (PIERRE and HOAGLAND 1972). The presence of cells with 45, X constitution, may be observed also in peripheral lymphocytes and is related to normal ageing. These are frequently also findings in males with chronic myelocytic leukaemia, pernicious anaemia, sideroblastic anaemia, and aplastic anaemia.

B. Red Blood Cells

I. Erythrocytes in the Aged

In the aged there is a tendency to a *slight decrease of erythrocytes, haemoglobin, and haematocrit* values. Differences between males and females are not as evident, as in the adult, due to the cessation of menses in females. Mean diameter and mean corpuscular volume of red blood cells are often reduced. In general these changes in erythrocytes are associated with anaemia, but not uncommonly they may be considered within the normal range, above all at extreme age.

In old age, *red cell survival time* is normal (HURDLE and ROSIN 1962; WOODFORD et al. 1962), but CASASSA et al. (1957) found that erythrocytes of young people transfused into old subjects show a longer half-life than that of the donors, while erythrocytes of old subjects transfused into young people are soon destroyed.

In the elderly, red cells may show a *decrease of osmotic resistance* (DETRAGLIA et al. 1974) and a *diminution of flexibility* (CERNY et al. 1972).

The following *biochemical changes* are particularly significant:
A decrease of the content of ATP and DPG (2,3-diphosphoglicerate) (BRAIN and CARD 1972; PURCELL and BROZOVIC 1974)
An increase of sodium concentration after 60 compared to the age group between 20 and 44 without sex differences (NAGAKI and TERAOKA 1976)
A decrease of Na^+K^+ATPase with age, apparently due to a changed requirement for potassium (PLATT and SCHOCH 1974)
A change of phospholipids and of fatty acids in plasma membrane composition (GOLD and ALTSCHULER 1972)
An increase of glutathione content (BERTOLINI 1969) and posttranslational modifications of some enzymes (G6PD, PK, aldolase) with a diminution of their molecular specific activity (DREYFUS et al. 1979).

A number of *vitamins*, which are essential for haemopoiesis, are decreased in the blood of the aged, for instance, ascorbic acid, and particularly folic, panthotenic, and nicotinic acid, mostly due to the reduced dietary intake and to malabsorption syndromes.

Absorption of vitamin B1 and B12 seems to be impaired in aged subjects (TAUBER et al. 1957; CHOW 1958), in spite of some contradictory results (HYAMS 1964). According to more recent observations (ADAMS and BODDY 1971) vitamin B12 turnover is not affected in the aged, and also the content of vitamin B12 in the liver of aged subjects was found to be unchanged as compared with young subjects (SWENDSEID et al. 1957).

The *erythrocyte sedimentation rate* is frequently increased in the aged, but the interpretation of such a finding is still debated, because many factors may affect

it, particularly in advanced age. The biophysical modifications of erythrocytes and the alterations of plasma proteins in the aged play a significant role in this respect.

These considerations also apply to the modifications of *whole blood viscosity*, which have been observed by some authors (DITZEL and KAMPMANN 1971; CERNY et al. 1972), but not by others (DINTENFASS et al. 1966). The values of *plasma viscosity* are reported to be lower in elderly than in younger patients with diseases of comparable clinical severity (ROE and HARKNESS 1975), thus representing a non-specific indicator of organic diseases, as erythrocyte sedimentation rate.

Iron metabolism is often altered in aged subjects. There is a progressive decrease of plasma iron and total iron binding capacity in elderly subjects. Values of 50 μg% of plasma iron are rather common and not always considered as abnormal. The percentage of saturation of total iron binding capacity is comparable to that of adult subjects.

Serum ferritin shows a progressive increase with ageing (COOK et al. 1976; LORIA et al. 1979). This finding is considered as a consequence of a reticulo-endothelial activation or as an epiphenomenon of increased iron deposition in the tissues. In fact, 1 ng/ml serum ferritin corresponds to nearly 10 mg iron stored in the tissue.

The amount of iron in tissues such as ferritin and haemosiderin increases with age and is considered as a characteristic histological marker of aged tissues, particularly in liver, spleen and marrow (CULTRERA et al. 1965; VENTURA et al. 1977). The progressive fibrosis of hypophysis and appendix after 40 has been related to an increased iron storage in these organs, which have, however, no direct action on iron metabolism (GREENBERG 1975). It has been suggested that such a finding is due to repeated episodes of passive congestion, with diapedesis of erythrocytes through the wall of anoxic capillaries and local accumulation of iron derived from haemoglobin breakdown. MARX (1979) suggests that the increased iron storage may be also due to loss of muscle mass, decrease of erythrocyte volume or ineffective erythropoiesis.

In advanced age, iron absorption seems to be reduced, probably due to a decrease of gastric juices and other alterations in senile intestine.

Iron utilization is impaired in the aged. The following mechanisms have been suggested: (1) a deficiency of transferrin, thus reducing the deposition of iron in tissues (HEILMEYER 1966); (2) an ineffective erythropoiesis (MARX 1979); and (3) an impairment of the reticulo-endothelial system.

Plasma iron and total iron binding capacity, but not serum ferritin show a circadian rhythm also in old age (CASALE et al. 1981).

II. Ageing of Erythrocytes

The lifespan of erythrocytes show species-specific differences: men (120 days), mouse (50 days), and turtle (500 days). The mechanism of red blood cell ageing is characterized by some *biophysical and biochemical changes*, such as increased density, decreased flexibility, decreased mechanical, and osmotic resistance and a marked alteration in redox and energy capacity (BREWER 1974a, b). The intracellular content of ATP diminishes as a consequence of the reduction of the glycolytic and pentose-phosphate shunt activity, because mature red blood cells have no

functioning Krebs cycle. The ATP and DPG deficit can explain the increased oxygen affinity for haemoglobin and the subsequent diminution of oxygen release to the tissue by old erythrocytes. Due to the decrease of ATP content and, probably, to the alteration of DPG, erythrocytes undergo a loss of the biconcave shape and become more spherical and less flexible. As a result, also the microcirculation of erythrocytes, i.e. their passage through the small vessels, is markedly impaired. All these changes can be due to many causes such as loss of water, increase of intracellular sodium and calcium, diminution of magnesium and potassium, decreased ability to maintain glutathione in reduced form, decreased efficiency of glycolysis and pentose-phosphate shunt, etc. Also erythrocyte membranes undergo a number of structural modifications, such as loss of sialic acid into glycolipoprotids, some modifications in the class distribution of phospholipids, a decrease in negative surface charge density, membrane microfragmentation, etc. These changes in old red blood cells may be produced by the formation of free radicals and peroxides.

Phagocytosis in senescent erythrocytes primarily occurs in the sinusoids of the liver and spleen by means of macrophages. They are destroyed by autologous macrophages by means of selective phagocytosis. They distinguish young and senescent erythrocytes because of the presence of immunoglobulin (IgG) on the surface of the senescent erythrocytes (KAY 1975).

III. Erythropoiesis in the Aged

Erythropoiesis depends on nutritional factors (vitamins, iron, aminoacids, etc.) and on several hormones, such as erythropoietin, corticosteroids, particularly those with an angular (5 alpha) configuration, androgens, and growth and thyroid hormones (ADAMSON et al. 1978).

Erythropoietin was investigated also with respect to ageing. It is a glycoprotein with a molecular weight ranging from 27,000 to 62,000 (GOLDWASSER 1976). It is largely released by the kidney in response to hypoxia. It is active on the erythropoietin response cells (ERC), i.e. erythroid-committed stem cells, and also on a more primitive stem cell, called erythroid burst-forming unit (BFU-E; AXELRAD et al. 1978).

In humans, erythropoiesis during ageing is more affected than leucopoiesis. Often there is a maturation arrest in the prehaemoglobin phase, perhaps in consequence of a decreased iron utilization. Reticulocytes are often reduced in number (MORSIANI et al. 1968). Erythropoietin responsive cells (ERC) significantly decrease in persons over 70, as compared with those under 50 (SHIRAKURA et al. 1978). A significant correlation between ERC size and absolute counts of reticulocytes was observed, without any correlation with erythroblasts in the bone marrow.

IV. Haemoglobin

A *decrease of haemoglobin* is found frequently in elderly persons, with values of 12%–14%, as compared with 14%–16 g% in young or adult subjects (GRAF et al. 1978). An increase of the A_{1c} fraction of haemoglobin may found during ageing. As this postsynthetic alteration of haemoglobin is a characteristic marker of dia-

betes, the increased incidence of diabetes with ageing may be related to such a finding.

Errors in human haemoglobin as a function of age have been observed (POPP et al. 1976). Human haemoglobin A does not contain coded isoleucine. Therefore, the incorporation of this amino acid into haemoglobin A may derive only from genetic and/or non-genetic errors.

According to POPP et al., a total isoleucine substitution may occur as a consequence of expressed mutations at a rate of about 1×10^{-5}/locus/generation. The remainder, 2×10^{-5}, may result from a non-genetic error, probably from a translational error in haemoglobin synthesis.

The average frequency of isoleucine substitution per amino acid residue in human haemoglobin should be 3×10^{-5}. An increase of this frequency with age has been considered as evidence of the error theory of ageing (ORGEL 1963, 1970), on the basis of the following mechanism:

1. An error in the transcription of DNA to mRNA
2. An error in transcription of tRNA
3. An error in misparing of tRNA anticodons and their proper mRNA codons
4. An error of amino acyl-synthetase with formation of a wrong amino acid tRNA complexes
5. A mutation in DNA with exchange of appropriate base pairs and formation of a mutant cell, the haemoglobin mRNAs of which contain isoleucine codons

This hypothesis has been submitted to some criticism (GERSHON 1979).

C. White Blood Cells

I. General Aspects

In the elderly there are no significant changes in the *number of leucocytes* in the blood. According to some observations there should be a slight tendency to decrease. For instance, CAIRD et al. (1972) have claimed that a count above 9,000/mm^3 may be considered as a sign of leucocytosis in the elderly, in contradistinction to the values of 10,000–11,000/mm^3 in the adult.

Some *enzymatic alterations* have been observed in the leucocytes of aged subjects, as for instance a diminution of piruvate kinase and transketolase (MARKANNEN et al. 1972; RUBISON et al. 1976).

The *concentration of vitamin C* in the leucocytes is often low in elderly subjects. Values below 15 $\mu g/10^8$ leucocytes are most frequent in aged long-staying hospital patients, probably due to a low intake of vitamin C (loss during cooking of foods?). Females tend to have higher vitamin C level than males (DHSS 1972) and also in the second half of the year the concentration of ascorbic acid can be higher than in the first 6 months (MILNE et al. 1971).

A correlation between the low vitamin C levels in the aged and mortality has not been confirmed.

II. Granulocytes

The *number of neutrophiles* in the blood is very variable in the aged (between 1,800 and 6,500/mm^3, i.e. 45%–85%, according to CAIRD et al. 1972).

In many cases there is a *shift to the right in the Arneth formula*, with hypersegmentation of the granulocyte nuclei. This may be due to an increased maturation threshold in the bone marrow, with circulating cells in a more advanced phase of maturation, or to a prolongation of the lifespan. The hypersegmentation was considered as an early morphological change in cases of megaloblastosis, above all vitamin B12 deficiency (ADAM et al. 1973).

The *turnover rate of neutrophiles*, as evaluated by the serum lysozyme activity, increases after 60 (RESNITZKY et al. 1978). Further data on the cytochemistry of neutrophiles are concerned with the behaviour of alkaline phosphatase. A score reduction of this enzyme was found in relation to ageing. In elderly subjects over 70 such a finding overlapped that of patients of similar age with chronic myelocytic leukemia (RAY and PINKERTON 1969). Some correlations have also been postulated with polycythaemia in the aged (CONI 1973). However, a slight increase of alkaline phosphatase in granulocytes was found by WAGNER (1974) in healthy aged subjects, and particularly in osteoporotic patients.

Due to the shorter lifespan of granulocytes, eventual modifications of protein synthesis during ageing may be demonstrable, thus confirming the theory of ORGEL (1963, 1970) about the production of altered proteins and nucleic acids in connection with ageing. However, out of seven granulocytic enzymes (also from lysosomes), none exhibited a lower molecular specific activity in old subjects (over 80) as compared to those of young and newborn individuals (RUBISON et al. 1976). For this reason, in newly formed cells there should be no "wear and tear" activity of newly synthesized enzymes, in spite of the many divisions and the many years during which the template DNA has been damaged.

Some functional properties of neutrophiles have been investigated with respect to ageing. The adherence of neutrophiles in vitro was found to be more marked in the aged than in young persons (SILVERMAN and SILVERMAN 1977). In females it should be greater than in males, and this difference is still demonstrable after the menopause up to 9th decade. In aged coloured subjects, values are slightly higher than in aged white subjects. A reduction of adherence was described in the elderly after ingestion of alcohol.

A reduction of chemotaxis in polymorphonuclears was found in only 5 out of 70 healthy aged persons (PHAIR et al. 1978). No significant modifications of phagocytosis for a number of microorganisms (*Staphylococcus aureus*, *Escherichia coli*, and others) have been found in the aged as compared with young subjects (PALMBLAD and HAAK 1978; PHAIR et al. 1978). However, in nearly 10% of healthy aged persons a transient reduction of phagocytosis has been evidenced (PHAIR et al. 1978).

Eosinophiles and basophiles of aged persons have a normal range similar to that of adults.

III. Monocytes

In the elderly, the *monocyte count* is usually normal, but there is indirect evidence of high turnover of these cells. In fact, the increased lysozyme level above the age of 60 (RESNITZKY et al. 1978), which has been interpreted as evidence of a high turnover of neutrophiles, might also be assumed to be evidence of an increased turnover of monocytes, these cells being the main secretors of lysozyme (DAVIES and ALLISON 1978).

Measuring the phagocytosis of opsonized sheep red blood cells, PERKINS and MAKINODAN (1971) demonstrated that the in vitro phagocytic activity of peritoneal macrophages of old mice was equal to or better than the phagocytic activity in young mice. The same authors also found that the activity of three lysosomal enzymes of mice peritoneal macrophages most frequently increased with age.

IV. The Regulation of Granulocyte-Monocyte Production

In old mice, the marrow leucopoietic activity seems substantially normal, but NIR et al. (1975) have found that the serum of old mice submitted to leucopheresis is less effective in inducing leucopoiesis than that of younger mice.

In the aged, TIMAFFY (1962) observed that the capacity of bone marrow to respond to granulopoietic factors is reduced. STANLEY et al. (1972) found in the elderly high levels of colony-stimulating factor (CSF) in urine, but EARNEY et al. (1975) have observed that healthy old subjects have serum CSF levels lower than that of healthy young subjects. During disease, in both age groups the CSF is variable. In the young group, those with acute disease have CSF levels above the normal value, and those with chronic disease have CSF concentration below the normal value. In the old group, those with acute disease also had CSF levels above the normal value, but those with chronic disease instead showed no variation. However, the aged patients with debilitating diseases had CSF below the normal values.

V. Lymphocytes and Lymphatic System

A *decrease of the lymphocytes* in the blood has been described during ageing after the 4th decade, with values of nearly 1,500 cells/μl, as compared with the values of the adult (2,000) (MACKINNEY 1978). Even though such a finding has not been definitely confirmed, it might be related with the age-related changes of immunity. With respect to the immunological system, humoral immunity is related to B-lymphocytes, while cellular immunity is controlled by T-lymphocytes. The number of B-lymphocytes in the spleen and lymph nodes does not seem to undergo any significant change during ageing in disease-free, long-lived mice. In auto-immune-prone, relatively short-lived mice there is an increase of plasma cells. The responsiveness of B cells to stimulation with T-cell-independent or with T-cell-dependent antigens decreases markedly in aged mice. The T-cell component of the immune system seems to deteriorate with ageing, while the B-cell component remains relatively intact (MAKINODAN et al. 1977; KAY and BAKER 1979).

In humans, a *decrease of T cells* and a concomitant relative *increase of B cells* have been found in advanced age (DIAZ-JOUANEN et al. 1975; REDDY and KONG-OO 1979).

The T-lymphocyte impairment is considered as a feature of immunosenescence, in part associated with the involution of the thymus during ageing (HIROKAWA 1977; MAKINODAN 1978). Also spleen and lymph nodes are reduced in volume in the aged. The number of lymphatic follicles is also decreased. In the spleen there is a marked fibrosis, with hyalinosis of the vascular components. The capsula is thickened. Interstitial fibrosis is observed also in lymph nodes.

D. Anaemias in the Aged

I. Introduction

Data on the *occurrence of anaemias* in the aged are rather variable. Figures ranging between 6.4% and 50.7% are reported (HYAMS 1978). Such differences may depend

on the diagnostic criteria, on the type of patients (in hospitals or at home) and also on the fact that anaemia becomes evident only when the compensation mechanism is exhausted. As in other diseases of the aged, anaemias may occur when a situation of unstable equilibrium is broken, thus causing an impairment of erythropoiesis in the bone marrow.

Clinical features of anaemias in the elderly are similar in general to those of adults, but with some differences. Pallor of the skin, for example, may be referred to ageing, thus giving the misleading impression of a normal skin. However, in mucosae and nailbeads, pallor is an important sign of anaemia also in the aged. Cardiovascular and cerebral symptoms of anaemia are often confused with some manifestations of ageing itself or other diseases of the aged, such as dizziness, asthenia, apathy, confusion, breathlessness, tachycardia, oedema in the legs or even congestive heart failure, angina or signs of cerebrovascular insufficiency. Also for these reasons, a routine blood examination is imperative in all aged subjects.

II. Carential Anaemias

A chronic anaemia may be due to a deficiency of iron, folic acid, vitamin B12, and other nutritional factors related to erythropoiesis. An insufficiency dietary intake, a malabsorption or a loss may be the cause of the deficiency. Under these conditions, anaemia may be various in nature, i.e. microcytic, hypochromic or macrocytic, hyperchromic or normocytic, and normochromic. After the depletion of the storage, anaemias develop slowly, with non-specific symptoms, so that a wrong diagnosis may be made. Diagnostic problems also arise from the difficulty in collecting history or in recognizing the nutritional deficiency. The criterium ex juvantibus is often helpful for an exact diagnosis.

Insufficient dietary intake of nutritional factors may be due to an unbalanced diet, with too much milk and not enough meat, liver, kidney, eggs, fresh vegetables, fruits, etc. Further causes of inadequate diets are alcoholism, loss of teeth with masticatory difficulties, dietetic prejudices (fear of atherosclerosis, hypertension, obesity, etc.) and also economic factors.

Malabsorption syndromes may provoke a deficiency of iron, folic acid and above all vitamin B12 (an insufficient dietary intake of vitamin B12 is exceptional). One of the most frequent causes of malabsorption in the aged is represented by gastric maldigestion. This is particularly true for atrophic gastritis, gastrectomy or malposition of the stomach, resulting in an impaired absorption of iron and of vitamin B12. *Atrophic alterations of the gastric mucosa* with secretory insufficiency become evident in the 4th decade, above all in males. They are enhanced by alcohol, tobacco, and certain auto-immunological processes. Due to the reduction of the gastric chlorhydric secretion, the conversion of Fe^{+++} into Fe^{++} is impaired. As a result, a nutritional deficiency due to defective absorption may affect on one hand erythropoiesis and on the other hand also the gastro-intestinal mucosa and its functions, through a vicious circle (gastric atrophy – sideropenia – anaemia – gastric atrophy) (Delamore and Shearman 1965; Jacobs 1971; Bird et al. 1977).

As far as *malposition of the stomach* is concerned, *hiatal hernia* should be considered among elderly patients as an important cause of anaemia. Its occurrence increase after the 5th decade. Because of painful dysphagia, adequate food intake

is often difficult. Patients avoid solid foods and prefer liquid or semiliquid diets, in which iron is poorly represented. Iron absorption is further reduced by an accelerated transit. Here again iron deficiency causes atrophy of the gastric mucosa, achlorydria, and, through a vicious circle, a malabsorption condition. Haemorrhages from hiatal hernia aggravate the loss of iron.

A nutritional anaemia may be due to malabsorption as a consequence of *extragastric alterations*, which are frequently observed in elderly patients. This is true for *infestations by tapeworms* and, furthermore, for *chronic inflammatory diseases* of the digestive tract, with an accelerated transit and impairment of iron absorption. The *abuse of laxatives* may result in an intestinal hypermotility with decreased iron absorption. Also *other drugs* may cause the same troubles, for instance, biguanides, antibiotics, anticonvulsivant drugs, anti-inflammatory drugs, diuretics, antiblastics.

Among carential anaemias, as described above, some of them deserve to be described with more detail, because of their characteristic, typical feature. This is particularly true for iron deficiency anaemias and for megaloblastic anaemias.

1. Iron Deficiency Anaemias

Iron deficiency anaemias are very common in the elderly and may be due to chronic loss of blood, to insufficient dietary intake or to malabsorption. Chronic haemorrhages are particularly frequent, thus inducing a progressive loss of iron. Haemorrhages may occur as a consequence of epistaxis, rupture of ectasic veins or varices (bronchiectasis, oesophageal varices in liver cirrhosis, haemorrhoids, etc.), hiatal hernia, repeated minimal bleeding from gastro-intestinal (GI) erosions, gastric, and duodenal ulcers, GI malignancies, enteritis, diverticulosis (colon and sigma), haematuria, etc. When haemorrhages are suspected as the cause of iron deficiency, faeces should be properly examined for occult blood (POWELL et al. 1979).

In the early phases, haemoglobin, erythrocytes, plasma iron and serum ferritin are within the normal range, whereas total iron binding capacity and iron absorption are increased. In a later phase, plasma iron also falls to under 50 μg%, serum ferritin to under 12 ng/ml and the percentage of saturation of transferrin is less than 16%. After the depletion of iron storage, a microcytic, hypochromic anaemia becomes manifest.

The typical symptoms of iron deficiency may be observed at the same time or later, such as asthenia, anorexia, effort dyspnoea, tachycardia, vertigo, precordial pains, painful dysphagia, atrophy of the oral mucosa and tongue, and fissuring at the angles of the mouth (Plummer-Vinson syndrome). Nails are often brittle and the plate may be concave (spoon nail).

2. Megaloblastic Anaemias

Megaloblastic anaemias are due to a deficiency of vitamin B12 or folic acid or both, which provokes a disordered synthesis of DNA in many tissues and particularly in the blood. There is a retardation in the cell division with abnormal nuclear patterns, without alterations in the cytoplasma. Due to the increase of cell size, megaloblasts, giant metamyelocytes and hypersegmented neutrophiles are found. In the

bone marrow there is a characteristic erythroid hyperplasia, due to an ineffective erythropoiesis. In the aged there may be a combined deficiency of folic acid (or vitamin B12) and iron. In this case the bone marrow is not megaloblastic but normoblastic. Therefore it is important in the aged to evaluate the plasmatic concentrations of vitamin B12 and folic acid.

a) Pernicious Anaemia

In the past, pernicious anaemia affected also young and adult subjects, whereas now it is rarely observed before the age of 50. This is probably due to better nutrition and to the abuse of liver extracts and vitamin B12. Impaired absorption of vitamin B12 (poor nutrition) and atrophy of the gastric mucosa are the actual cause of the disease. In the elderly, the lability of the bone marrow makes them particularly susceptible to pernicious anaemia and also some contributory factors may be important, such as the presence of a latent, senile pancreatic insufficiency that may impair vitamin B12 absorption (NIEWEG et al. 1962) or a prolonged antibiotic treatment with an indiscriminated inhibition of the bacterial flora in the bowel, which may disturb the synthesis of the B-group vitamins.

Auto-immune mechanisms have also been considered for the defective vitamin B12 absorption. Auto-antibodies against gastric parietal cells were found in 84% of patients with pernicious anaemia. Similar antibodies were also found in subjects with atrophic gastritis without anaemia. In nearly half of patients with pernicious anaemia it is possible to find auto-antibodies against intrinsic factor; these auto-antibodies are not present in patients with only atrophic gastritis.

Symptoms of pernicious anaemia in the aged are in part different from those in young patients. Often some neurological, GI and cardiovascular symptoms (stomatitis, dysphagia, paraesthesias, asthenia, anorexia, etc.) are referred to the general ageing process. Atrophic glossitis is often very marked and is similar to the finding in other deficiency states occurring an advanced age. Mental symptoms are often considered as a sign of cerebrovascular insufficiency (cerebral arteriosclerosis).

Blood and bone marrow alterations are less pronounced than in young patients, and very low counts of erythrocytes are often well tolerated.

b) Folic Acid Deficiency Anaemia

Folic acid deficiency anaemia is a megaloblastic anaemia, which often occurs in chronic alcoholics (mostly wine and whisky, but less in beer, because of its high content in folic acid). Also antagonists of folic acid (6-mercaptopurine, methotrexate, etc.) may cause a folate deficiency. In the aged, the following causes may be considered: inadequate dietary intake, malabsorption, increased utilization (malignancies, infections, thyreotoxicosis, blood disorders, etc.) and loss of vitamins (liver disease, enteritis, psoriasis, etc.).

The clinical patterns are similar to those of vitamin B12 deficiency.

3. Other Macrocytic, Non-Megaloblastic Anaemias

Other macrocytic, non-megaloblastic anaemias may occur in chronic liver diseases, in hypothyroidism and in a few other conditions. Their pathogenesis is unclear.

4. Therapy of Carential Anaemias in the Aged

Therapy of carential anaemias in the aged is similar to that of other ages. In elderly patients particular attention should be paid to the following aspects.

Dietary deficiencies should be corrected and diet should be supplemented with vitamins. Unilateral diets should be avoided, as well as the undiscriminative use of laxatives. Social and psychological advice should be given to combat dietetic prejudices and to identify economical reasons of a nutritional deficiency. Defective chewing should be given a proper treatment.

In sideropenic anaemias, 150 mg iron are generally necessary to obtain an increase of 1 g% haemoglobin. The intravenous route is preferable to the oral or intramuscular routes because of the better absorption. In macrocytic and megaloblastic anaemias, the usual treatments (liver extracts, vitamin B12, folinic acid, etc.) are effective also in the aged. As iron is often deficient under these conditions, it should be administered, particularly in the erythropoitic stimulation phase. Neurological and GI symptoms respond to this therapy also in the aged, but with some delay. When an auto-immune mechanism is present, corticosteroids are the only effective treatment. Anabolic compounds are indicated in macrocytic carential anaemias, if the bone marrow is hyporegenerative. The cause of bleeding should be identified and corrected in cases of anaemias due to chronic bleeding, and transfusions and/or iron are then indicated.

III. Haemolytic Anaemias

Haemolytic anaemias are characterized by a decreased life span of erythrocytes due to extrinsic or intrinsic factors. Haemolysis may be acute, or chronic or episodic. In general there are no differences between aged and young patients. Acute haemolysis may cause in the elderly a rapid, sudden worsening of mental functions, thus misleading the diagnosis.

Among haemolytic anaemias due to intrinsic factors there are many hereditary disorders, which may reach old age only when they are in a heterozygous state (e.g. thalassemia syndromes, sickle cell anaemia). However, rare cases of hereditary spherocytosis have also gone undiagnosed beyond the age of 50 or even in 7 th decade (KRAVITZ 1978).

Haemolytic anaemias due to extrinsic (extra-erythrocytic) factors may be due, also in the elderly, to incompatible blood transfusions, certain chemical agents and drugs (alpha-methyl-dopa, penicillin at high dosage, phenacetin, mephenamic acid, lead, etc.), some infections (malaria, beta-haemolytic streptococci, *Escherichia coli*, *Salmonella*, etc.) and physical agents (severe thermal burns).

Auto-immune haemolytic anaemias may occur in the course of chronic lymphocytic leukaemia, lymphomas, gammaglobulinaemias, etc., besides the classical idiopathic auto-immune haemolytic anaemias and the paroxysmal cold haemoglobinuria, which are rare also in aged patients.

IV. Aplastic Anaemias and Pancytopenias

Aplastic anaemias and pancytopenias (bone marrow failure) may be idiopathic or due to chemical or physical agents. The former are most common in the aged. Sev-

eral myelotoxic agents (e.g. cytostatic drugs), as well as ionizing irradiations, are frequently related to the onset of an aplastic anaemia. Some infectious diseases, but above all many blood diseases, may be the cause of an aplastic anaemia, associated with a mild to marked bone marrow insufficiency. If there is a reduction not only of erythrocytes, but also of leucocytes and platelets, the haematological patterns are characterized by a pancytopenia, also called global bone marrow aplasia, in contradistinction to the partial bone marrow aplasias, as occurs in aplastic anaemias, agranulocytosis or thrombocytopenias.

Pancytopenia or bone marrow failure may be related to a proliferative syndrome (cancer, haemoblastosis), as often occurs in the elderly, or to aregenerative syndromes, as well as to nutritional, metabolic or hereditary disorders.

A particular type of anaemia due to bone marrow exhaustion may be observed in *elderly subjects with thalassaemia minima.* They often present an erythropoietic hypoplasia in the bone marrow and a hypochromic, microcytic anaemia in the blood. Probably, the haemopoietic tissue, after many years of a particularly intense regenerative activity, finally undergoes a regenerative exhaustion (Baserga and Morsiani 1975). In these cases the bone marrow failure may be due to other causes such as deficiency of folic acid or nutritional factors.

The onset of aplastic anaemia may be extremely sudden, but generally it is insidious, especially in the aged. Mild purpura is often the first symptom. Angina, severe infections and haemorrhages are observed in the course of the disease. In the aged, heart failure, as related to anaemia, may occur at the beginning of the disease. A decrease of erythrocytes, leucocytes, and platelets, as well as of reticulocytes, is observed in the peripheral blood. Serum iron and total iron binding capacity are moderately decreased. Bone marrow examination is fundamental for the diagnosis.

Prognosis is very poor, with survival less than 6 months in many cases. Treatment is symptomatic and based on transfusions, antihaemorrhagic drugs, drugs active on microcirculation, antibiotics, and corticosteroids. Transplantations of bone marrow in aged persons might be advantagous.

V. Anaemias Due to Chronic Diseases

Anaemias due to chronic diseases are usually normocytic and normochromic, but sometimes also microcytic and hypochromic. Chronic infections are often concerned with this type of anaemia in the aged, such as tuberculosis, subacute bacterial endocarditis, bronchiectasis, chronic bronchitis, chronic colitis, relapsing angiocolitis, and cystopyelonephritis. Also in other chronic diseases, such as malignancies, inflammatory disorders and renal insufficiency, there is often anaemia. This finding is frequent in rheumatoid arthritis and other collagenosis.

According to a description of Cartwright and Lee (1971), anaemias due to chronic diseases are usually mild and characterized by a decrease of plasma iron, total iron binding capacity and saturation of transferrin. However, in contrast to iron deficiency anaemias, serum ferritin is not low, but over 12 ng/ml (Jacobs and Worwood 1975). In the pathogenesis of these anaemias the following factors have been considered: shortened survival of erythrocytes; impaired response of bone marrow to anaemia; and impaired flow of iron from the reticulo-endothelial cells

to the bone marrow. There is often an increase of plasma copper and free erythrocytic protoporphyrin. In malignancies and particularly in renal insufficiency a deficiency of erythropoietic factors has been postulated, even though a toxic pathogenesis may be considered, above all in uraemia.

VI. Sideroblastic Anaemias

Sideroblastic anaemias are rather common in the aged. DATTA (1977) suggests that in a geriatric unit of average size (over 1,000 referrals per annum) at least two cases of primary sideroblastic anaemia would occur every year.

Sideroblastic anaemias are characterized by circulating hypochromic, microcytic erythrocytes or by a dimorphic appearance, i.e. with marked polychromasia and presence of Howell-Jolly bodies, nucleated red cells and stippled cells (DATTA 1977). In the bone marrow there is an increased erythropoietic activity and normoblasts contain ionizable iron granules around the nucleus (sideroblasts). These anaemias are also called sidero-achrestic anaemias, because the erythropoietic tissue is not able to use iron for haemoglobin synthesis. Since iron is not incorporated into heme, total body and serum iron and saturation of transferrin are markedly increased. Ferrokinetic studies show an "ineffective erythropoiesis" with normal reticulocyte count.

Acquired sideroblastic anaemias may be idiopathic or associated to lead or drugs (alcohol, isoniazide, chloramphenicol, antineoplastic drugs, etc.), or also other complicating diseases such as some haemoblastosis, rheumatoid arthritis, uraemia, etc.

Pathogenesis of sideroblastic anaemias is not clear; it has been suggested that the deficiency of piridoxine may provoke a defect in synthesis of heme. In fact pyridoxal-5-phosphate (active form of piridoxine) is a necessary co-enzyme required for the synthesis of aminolevulinic acid (ALA), which is an intermediate step in the formation of protoporphyrin. Therefore in the treatment of the sideroblastic anaemias the use of piridoxine or piridoxal-5-phosphate is justified. Nevertheless, only secondary acquired sideroblastic anaemias show a good response to such a treatment.

E. Disorders of Leucocytes in the Aged

I. Idiopathic Granulocytic Dysfunction

Idiopathic granulocytic dysfunctions are very rare in the aged and in general are secondary to other diseases, such as myeloproliferative disorders or dysmetabolic diseases (diabetes mellitus, uraemia, etc.). A granulocyte defect in the aged was found to be related to the presence of auto-antibodies (MORONI et al. 1976); phagocytosis of bacteria was impaired, irrespective of the presence of auto-antibodies in nearly 40% of all aged patients under study.

A syndrome of anaemia, thrombocytopenia, and subnormal granulocytic function has been described in four aged patients (BERG and BRANDT 1973), but should be reinterpreted, because in two of them a leukaemia developed after a few months and three of them died within 10 months (initial, latent phase of leukaemia?).

II. Neutropenia (Agranulocytosis)

Neutropenia or agranulocytosis may be observed in the aged, within the general patterns of pancytopenia. Cyclic neutropenia is extremely rare in the elderly. Granulocytopenia may be found in systemic infections (e.g. severe bacterial sepsis) or in some lymphomas.

Drug-induced agranulocytosis is most common and of secondary importance after thrombocytopenia and before aplastic anaemia (DE GRUCHY 1975). In addition to antineoplastic drugs, several other compounds may be considered, such as aminopyrine, phenylbutazone, sulphonamides, chloramphenicol, gold salts, antithyroid drugs, etc.

The mechanism of drug-induced agranulocytosis may be immunological, with formation of antibodies, which destroy neutrophiles in the presence of the drug (e.g. aminopyrine). Another mechanism is represented by the direct action on the myelocytic stem cells in the bone marrow and their suppression (e.g. phenothiazine). During the recovery, after the offending drug has been discontinued, the patterns of a hypercellularity in the marrow may give the false impression of a maturative block or even of an acute promyelocytic leukaemia.

In *acute agranulocytosis* there are the signs of a severe septicaemia, with high fever and Schultz angina (ulcerations of the mucous membranes). In chronic agranulocytosis, localized infections (bronchopulmonary system, perirectal region, skin) are more frequent. Phagocytosis and bactericidal activity of neutrophiles are reduced. The risk of bacterial infections is slight when the number of neutrophiles is 1,000 to 1,500 cells/μl, but is greatly increased below 500 cells/μl. Shock due to Gram-negative micro-organisms (*Escherichia coli*, *Pseudomonas*, *Proteus*, *Kleibsiella*, *Staphylococcus aures*, etc.) is frequent in old patients with agranulocytosis, with atypical manifestations (unexplained hypotension, confusion, disorientation). In the absence of fever the correct diagnosis may be delayed until coma and death occur, due to pulmonary oedema, disseminated intravascular coagulation or cardiac arrhythmias.

Treatment is based on antibiotics, corticosteroids and anabolic drugs and, in a few cases, gammaglobulins and specific vaccinations.

III. Leukaemias and Allied Disorders

Recently RAPP (1979) noted that in 1978 there were an estimated 88,300 cases of leukaemias and lymphomas in the United States, resulting in approximately 57,900 deaths. Translated onto a world-wide level, these estimates suggest that 1,766,000 new cases developed during 1978 and that approximately 1,160,000 deaths have occurred because of these diseases. Leukaemia alone will claim 21,500 new victims in the United States and 430,000 victims globally, causing an estimated 15,100 deaths in the United States and approximately 300,000 deaths per year on an international basis.

Acute and chronic leukaemias particularly affect aged persons, besides infants and adolescents. Age distribution is reported in Fig. 1. Chronic myelocytic leukaemia is rare before the age of 40, but then rapidly increases, according to a hyperbolic curve, with a decrease after the age of 75. Lymphocytic leukaemia is most

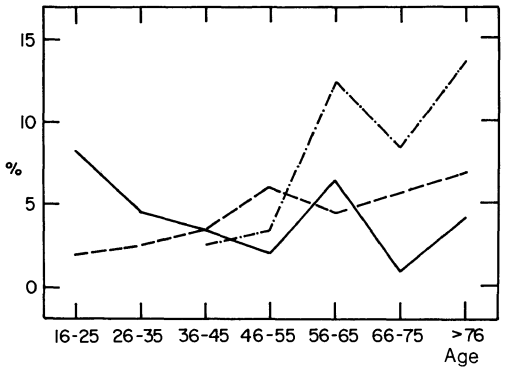


Fig. 1. Frequency of leukaemias in different decades. ------, acute leukaemias; - - - - -, chronic myelocytic leukaemias; - . - . - ., chronic lymphocytic leukaemias

frequent in the 7th decade. Acute leukaemias in the aged are mostly of the myeloblastic type and their occurrence reaches a maximum in the 7th decade. A similar age distribution is true for mortality. Males are more frequently affected than females in the 5th and 6th decades, whereas an equal distribution is observed in the 7th decade, after which males are once again more frequently affected than females by chronic lymphatic leukaemias. For chronic myeloid leukaemias, a ratio of 1:5 has been observed between males and females after the age of 50.

The increasing frequency of leukaemias and allied disorders, as well as of cancer during ageing has been related to the biochemical hypothesis of the free radicals (HARMAN 1968). The concept of myeloproliferative disorders has been suggested for some leukaemias and allied disorders, with reference to the excessive growth of all cells which are normally formed in the bone marrow and may be produced also in other sites (DAMESHEK 1951). For lymphatic leukaemias, which are particularly frequent in the aged, the term lymphoproliferative disorders has been proposed, also including lymphomas and gammapathies, on the basis of more recent knowledge on T/B-lymphocytes (DAMESHEK 1966).

1. Acute Leukaemias

In the aged, the onset of acute leukaemias may be insidious and slow, in contrast to the usual, almost explosive patterns in other ages, in which fever, bone and joint pains, enlargement of spleen and lymph nodes and oral necrotic and ulcerative lesions occur. While these symptoms are uncommon in the aged, cutaneous manifestations are rather frequent. However, the subsequent evolution may be more rapid in the aged than in young patients, with anaemia, thrombocytopenia (haemorrhages!) and bacterial infections (pneumonia, urinary infections, abscesses). The signs of a disseminated intravascular coagulation haemorrhagic syndrome may be present. Although such a behaviour has been widely confirmed, some reports are not in keeping with the difference between aged and young patients in the clinical and haematological patterns of acute leukaemias (BLOOMFIELD and THEOLOGIDES 1973).

The so-called *myelodisplastic syndromes* (acquired idiopathic sideroblastic anaemia, refractory anaemia with an excess of blasts and chronic myelomonocytic leukaemia) may develop an acute leukaemia in nearly 30% of cases. They are also

called *smouldering leukaemias*, are found in patients aged over 50 and frequently exhibit chromosomal abnormalities (ROWLEY and POTTER 1976; KOEFFLER and GOLDE 1978).

On the basis of cytochemical investigations, acute leukaemias have been classified into two groups: acute lymphoblastic leukaemias (ALL) and acute non-lymphoblastic leukaemias (ANLL). Further classifications of the latter are based on the predominant cell type involved.

For the treatment of acute leukaemia in the aged, there is no agreement between the conservative, supportive approach and the use of modern antiblastic drugs, such as vincristine, methotrexate, 6-mercaptopurine, arabinoside, thioguanine, and adriamycin (HOLMES et al. 1979; CROWELL et al. 1978). Immunotherapy has also given some positive results.

2. Chronic Myelocytic Leukaemia

A peak incidence of chronic myelocytic leukaemia has been observed between 50 and 60 (MOLONEY 1977), with 36.4% of the cases over 60. For chronic myelocytic leukaemia the onset is often also insidious in aged patients. However, in the elderly, some symptoms are less pronounced, such as the enlargement of liver, spleen, and lymph nodes and the increase of leucocytes (mostly immature).

In the aged, leucocyte alkaline phosphatase may be increased, in contrast to the decrease observed in adult patients. Platelet counts may be very high. Herpetic vesicles with necrotic or gangrenous complications are rather frequent in the aged (Fig. 2).

The most significant pattern of chronic myelocytic leukaemia is the presence of the Philadelphia chromosome (Ph^1), that is, the deletion of long arm of chromosome 22 in myelocytic, erythrocytic, megakaryocytic marrow cells, and in circulating leukaemic cells. This chromosomal abnormality in chronic myelocytic leu-

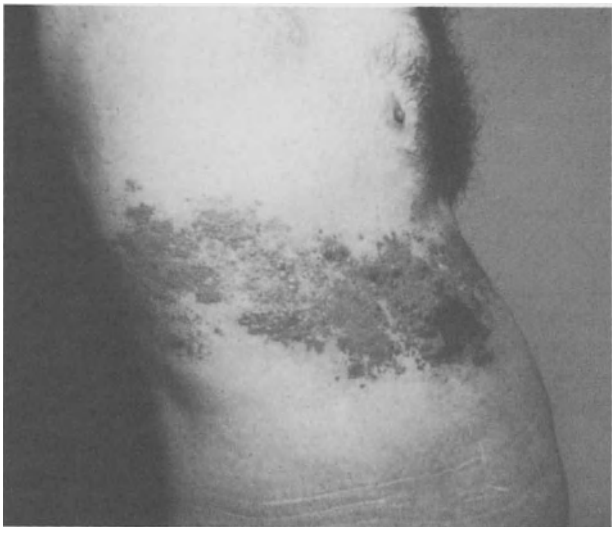


Fig. 2. Herpes zoster in chronic myelocytic leukaemia

kaemia seems an apparently balanced reciprocal translocation between 9 and 22 chromosomes, t (9;22) (q34;q11) (ROWLEY and POTTER 1976). The Philadelphia chromosome is absent in lymphocytes, and is present in nearly 90% of cases of chronic myelocytic leukaemia. The Ph^1 negative cases of chronic myelocytic leukaemia have been considered as typical cases of leukaemia of the elderly (EZDINLI et al. 1970).

Busulphan is the most satisfactory treatment of chronic myelocytic leukaemia also in the aged, in addition to the supportive care (transfusions, antibiotics, etc.). Ionizing irradiations on the spleen and splenectomy may be applied only occasionally.

3. Chronic Lymphocytic Leukaemia

Chronic lymphocytic leukaemia is a disease of elderly patients and is considered a monoclonal immunoproliferative disorder, with abnormal development and accumulation of lymphocytes in the blood and tissues. As in chronc myelocytic leukaemia, the onset is often insidious in the elderly. *Atypical patterns* have been described in presenile and senile ages:

a) Features resembling lymphosarcoma and reticulum-cell sarcoma;
b) Predominant anaemia without other blood changes;
c) Absence of lymphoadenopathy and splenomegaly;
d) Lymphoid metaplasia restricted to the bone marrow, slightly elevated lymphocyte count in peripheral blood and occasional thrombocytopenic haemorrhages; this pattern may remain uncharged during the whole course of the disease, without involvement of the lymph nodes;
e) Enlargement of the spleen only, or of a few lymph nodes.

Cutaneous involvement is the most frequent feature among the atypical patterns of chronic lymphatic leukaemia in the aged. The lesions are very variable in aspect, with infiltrative, ulcerated nodules and papules, generalized erythrodermia ("homme rouge"), allergic or toxic papular eruptions, itching, erythema, vesicles, bullae, lichenification, pemphigoid lesions; and eczema. The morphological and histological patterns are non-specific. The most interesting and frequent cutaneous lesions in these patients are represented by the herpetiform eruptions. Complications, such as severe necrotic lesions, are particularly dangerous when the face and ocular conjunctiva are involved.

The association of chronic lymphocytic leukaemia and malignancy is rather frequent (nearly 25% of cases, according to MOAYERI et al. 1976).

As chronic lymphatic leukaemia is typical of advanced age, some *haematological patterns* mostly apply to elderly patients. The increase of leucocytes (mostly lymphocytes) is marked, but not as marked as in chronic myelocytic leukaemia. In the peripheral blood there are above all small lymphocytes with a few prolymphocytes and lymphoblasts. In the bone marrow, small lymphocytes diffusely infiltrate the haemopoietic tissue. In nearly 90% of patients the leukaemic cells have B-markers and therefore chronic lymphocytic leukaemia has been considered as a clonal proliferation of B-lymphocytes. Many findings are consistent with the hypothesis that a single B-clone is blocked along the differentiation pathway. The leukaemic cells have a reduced recirculation activity and a longer lifetime potential,

and their mitogenic responses are depressed and delayed or show a wide degree of asynchrony. The T-lymphocyte absolute number in B-chronic lymphocytic leukaemia is generally increased. There are also chronic lymphocytic leukaemias with T-markers, T-B-markers or null-markers.

The evolution of chronic lymphocytic leukaemia in the aged may be relatively benign in some cases, but in general it is more rapid than in young patients. Survival is inversely proportional to age, being no more than 10 months beyond the age of 75.

In the initial phases of chronic lymphocytic leukaemia no treatment is indicated for aged patients. In advanced phases, chlorambucil or ionizing irradiations should be used. When an auto-immunological mechanism is involved, corticosteroids are indicated.

In the elderly patients with anaemia of elevated degree, an auto-immune haemolytic mechanism with positive Coombs test may be observed. In these cases sedimentation rate exhibits an unusual pattern, with low values at the 1 st hour and high values at the 2nd hour (LOELIGER 1976). A decrease of immunoglobulins (IgM, IgG, and IgA, in this order of frequency) is often observed. It is possible to find a M-component in serum, usually IgM type, but less pronounced than in Waldenstrom macroglobulinaemia (ALEXANIAN 1975; PANGALIS et al. 1977).

4. Malignant Lymphomas

Malignant lymphomas are malignancies arising in the lymphatic tissue. Some of them are very frequent in advanced age. In mice, lymphomas are considered as a consequence of the decreased immunity during ageing (ALBRIGHT and ALBRIGHT 1978). In BC3F1 mice (CHINO et al. 1971) the incidence of tumours increases with advancing age. Up to 80% of the animals that died naturally in old age had tumours. Reticulum-cell sarcomas are most frequent. Also NZB mice, which are animals prone to development of auto-immune disorders, frequently show immunoblastic lympho-adenopathy with advancing ageing (YUMOTO et al. 1976).

In humans, malignant lymphomas usually include Hodgkin's disease and non-Hodgkin's malignant lymphomas. The former is rather rare in advanced age, whereas the latter are most frequent in the elderly. Palpable lymph nodes represent the most important clinical pattern of malignant lymphomas, but also deep lymph nodes are frequent and may be discovered occasionally (e.g. during an abdominal surgical operation). An acute onset of the disease may be observed, with chills, fever, nocturnal sweats, malaise, weight loss and, in Hodgkin's disease, itching. Anaemia, bleeding and progressive general decay may appar in the course of the disease. Also amyloidosis, bone and skin alterations are found and are similar to those of chronic lymphatic leukaemia, mycosis fungoides and Sezary's syndrome.

Immunodepression is a common finding in malignant lymphomas, and particularly in Hodgkin's disease. In old patients it may predispose to infectious diseases.

a) Non-Hodgkin's Malignant Lymphomas

Non-Hodgkin's malignant lymphomas have been classified (RAPPAPORT 1966) with respect to their extension (nodular or diffuse) and to the type of cells (undifferentiated, lymphocytic, mixed, hystiocytic). Recently LUKES and COLLINS (1975),

BENNETT et al. (1974), DORFMANN (1974), MATHÉ et al. (1974), and LENNERT (1978) have also considered them as related to the immune system and have proposed new classifications of non-Hodgkin's malignant lymphomas, for example, as B-cell-derived malignant lymphomas and T-cell-derived malignant lymphomas. The former include lymphocytic, lymphoplasmacytoid, follicular, and immunoblastic lymphomas, and may be similar to Waldenström's disease, a monoclonal gammapathy. The latter include the T-lymphoblastic malignant lymphoma (rare in the aged), the T-zone malignant lymphoma, mycosis fungoides and Sezary's syndrome. Most of these lymphomas are frequently or particularly observed in the aged.

b) Hodgkin's Disease

Hodgkin's disease is uncommon in advanced age, males being more frequently affected than females. Some cases have been observed beyond the age of 70. The patterns of the disease are similar in aged and non-aged patients.

5. Monoclonal Gammapathies

Monoclonal gammapathies are diseases characterized by the increase in the plasma of a monoclonal immunoglobulin protein (the M-component), which can be easily detected in the electrophoretic tracing and is due to an abnormality involving one clone of the B-lymphocyte line. They include, first of all, myeloma, Waldenström's disease, and the presence of the M-component in a number of diseases (lymphomas, malignancies – cancer of the colon, breast, and biliary tract – chronic cholecystitis, chronic obstructive lung disease, primary systemic amyloidosis, pyelonephritis, etc.). Furthermore, there are monoclonal gammapathies of unknown significance, which are frequently observed in advanced age and may be present in apparently healthy persons. If urinary monoclonal gammapathies are also considered, up to 30% of old subjects may be affected, whereas nearly 3%–5% of aged persons present only plasma monoclonal gammapathies (TRIDENTE 1979). The benign monoclonal gammapathy is characterized by the presence of an M-component, usually IgG or IgA, with gammaglobulins less than 2.5% and without clinical signs or plasmocytosis in the bone marrow (plasma cells below 10%). Some monoclonal gammapathies may be initially benign, but may represent an early phase of myeloma, which will appear later.

a) Myeloma

Myeloma is the most common plasma cell dyscrasia and affects persons aged over 40. Of all cases, 66% are found between 60 and 80, both sexes being almost equally affected. Myeloma is a malignant, progressive, infiltrating, bone-marrow-destroying process in one plasma cell clone (WALDENSTRÖM 1970). Due to the marked increase of plasma cells in the bone marrow, it has been also called plasmocytoma. Plasma cells make up more than 15% and often up to 90% of the myelogram.

It has been suggested that some antigens may lead (perhaps only in genetically predisposed hosts) to the premalignant monoclonal B-cell proliferation. Another possibility is that an oncogenic or mutagenic stimulus leads to the neoplastic

growth of a susceptible subclone (SALMON and SELIGMAN 1974). Experimental (spontaneous myeloma models in mice; peritoneal irritation with mineral oil; protracted antigen stimulation) and clinical data support these viewpoints.

The neoplastic transformation of the plasmocyte has been considered as a mutation (BURNET 1968; HOBBES 1968) or as a derepression of the genetic programme (WALDENSTRÖM 1970). The tumour mass may have reached the weight of nearly 200 g (0.2×10^{12} cells) at the moment the diagnosis is established, going up to a weight of as much as 1,000 g (SALMON 1973). Therefore, the physiological immunocompetent population (about 3×10^{11} cells or about 300 g of tissue) is reduced at least to 90% in consequence of feedback, due to expansion of the monoclonal population or to inhibition of B cells by host suppressor cells (BRODER et al. 1975).

A gompertzian growth pattern of myeloma has been proposed by SULLIVAN and SALMON (1972). With an initial doubling time of 1–3 days, 1–2 years are needed between the first development and the first clinical signs (SALMON 1973). At the beginning, myeloma might be polyclonal, but then it becomes monoclonal, with a predominant clone and regression of all other immunoglobulin secretor lines (PILERI and CONTE 1977).

In elderly patients, the most common symptoms are anaemia, renal failure or recurrent bacterial infections (pneumococcal pneumonias, pyelonephritis). In 20%–25% of all myelomas the diagnosis is occasional. Persistent, unexplained skeletal pains, usually in the back (simulating osteoarthritis), diffuse ostoporosis and pathological fractures may be the first signs. In some cases, osteocondensating lesions may be seen. In the course of the disease, central or peripheral neurological manifestations, amyloidosis, and liver insufficiency may appear.

The sedimentation rate of erythrocytes is very high. Normochromic anaemia and high levels of BUN, uric acid and creatinine become more and more evident in the course of the disease. In the electrophoretic and immuno-electrophoretic tracing there is an M-spike, monoclonal (rarely biclonal), with increase of immunoglobulins. In 70%–75% of all cases these spikes are due to IgG or IgA. The presence in urine of the kappa or lambda chain of immunoglobulins is responsible for Bence-Jones protein, in nearly 80% of cases. Bence-Jones protein may be found also in other lymphoproliferative disorders. In 90%–95% of cases, plasma cells in the bone marrow are increased in number and are abnormal. The so-called flaming plasma cells are considered to be most frequent in IgA myeloma.

Particular aspects of myeloma are the solitary myeloma (a bone "cyst") and the so-called extramedullary myeloma, in the submucosa of the respiratory system, present in 75% of cases.

The classical treatment of myeloma is represented by melphalan, often in association with prednisone. Radiation therapy is effective against bone pain. Survival is about 24 months.

b) Waldenström Macroglobulinaemia

Waldenström macroglobulinaemia is a lymphoproliferative disorder, characterized by the presence in plasma of large amounts of macroglobulins. In the electrophoretic tracing there is an abnormal increase of IgM, due to the M-component.

Many IgM are cryoglobulins, some are cold agglutinins or rheumatoid factors. The sedimentation rate of erythrocytes is very high. In urine the Bence-Jones protein may be found, or more frequently an increase of light chain output. On histological examination there may be the patterns of a lymphoplasmacytoid malignant lymphoma. In the bone marrow there is often an increase of the mast cells.

Waldenström macroglobulinaemia is a typical disease of advanced age. Generally its course is mild or benign, but often it is aggressive and progressive. The most important clinical symptoms, besides the modest enlargement of lymph nodes, liver, and spleen, are due to the hyperviscosity syndrome and include: neurological disturbances (weakness, fatigue, headache, tinnitus, somnolence), visual alterations, frequent cardiopulmonary insufficiency and also a bleeding tendency. Amyloidosis may be found. Bacterial infections are a frequent complication.

6. Miscellaneous Conditions

Some myeloproliferative disorders may be found in the aged, such as polycythaemia vera, myelofibrosis, and idiopathic thrombocythaemia.

a) Polycythaemia Rubra Vera

Polycythaemia rubra vera (Vaquez's disease) is a chronic disease of the mature or advanced age (average age of onset: 60 years), and is more common in males than in females. The incidence is four to seven cases out of one million persons. It is characterized by an abnormal increase of the total erythrocyte mass, the origin of which is unknown. It is different from haemoconcentration, which occurs when there is a loss of plasma volume, and from erythrocytosis, which is secondary to some known stimuli, e.g. hypoxia in chronic bronchopulmonary diseases.

The onset of the disease is often insidious, and several symptoms resemble those of chronic cerebrovascular insufficiency, thus causing diagnostic difficulties. This is true for headache, fatigue, diminution of the concentration capacity, dizziness, tinnitus, and visual disturbances. Itching after a hot shower or bath is a typical symptom. GI disturbances may be due to the enlargement of spleen or liver. Lips, finger-nails, and mucosae are a dusky red. Haemorrhages and thrombosis are among the most frequent initial symptoms. Neurological, cardiac, and pulmonary disorders may cause further diagnostic difficulties.

The laboratory findings are typical: haematocrit value is markedly increased, due to the increase of the erythrocyte mass (up to twice normal). Oxygen saturation (SaO2) is normal in polycythaemia and represents an important diagnostic criterion. Blood viscosity is greatly increased. In the bone marrow there is a hyperactivity of all cellular lines.

Gaisböck syndrome represents a variety of polycythaemia, with hypertension, high level of cholesterol and uric acid and a marked tendency to thrombo-embolic complications.

Treatment includes phlebetomy, radiophosphorus, chemiotherapy, and allopurinol for hyperuricaemia. Most important is the prevention of haemorrhages and thrombosis, particularly in the brain. Therefore, haematocrit value, and blood viscosity should be brought as near as possible to normal limits.

b) Myelofibrosis

Myelofibrosis (agnogenic myeloid metaplasia)

May occur as a primary myeloproliferative disorder, mostly in patients over 60 (60% of all cases). There is a hyperplasia of the bone marrow reticular network, splenomegaly, and, often, hepatomegaly, and a polymorphous blood picture. Because of some puzzling features, it has been called by several names (WARD and BLOCK 1971, found 37) such as agnogenic myeloid metaplasia, splenic non-leukaemic myelosis, myelosclerosis, osteomyelosclerosis, myeloid megakaryocytic hepatosplemegaly, etc.

The onset of the disease is often insidious, particularly in the elderly, with irregular fever, arthralgia, and bone pains. Thrombosis and haemorrhages may occur, as well as superimposed infections. There is an increased opacity of the bones on radiological examination, with thickening of the spongiosa and even eburnation, especially in the so-called osteomyelosclerotic variety.

The aim of the treatment is to inhibit extramedullary haemopoiesis.

c) Idiopathic Thrombocythaemia

Idiopathic thrombocythaemia is mostly observed in the 7th decade of life (TURA 1979). Haemorrhages, thrombosis, and enlargement of liver and spleen are common symptoms. Acroparesthesias, acrocyanosis, moderate leucocytosis, and anaemia may be present. Platelet count is over 700,000 µl. In the bone marrow there is a megakaryocytosis without myelofibrosis. Platelet ATP, ADP, serotinin, adhesion, and aggregation are decreased. Philadelphia chromosome is absent, but 21q-karyotype may be present.

F. Disorders of Haemostasis in the Aged

I. Blood Coagulation and Haemostasis in the Aged

During ageing there are significant modifications of blood coagulation and haemostasis, which should be considered in the evaluation of the actual diseases, i.e. haemorrhagic and thrombo-embolic diseases in the aged. As a rule, there is an increase of blood coagulability at presenile age, between 45 and 60, with an increase of platelet aggregation and a reduction of fibrinolytic activity (DE NICOLA and MORSIANI 1975). These modifications also represent a sign of the typical thrombophilic tendency in this age, within the humoral sign or "spies" of presenile age (increase of cholesterol, blood sugar, uric acid, etc.). In very advanced age, a tendency towards normalization or even towards hypocoagulability may take place, in association with an increased capillary fragility and predisposition to haemorrhages (Fig. 3).

The increased blood coagulability in the aged (COCCHERI and DE NICOLA 1979 a, b) may be due to an *increase of some coagulation factors*, especially factor I (fibrinogen), factor VIII (antihaemophilic globulin), factor XII (HAGEMAN factor), and factor XIII (fibrin-stabilizing factor). As far as factor I is concerned, in addition to the actual increase of its level, there is an increased fibrinogen turnover, with a reduction of the half-life time. Such a finding has been interpreted as a sign

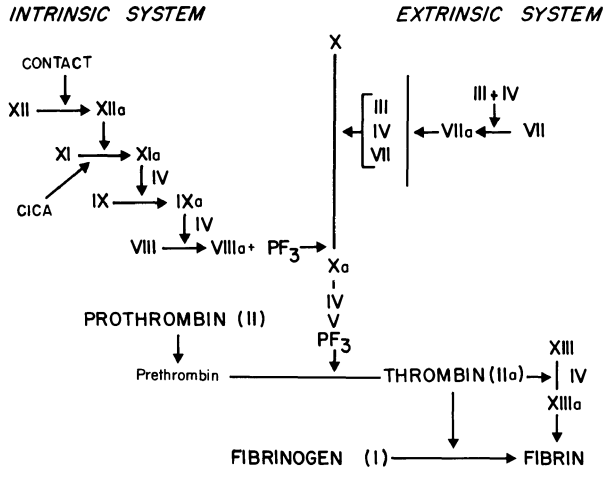


Fig. 3. Scheme of blood coagulation

of a latent disseminated intravascular syndrome, without haemorrhagic manifestations, but with a thrombophilic tendency (see below) (Fig. 4).

The new developments in the physiopathology of blood coagulation have shown that *fibrinogen and split products* during intravascular coagulation may be important for the recognition of a latent phase of disseminated intravascular coagulation. These split products or fragments of fibrinogen and fibrin are known as fibrinogen degradation products (FDP) and fibrin monomeres (GORDON et al. 1975; MARDER et al. 1975; HAFTER and GRAEFF 1975; NOSSEL et al. 1974; MÜLLER-BERGHAUS 1977; KOPEC and LATALLO 1978; BLOMBACK 1978). The latter may be easily identified by means of a new technique and actually represent the most direct and dependable demonstration of the presence of an intravascular coagulation, in other words of a thrombophilic state due to increased coagulability.

The increase of *factor VIII* is due to the increased level of the fraction of factor VIII, which are concerned with blood coagulation. For factor Xa, more details will be given in relation to antithrombin III.

Factor XII (Hageman factor) is also called contact factor, and its role in regulating the haemostatic balance has been better characterized on the basis of its chemical structure (REVAK et al. 1974; MEIER and KAPLAN 1975; CHAN and MOVAT 1976; GRIFFIN and COCHRANE 1976). An increase of factor XII may be postulated

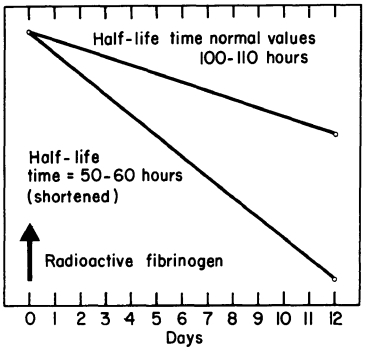


Fig. 4. Reduction of fibrinogen half-life time in arteriosclerotic, thrombophilic aged subjects, as compared with normal values

as a trigger mechanism for the onset of hypercoagulability state (MOVAT 1979). Also for *factor XIII* (fibrin-stabilizing factor), an increase in presenile age was related to a thrombophilic tendency (COCCHERI and DE NICOLA 1979 a, b).

As far as the *fibrinolytic activity* is concerned, new data are concerned with the modifications of some single factors of fibrinolysis (reduction of plasminogen; increase of antiplasmin; OGSTON 1978; NILSSON et al. 1978; LANDMANN 1978; COLLEN and WILMAN 1978; BALKUV-ULUTIN 1978) in thrombophilic states of presenile age.

In the pathogenesis of thrombosis, fibrinolysis was also taken into consideration as a counterpart of blood coagulation, on the basis of the well-known *theory of the haemostatic balance;* namely, it was postulated that under normal conditions there should be a balance between coagulation and fibrinolysis, thus ensuring a normal haemostasis. The onset of haemorrhages should be due to a deficiency of the coagulation mechanism or to an excess of fibrinolytic activity, and the opposite should take place in case of thrombosis, with a reduction of fibrinolysis and an excess of coagulation or hypercoagulability (DE NICOLA 1974; CHESTERMAN 1978). Several data are in agreement with such an assumption, but are, however, not able to explain all cases of haemorrhages or thrombosis. The use of anticoagulants or drugs enhancing fibrinolysis should be justified by the theory of the haemostatic balance.

Inhibitors have been given much importance in the study of the hypercoagulability of the aged. Particularly the reduction of *antithrombin III*, acting as inhibitor of factor Xa, is of fundamental importance for the onset of a thrombophilic state (HEDNER and NILSSON 1973; WESSELER and YIN 1974; ØSTERUD et al. 1976; DAMUS and WALLACE 1975), as also happens in women under treatment with contraceptive drugs (POLLER 1978; GIBELLI et al. 1978). An absolute or relative increase of factor Xa may be therefore considered as one of the most relevant mechanisms concerned with thrombophilia (COCCHERI and DE NICOLA 1979 a, b). On the other hand, an inhibition of factor Xa may result in an increase of antithrombin III activity, as happens during the treatment with heparin(oids) (BARROWCLIFFE et al. 1978).

Recently, due to the discovery of the *molecular structure of prothrombin* (REUTERBY et al. 1974; MAGNUSSON et al. 1975; HEWETT-EMMETT et al. 1975; BUTKOWSKI et al. 1977; WALTZ et al. 1977) (Fig. 5), the formation of abnormal coagulation factors, and above all of prothrombin and factor Xa, during the treatment with indirect anticoagulants (coumarin derivatives) has been further analysed (REEKERS et al. 1973; STENFLO 1975; BROZOVIC 1976; SUTTIE and JACKSON 1977). It has been established that these abnormal factors actually inhibit factor Xa, thus enhancing antithrombin III activity and acting like direct anticoagulants [heparin(oids)], through a mechanism of competitive inhibition due to structural analogy. Indirect anticoagulants, therefore, do not only reduce the concentration of certain coagulation factors (factor II = prothrombin, factor VII, IX, and X), but also modify the molecular structure of some factors, like prothrombin and factor X (ESMON et al. 1975; MAGNUSSON et al. 1975; HOWARD and NELSESTUEN 1975). The abnormality consists in the absence of gamma-carboxy-glutamic acid in the molecule of prothrombin and factor Xa, which is fundamental for the mechanism of action of these factors (SUTTIE and JACKSON 1977).

The *increase of platelet aggregation* is definitely more important and significant in the pathogenesis of thrombophilic states (WHITE and HEPTINSTALL 1978; COC-

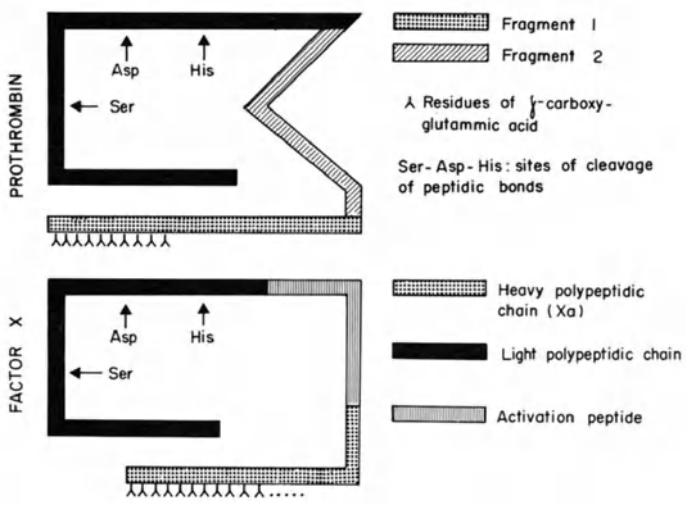


Fig. 5. Molecular structure of prothrombin and factor X

CHERI and DE NICOLA 1979a, b), above all after the discovery of the role of ADP and the newer developments on the intermediate stages which lead to platelet aggregation with the participation of prostaglandins and cAMP (cyclic AMP) (FLOWER 1978) (Fig. 6).

Under the action of ADP, arachidonic acid is released by the platelets, as a result of hydrolysis of membrane phospholipids (phospholipase). In this phase, platelet aggregation may be inhibited by substances such as nicergoline or adenosine, the latter acting on ADP through the well-known mechanism of competitive inhibition due to structural analogy. In

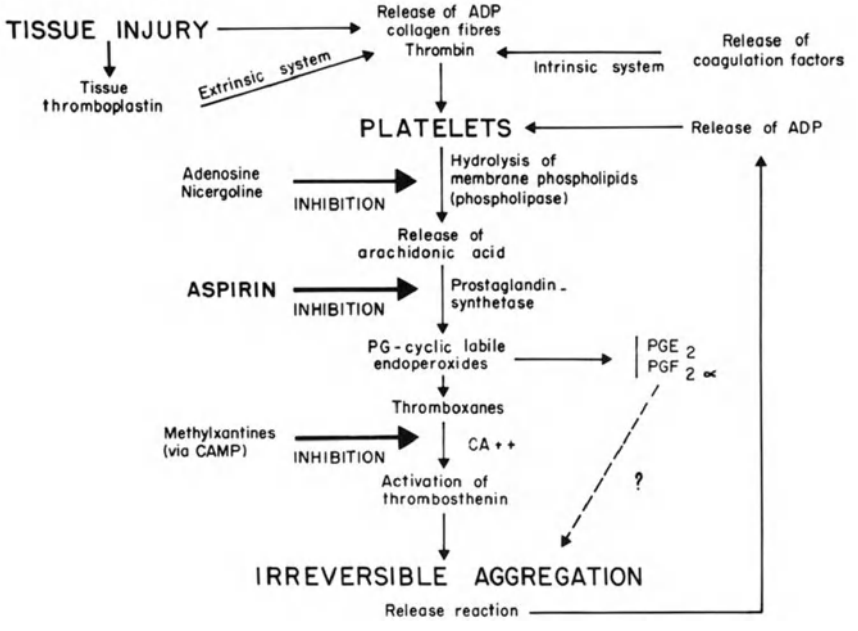


Fig. 6. Scheme of platelet aggregation

the presence of prostaglandin-synthetase, labile, cyclic PG-endoperoxides are formed. In this phase, acetylsalicylic acid may act as inhibitor of platelet aggregation. PGE_2 and $PGF_{2\alpha}$ are thus formed from the labile, cyclic PG-endoperoxides, and might enhance directly the irreversible aggregation of platelets, without any intermediate reaction. Thromboxanes are then formed from the labile, cyclic PG-endoperoxides, and their function is to bring about the activation of thrombosthenin in the presence of calcium, and, subsequently, the irreversible platelet aggregation, with the so-called release reaction. Cyclic AMP may inhibit thrombosthenin activation through its action on thromboxanes. As cyclic AMP is formed from ATP and is then transformed into AMP, any factor which inhibits the formation of cyclic AMP from ATP, or its transformation into AMP, may cause a diminution or an increase of the cyclic AMP available, and subsequently an increase or a diminution/inhibition of platelet aggregation. PGE_1, by blocking adenylcyclase, is able to inhibit the transformation of ATP into cyclic AMP, thus causing an increase of platelet aggregation. Other substances, which are known as inhibitors of platelet aggregation, like methyl-xanthines or dipyridamol, inhibit the transformation of cyclic AMP, thus causing an increase of the cyclic AMP available and subsequently an inhibition of platelet aggregation at the step of thrombosthenin activation by thromboxanes.

Another mechanism, which is concerned with the pathogenesis of thrombophilia and thrombosis, was recently discovered in connection with platelet aggregation. A substance derived from arachidonic acid, prostacyclin (PGI_2 or PGX), is able to inhibit platelet aggregation, in contradistinction to thromboxanes, which are also derived from arachidonic acid. Prostacyclin is also able to cause a relaxation of smooth muscle fibres, especially in coronary arteries, thus representing an additional pathway for preventing thrombosis. Due to the presence of prostacyclin, which is formed in the endothelial layer of the vessels, platelets do not adhere to the intact vessel wall (GRYGLEWSKI et al. 1976). Some lipoperoxides, which are involved in the pathogenesis of atherosclerosis through the peroxidation of membrane lipids, inhibit the formation of prostacyclin, and this represents another link between atherosclerosis and thrombosis.

Among *inhibitors of platelet aggregation*, acetylsalicylic acid inhibits the formation of both thromboxanes and prostacyclin, thus reducing the inhibition of platelet aggregation due to prostacyclin and also reducing the relaxation of smooth muscle fibres in the vessel walls.

The new developments on platelet aggregation are concerned with the quantitative evaluation of the plasma level of thromboxanes and prostacyclin as related with a thrombophilic tendency. Even though these studies are still in progress, it is likely that such findings may be even more pertinent than the simple evaluation of platelet aggregation.

The *increase of capillary fragility* during ageing may be related to the general impairment of the vascular system in the aged, due to degenerative, nutritional, and other factors, and is also concerned with the actual mechanism of ageing.

II. Haemorrhagic Diseases in the Aged

1. Congenital Hereditary Haemorrhagic Diseases

Congenital hereditary haemorrhagic diseases include *haemophilia and haemophilic syndromes*. They are usually not observed in the aged. However, due to the advances in the treatment and prophylaxis of these diseases, several cases have reached presenile and senile ages, and some cases of myocardial infarction and arteriosclerotic diseases have been observed in haemophiliacs.

2. Acquired Haemorrhagic Diseases

a) Acquired Coagulation Disorders

Among acquired coagulation disorders in the elderly, some liver diseases, *liver cirrhosis* in particular, are often accompanied by a haemorrhagic syndrome. It is characterized by a reduction of plasma factors (I = fibrinogen; II = prothrombin; V; VII; IX; X) and of antithrombin III, an impairment of platelet function and an increased capillary fragility (KUMAR and DEYKIN 1979).

Deficiency states also occur in the *malabsorption syndromes* of the aged, within the general protein deficiency.

Infectious agents and drugs may also provoke secondary coagulation defects. Elderly patients are more sensitive to drugs than adults; this particularly applies to indirect anticoagulants, and these should be administred with caution in the aged (see below).

b) Thrombocytopenias

Idiopathic and secondary thrombocytopenias may occur in the aged. Their patterns are similar to those found in other age groups. Infections and drugs are frequently the cause of secondary thrombocytopenias in old persons and they are also due to the increased sensitivity and vulnerability of the bone marrow.

c) Haemorrhagic Syndromes Due to Intravascular Coagulation

Haemorrhagic syndromes due to intravascular coagulation may be observed also in the aged, for instance, in liver cirrhosis, malignancies, and haemoblastosis, and, following shock, surgical operations, etc. There is an increase of blood coagulability, with subsequent intravascular coagulation and consumption of blood coagulation factors, including platelets, resulting in a secondary coagulation and haemostatic defect.

Fibrinolytic activity increases as a consequence of the intravascular coagulation, in order to counteract it, and should be considered, therefore, as a defence mechanism against the intravascular coagulation.

Thrombophilia in the aged may be considered as a manifestation of a latent intravascular coagulation syndrome (see below).

d) Haemorrhagic Syndromes Due to Vascular Factors

Haemorrhagic diseases due to vascular factors are rather frequent in advanced age, more than those due to coagulation defects. Haemorrhagic familiar teleangiectasia (Osler-Weber-Rendu disease) may be seen in the elderly, because of the long survival of these patients. It frequently affects the ears, lips, and finger tips. The capillaries and small veins are dilated, sometimes forming small angiomas.

Schönlein-Henoch disease (anaphylactoid purpura) also affects elderly persons, in whom hypersensitivity may play a role in the immuno-allergic pathogenesis of the disease.

More important in the aged are other haemorrhagic manifestations due to vascular factors, e.g. those due to hypertension, diabetes, kidney diseases, deficiency of vitamins C and P, cachectic conditions, malignancies, etc.

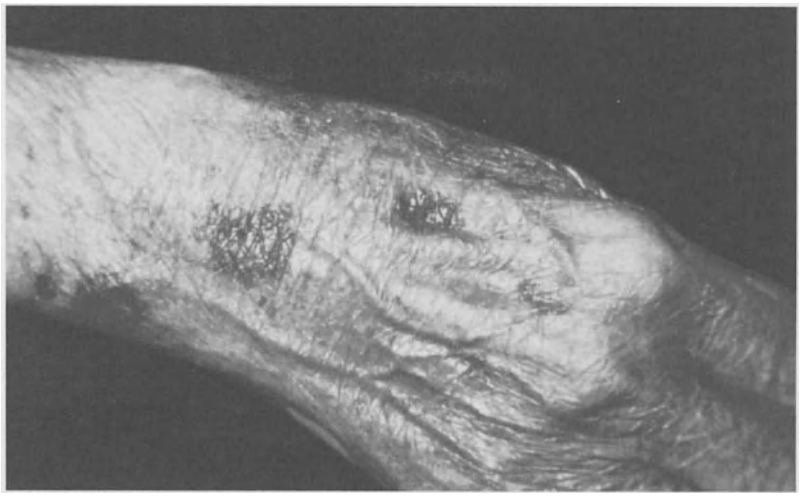


Fig. 7. Bateman's purpura

e) Bateman's Purpura

The most typical purpura of old age is the senile purpura, also called Bateman's purpura. Characteristic cutaneous haemorrhages occur chiefly on the extensor surface of the distal portion of the limbs, but also on mucosal areas (e.g. the base of the tongue). They usually disappear, leaving pigmental spots, particularly on the backs of the hands (Fig. 7).

Senile purpura is generally observed after the age of 60, but chiefly in persons over 80. There are atrophic and degenerative lesions in the different layers of the skin. The epidermis becomes thin and the basal layer is pigmented. Sclerosis and hyaline degeneratin are present in the vessels. The walls are thin, with localized or disseminated dilatations, and the small vessels are congested, particularly the small veins.

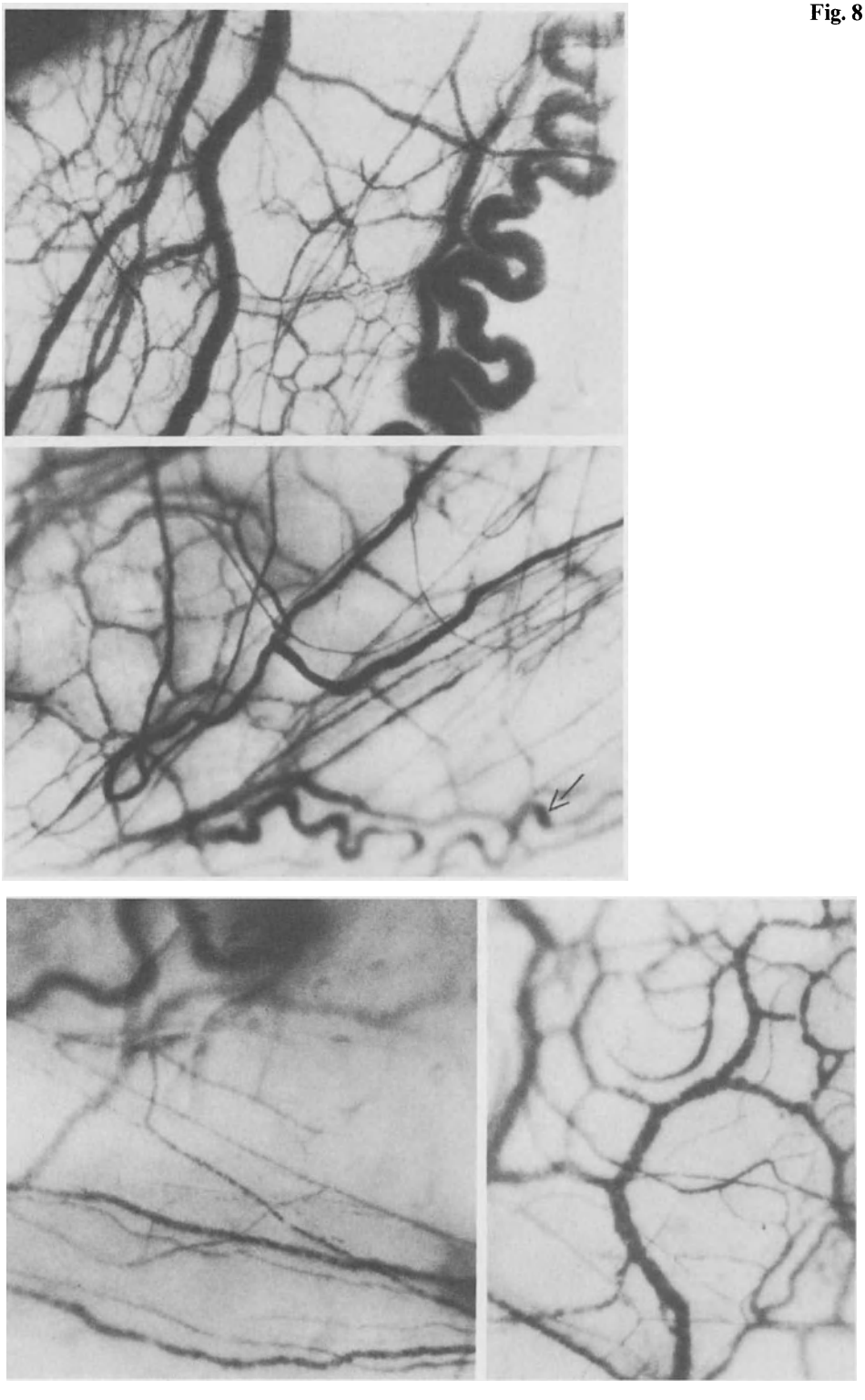
III. Thrombosis and Thrombo-Embolic Diseases in the Aged

Thrombosis and thromboembolic diseases have for a long time been considered as typical diseases of presenile and senile age, due to the progressive increase of their frequency after the 4th/5th decade of age.

In this respect the *geriatric implications* of these diseases are quite evident, while on the other hand the haematological implications are concerned with pathogenesis, diagnosis, and therapeutic and/or prophylactic measures with drugs, which are able to interfere with the various mechanism of haemostasis, including blood coagulation, fibrinolysis, and platelet aggregation.

Furthermore, for thrombo-embolic diseases, the geriatric implications are also due to the fact that these diseases often affect organs of vital importance, such as brain and heart, thus causing the onset of *invalidity states* and requiring *rehabilitation measures*. On the other hand, one should not forget the *social, psychological, and economical consequences of thrombo-embolic diseases*, due to the increased needs for care and the reduction of the working and productive capacity, i.e. of income.

Fig. 8



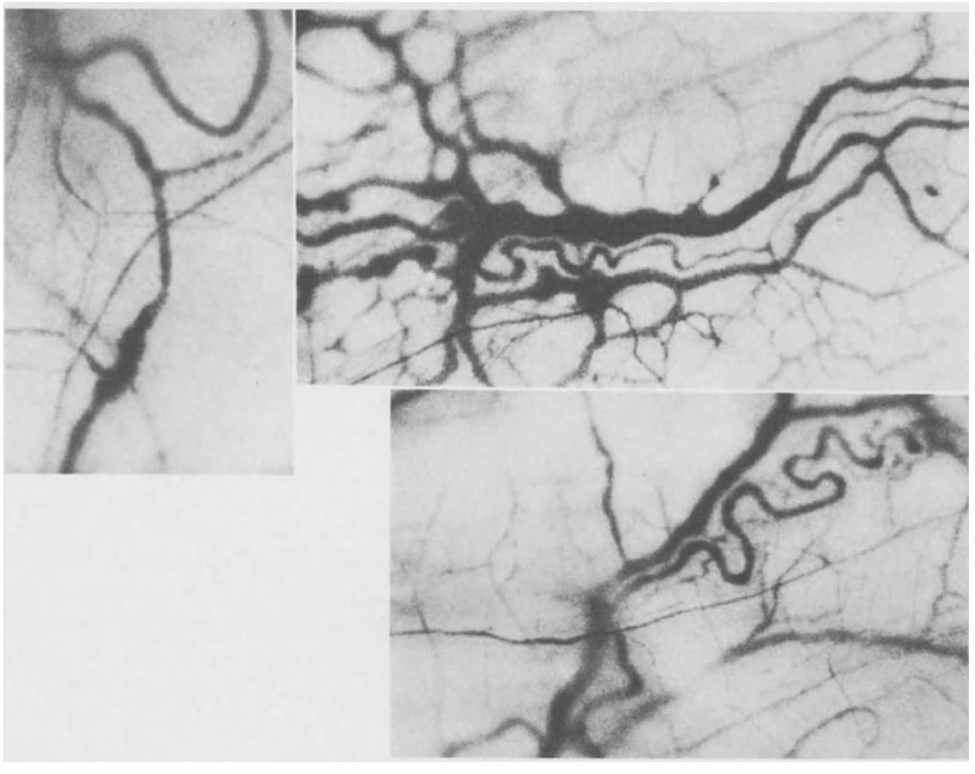


Fig. 8. Microcirculatory findings in the conjunctiva of the aged.
Page 280. *Above:* marked tortuosity with dilatation of venous vessels. *In the middle:* tortuosity of a venous vessel with small sacculation (*arrow*); thin, rigid arterial vessels, with signs of red cell intravascular aggregation. *Below:* evident red cell intravascular aggregation in small and larger vessels.
Page 281. *At left:* sacculation in a small vessel, with signs of red cell intravascular aggregation. *At right, above:* multiple microaneurysms, with irregular configuration of the small vessels; *below:* tortuosity and irregular caliber of the small vessels, with a thin, scarcely perfused terminal capillary net

1. Pathogenesis of Thrombophilia

The pathogenetic aspects of thrombophilia may be still considered on the basis of the *classical triade of Virchow*. Some more details have been added in connection with the present views on atherosclerosis, and above all, on the role of blood factors, not only including coagulation, but also fibrinolysis and platelet aggregation (see above), and furthermore the role of haemodynamic factors, such as rheological aspects and the newly developed trends in microcirculation.

The *importance of atherosclerosis* in the pathogenesis of thrombophilia is well known, especially after the identification of an increased thromboplastic activity and of a reduced fibrinolytic activity in the arterial walls due to atherosclerosis, particularly at the cerebral level. Further data are concerned with the role of platelets in atherosclerosis, the old, but still valid, theory of DUGUID (1976), with some new developments regarding the mechanism of platelet aggregation (see below).

As far as *rheology and microcirculation* are concerned, the old observations of Virchow about the slowing down of the blood stream as a pathogenetic factor of thrombosis were precisely documented by means of intravital microscopy, also in humans. This phenomenon is due in part also to the morphological modifications of the small vessels and capillaries (Fig. 8), as has been clearly observed only recently, particularly in the aged, and in part to the erythrocyte aggregation (sludge phenomenon), which indirectly enhances the onset of thrombosis, through a mechanism later than platelet aggregation.

2. Diagnostic Problems in Thrombophilia

In the diagnosis of thrombophilia there are first of all some clinical criteria, which should be taken into consideration in addition to the laboratory data. History of the patient is of fundamental importance, also because there are cases of hereditary thrombophilia, which are well documented from the hereditary and biological viewpoint (e.g. SAS et al. 1974). Among past and present diseases, which may enhance the onset of thrombophilia, the identification of a state of diffuse or localized arteriosclerosis is obviously important, especially in cases of cerebrovascular insufficiency, of chronic coronary diseases, and of peripheral artery diseases. Furthermore, hypertension, diabetes, and obesity are diseases which are often accompanied by a thrombophilic state, particularly in advanced age. The well-known risk factors of arteriosclerosis, such as smoking, diet, stress of life, etc., are also true in thrombophilia and thrombosis and should be identified.

As far as laboratory studies are concerned, the detailed analysis of certain *coagulation factors*, such as prothrombin (factor II), factor V, VII, X, and prothrombin time, reflecting the variations of all these factors (II, V, VII, X), has no practical importance. The same also applies, within certain limits, to the study of whole blood clotting time and recalcification time. A more definite role has been attributed to the increase of factor VIII in the pathogenesis and diagnosis of a thrombophilic state (LIAN et al. 1976; SWITZER and MCKEE 1977; PANDOLFI et al. 1974; EKBERG et al. 1975), but above all to the reduction of antithrombin III (HEDNER and NILSSON 1973; ØDERGAARD et al. 1973; WESSELER and YIN 1974; ROSENBERG et al. 1978; ØSTERUD et al. 1976; DAMUS and WALLACE 1975; SEEGERS 1978; ØDERGARD et al. 1976).

Further data of practical value are obtained by means of *platelet aggregation*, which is markedly increased in cases of thrombophilia. This may be evidenced by the aggregation curve in the aggregometer, according to Born, this being particularly suitable for research, while the method of BREDDIN (1969) may be recommended for clinical purposes. For routine purposes, *thrombelastography* is also able to give some practical information about the presence of a thrombophilic state (DE NICOLA 1979). In the thrombelastographic tracing the reaction time (r) is, within certain limits, the equivalent of the recalcification time or of the whole blood clotting time, and may be shortened in cases of thrombophilia. The same applies also to the clot formation time (k), which is more sensitive to the influence of platelet factors. The maximal amplitude is markedly increased in thrombophilia and makes it possible to establish the diagnosis just by looking at the patterns of the tracing.

The role of the *latent disseminated intravascular coagulation* in thrombophilia may be identified, also for diagnostic purposes, by studying fibrinogen turnover (shortening of the half-life), which is, however, time-consuming. The evaluation of fibrin monomers may be easily applied, but is less frequently positive.

Some data have been obtained by the determination of factor XIII, as well of fibrinogen, which are both increased in thrombophilia. Heparin tolerance in vivo and in vitro was very feasible years ago, but is now no longer of interest, even though an increase of heparin tolerance may be useful for both diagnostic and therapeutic purposes in cases of thrombophilia and thrombosis.

3. Prophylaxis of Thrombophilic States

The complexity of the pathogenetic mechanism in thrombophilic states represents the background for a variety of prophylactic measures, thus preventing the onset of thrombo-embolic disease. On the basis of the pathogenetic importance of athero- and arteriosclerosis alterations of the arterial walls, one of the most adequate treatments should be represented by drugs, which are able to reduce the extension and the entity of already present lesions and to prevent the occurrence of further lesions. Drugs acting on hyperdyslipidaemia may also favourably influence atherosclerotic lesions and thrombophilia at the same time. Such a trend was confirmed by the recent experience on prolonged prophylactic treatments by means of various drugs.

Furthermore, also other predisposing factors and diseases should be properly treated, in order to remove or at least reduce them. This is particularly true for hypertension, diabetes, obesity, and others. As soon as such a goal is reached, other treatments against thrombophilia may be discontinued.

The *prolonged treatment with anticoagulants* for prophylactic purposes has been used for a long time and is still widely discussed and criticized. For a long-term treatment, oral anticoagulants have been mostly employed, as mono- and dicoumarinic compounds and indanedione derivatives. These drugs are only able to reduce blood coagulability, thus influencing only one of the pathogenetic factors, but just in a superficial, symptomatic, and transitory way, without modifying the conditions, which caused the increase of blood coagulability. Prothrombin (factor I) and factor VII, IX, and X i.e. the so-called vitamin-K-dependent factors, are reduced under the action or oral anticoagulants. The effect takes place after a latency period, around 24 h, and, unless a tendency to cumulation is present, the effect is no longer demonstrable within 24–48 h after the last therapeutic dose.

Oral anticoagulants require regular and reliable controls by means prothrombin time, reflecting the variations of prothrombin (factor II), factor VII and X, among the factors affected by oral anticoagulants, or by means of thrombotest, reflecting the fluctuations of all these factors [prothrombin (factor II), and factors VII, IX, and X]. Controls are necessary in order to avoid an excessive anticoagulant effect, with risk of haemorrhages or an insufficient therapeutic effect, thus predisposing to relapses of thrombosis or embolism.

A therapeutic level was suggested on the basis of the evaluation of percent values of prothrombin time, i.e. around 20%–25%. Therefore, values of 40%–50% are insufficient, especially if we also consider the fact that normal values range between 70% and 130%. Even when laboratory data are accurate and therapeutic levels are regularly obtained, the risk of haemorrhages is not completely avoided, insofar as other factors, besides blood coagulation, may be concerned with the onset of haemorrhages, above all capillary fragility, which is increased in aged persons.

The effect of oral anticoagulants may be increased or reduced by concomitant diseases, by drugs, by stress, and by other factors, which should be accurately evaluated during a long-term anticoagulant treatment. Typical examples in this respect are represented by the increased response to anticoagulants in cachectic patients, in malnutrition, liver, and renal diseases, and in congestive heart failure with liver enlargement, in which there is an increased sensitivity to oral anticoagulants, thus requiring more frequent and accurate controls. Cortisone and derivatives reduce the effect of oral anticoagulants, while barbiturates, MAO-inhibitors, and other drugs potentiate it.

The actual value of a prolonged treatment with oral anticoagulants is still debated. After the initial enthusiastic statements about the prophylactic effect of anticoagulants in avoiding relapses of thrombo-embolism, especially in coronary heart disease, a more cautious revaluation took place, and, without denying any favourable effect of oral anticoagulants, the present attitude is to administer them when a marked thrombophilic state is demonstrable on the basis of clinical and laboratory data. This particularly applies to obese, atherosclerotic, hyperdyslipaemic, diabetic patients, in which there is also a history of previous thrombo-embolic accidents. Such a treatment may be continued as long as these predisposing factors are present, and a good policy is to start as soon as possible a correct treatment of these factors, as already mentioned, so that the anticoagulant treatment may be discontinued as soon as conditions permit.

No anticoagulant treatment should be prescribed if no reliable laboratory controls are possible and if the attending physician has no experience in the correct way of conducting the treatment. In the aged, anticoagulants may be used with some more caution than in other ages and if the general contraindications are not present.

Heparin and heparinoid substances have not been currently used for a long-term anticoagulant treatment, insofar as the anticoagulant effect may be reached only by using high doses and parenteral routes, which are not always feasible for a long time, and predispose to the onset of haemorrhages even more than in the use of oral anticoagulants. Heparin(oids) may be used for prophylatic purpose at low doses, which do not significantly affect blood coagulation as, for instance, 5,000 unis subcutaneously twice a day, while the high intravenous or intramuscular (retard) doses are indicated in the early phases of thrombosis and embolism, by properly evaluating the possible contraindications. For instance, heparin treatment is in general less suitable for cerebral accidents than for peripheral thrombosis.

Today the most recommended trend is represented by the administration of drugs which exert a complex effect on various pathogenetic factors of thrombophilia, including fibrinolysis, platelet aggregation and vascular factors. One of the first trials in this respect used nicotinic acid, which proved to enhance fibrinolysis, in addition to its already known cardiovascular action and to the antihyperdyslipidaemic effect.

A prolonged activation of fibrinolysis of slight degree (i.e. not to be compared with the actual thrombolytic drugs) may be justified as the prolonged anticoagulant treatment, insofar as they are acting on either one of the plates in the haemostatic balance. However, drugs acting on fibrinolysis are also often able to influence other pathogenetic factors of thrombophilia, such as the increased platelet aggregation and hyperdislipidaemia.

Several drugs are chiefly concerned with the *inhibition of platelet aggregation.* After the first trials with adenosine derivatives, which are able to inhibit platelet aggregation through a mechanism of competitive antagonism due to structural analogy (as for sulphonamides and PABA), but not always well tolerated, consistent effects were obtained by means of dipyradamole, sulphinpirazone, and acetylsalicylic acid, which are at the present time the most recommended drugs for the inhibition of platelet aggregation. In many other drugs this effect was observed, with or without a concomitant activation of fibrinolysis. For instance, anti-inflammatory drugs often inhibit platelet aggregation. The mechanism of action at the different phases of platelet aggregation has been identified for several drugs. The administration of acetylsalicylic acid may be accompanied by haemorrhagic complications, which may particularly occur in aged persons, as epistaxis, GI haemorrhages, cutaneous haemorrhages, etc. The site of gastro-intestinal bleeding cannot be easily identified, also because the small erosions of the mucosa due to ageing are often the very cause of the haemorrhages. Gastroduodenoscopical observations may locate them. Other drugs are not concerned with the risk of haemorrhages, e.g. dipyridamole, which is also able to favourably act on coronary circulation.

Intravital therapeutic defibrination by means of purified extracts of viper venom (ancrod and batroxobin) has been suggested on the basis of occasional observations in a woman after snake bite, and preliminary favourable observations in myocardial infarction and other cases of thrombosis. The indications of the intravital defibrination should be still clearly established (STOCKER 1978), and some perspectives have been opened by the possible use of these agents also for a prolonged prophylaxis.

4. Thrombolytic Therapy

The first trials of thrombolytic therapy are concerned with the infusion of purified plasmin, which proved, however, to be neither suitable nor effective enough. *Streptokinase* is at present one of the most active thrombolytic agents and may be used also in the aged, with caution and regular controls (above all: thrombin time). Definite indications for thrombolytics therapy with streptokinase are represented by peripheral occlusions, pulmonary, and renal thrombosis. Some benefits have been observed also in myocardial infarction (reduction of mortality), after the first disappointing results. Thrombolytic therapy may be used also in carotideal occlusion, while some perplexities are still concerned with its use in cerebral thrombosis. The same also applies to *urokinase*, which does not present antigenic properties at the same degree of streptokinase (KAKKAR 1978).

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Respiratory System

Physiological and Pathological Aspects of the Respiratory System

J. E. STARK and D. J. LIPSCOMB

A. Changes in Structure of the Lungs with Age

Various aspects of aging of the lung have been reviewed by CANDER and MOYER (1964) and more recently by KENT (1978). LAENNEC (1827) in his *Treatise on Diseases of the Chest* described the lung in old age as "atrophic" and noted that although the lung collapsed on opening the chest, it no longer had elasticity so that, when prodded with a finger, the dimple smoothed itself out slowly. The lungs in old age are lighter and fluffier than in youth and although the architecture is intact, inspection of the cut surface shows abnormally large alveoli which, unlike those of younger subjects, are visible to the naked eye. The cut surface retracts, causing the bronchi and blood vessels to protrude. REID (1967) described the changes in alveoli as panacinar in distribution. The distinction between these appearances and those of emphysema is discussed elsewhere in this review. EDGE et al. (1964) performed post-mortem pulmonary arteriograms on lungs of elderly subjects who had had no known respiratory disease and found no difference from young subjects in the number of branches from axial pulmonary arteries, the diameter of successive branches and the distance between branches. There was, however, probably reduction in the number of finer blood vessels.

I. Changes in the Alveoli

Microscopic examination confirms that alveoli of aged lungs are several times larger and have a smoother and simpler outline than those of healthy young lungs. The thickness of the alveolar wall is reduced with fewer elastic fibres and fewer capillaries. Hence not only is the area of alveolar wall reduced but so too is the concentration of capillaries per unit area of alveolar wall. SPENCER (1977) comments on the increase in size and number of the pores of Kohn which, he says, is sometimes considered the first evidence of alveolar wall destruction and the first stage in the production of panacinar emphysema. The evidence from physiological measurements that lung elasticity diminishes with advancing age is discussed elsewhere in this review. As there is no change in dry weight of lung after the age of 20 (HIERONYMI 1961) and no loss of total collagen (BRISCOE et al. 1959) or fibrous protein (PIERCE 1963), attention has been focused on change in elastin content. PIERCE (1963) and others, however, have reported an *increase* of total elastin in the aging lung rather than the decrease which might have been predicted from physiological findings, but TURNER et al. (1968) have suggested that these findings might be the result of an artefact due to greater resistance of elastin in elderly lungs to solution

during assay. PIERCE and EBERT (1965) on the other hand suggest that collagen may be important in determining the elasticity of the lungs for, although collagen itself has little longitudinal distensibility, it is located in a helical distribution in the primary lobule and could therefore function as a coiled spring.

II. Changes in Pulmonary Blood Vessels

HEATH (1964) has reviewed the structural changes in the pulmonary vasculature associated with aging. He describes the early transition from the fetal pulmonary arteries with a thick muscular wall reflecting systemic intravascular pressures to the thin-walled pulmonary arterial tree of adult life, which conducts blood at a pressure of about one-sixth of that in the systemic circulation. As aging continues, and probably as a continuous process starting in early adult life, there is progressive loss of elastic tissue and a relative increase in fibrous tissue and ground substance. The media of the main pulmonary artery comes to contain a predominance of fibrous tissue. There is not only a reduction of elastic tissue but that which remains stains poorly with the usual stains for elastin and many of the fibres are split. Associated with this are changes in physical properties of the vessel walls with loss of extensibility on traction. Intimal fibrosis is a regular occurrence in pulmonary arterioles and venules after the age of 40. Heath finds no evidence that this arises from organised thrombi and agrees with BRENNER (1935) that it reflects "wear and tear of a long life." Progressive atherosclerosis occurs in the pulmonary vasculature and is an aging process which is not necessarily more often associated with increased pulmonary vascular pressure or flow.

B. Changes in Lung Function with Age

It is not as simple as might at first appear to obtain reliable information on the effect of aging on function of the lung. Many early studies included subjects who smoked and it was unclear to what extent the documented changes reflected in part smoking-induced disease. Height is an important determinant of lung size and thus of lung function; since successive generations are taller, the normal values for old men and women of today may not apply to the elderly of the future. Most published studies are not longitudinal and fail to take this point into account. Alterations in tests of pulmonary mechanics and volume are not only affected by changes in the lung, but also by changes in the chest wall and respiratory muscles.

Nevertheless, despite these difficulties, many careful studies in normal, nonsmoking subjects of both sex, have shown that deterioration in pulmonary function is a true consequence of age. The key change is loss of elastic recoil (GIBSON et al. 1976; KNUDSON et al. 1977) and it is this which is responsible for many of the other functional changes.

I. Elasticity and Distensibility of the Lungs

To study the elastic properties of the lungs and measure lung recoil, it is necessary for the subject to swallow an oesophageal balloon. The difference between mouth pressure and oesophageal pressure gives the transpulmonary pressure or recoil

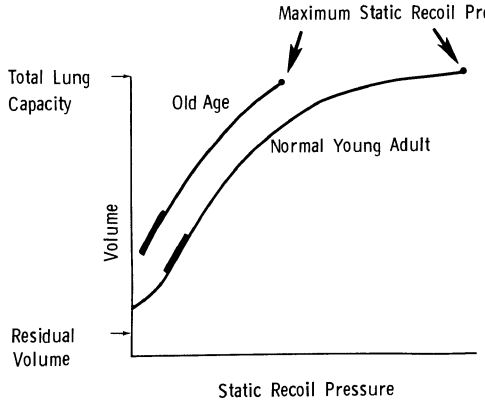

Fig. 1. Static expiratory pressure-volume curve of the lungs in a normal young adult and in old age. The slope in the tidal range *(heavy line)* indicates compliance

pressure. The early "dynamic" measurements of pressure and volume were recorded during tidal breathing but this measurement is affected by changes in the airways as well as changes in the lung parenchyma, and "static" measurements at a point of no flow are therefore preferred. Simultaneous recordings of pressure and volume make it possible to construct a pressure-volume (p-v) curve (GIBSON and PRIDE 1976) (see Fig. 1). The effect of loss of elastic recoil on the static p-v curve of the lung is a shift to the left, resulting in a greater change of volume for the same pressure difference in the older lung (see Fig. 1). The influences of extrapulmonary factors need to be considered when assessing the p-v curve. The strength of the respiratory muscles diminishes with age (RINGQUIST 1966) and changes occur in the bony cage, which serve to diminish thoracic wall compliance (MITTMAN et al. 1965). The compliance of the chest wall decreases with advancing age (MITTMAN et al. 1965) and TURNER et al. (1968) calculated that whereas in a 20-year-old only 40% of the elastic work of breathing is expended on the chest wall, a person of 60 expends 60% of elastic work on the thoracic cage. This more than compensates for the loss of elastic work on the lungs and the same workers suggest that a person of 60 years would have to do 20% more elastic work at a given level of ventilation than a 20-year-old. GIBSON et al. (1976) showed, however, that the shift of the curve to the left was not merely a result of reduced power. Static compliance is either unchanged (GIBSON et al. 1976; KNUDSON et al. 1977) or slightly increased (BEGIN et al. 1975), suggesting that there may be an increase in lung distensibility with age. All studies have shown a reduction in the maximum static recoil pressure (the maximum negative pressure which can be generated at full inflation) with age due to reduced muscle power. The changes in overall elastic properties are probably the same in both sexes and any observed differences were due to lung size or muscle power (GIBSON et al. 1976; KNUDSON et al. 1977).

Summary. The lungs lose elastic recoil with age and become more distensible. This causes the p-v curve of the lung to shift to the left independently of a diminution in muscle strength. The chest wall becomes stiffer with advancing age.

II. Lung Volume

All studies have shown a decline in forced expiratory volume in 1 s (FEV1) and vital capacity (VC) and a rise in functional residual capacity (FRC), residual volume (RV), and RV/TLC ratios (TURNER et al. 1968; KNUDSON et al. 1976).

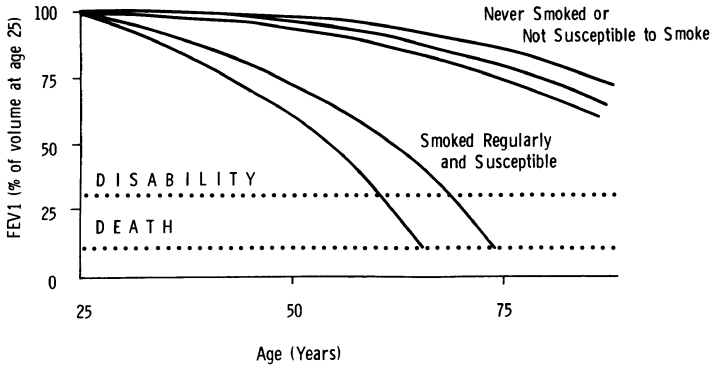

Fig. 2. Gradual decline in FEV1 in non-smokers or individuals not susceptible to smoke. Note more rapid decline in FEV1 in smokers susceptible to effects of smoke. (With modification from FLETCHER and PETO 1977)

FEV1 and VC reach a peak at about the age of 30 and decline thereafter; the rate of fall of FEV1 with age is usually quoted as 30 ml per annum (COTES 1979). FLETCHER et al. (1976) observed a fall of 42 ml per annum and suggested that the rate of loss of FEV1 seemed to accelerate with age, a finding confirmed by the study of MILNE (1978). This effect is more marked in smokers (FLETCHER and PETO 1977) as illustrated in Fig. 2.

The shift in the p-v curve accounts for an increase in RV, FRC, and RV/TLC ratio. Regional studies with the radioactive gas xenon-133 (JONES et al. 1978) confirmed these findings and showed that regional RV/TLC ratios were higher at the apex than the base. In other words the apices of the lungs are more distended or inflated at the end of expiration than the lower zones.

The position of full inflation (TLC) is set by the balance of the recoil of the whole of the respiratory system and the maximum inspiratory pressure generated by the respiratory muscles. Reduction in lung recoil which would tend to increase lung volume (thus causing an increase in RV) is offset by diminished muscle power and reduced thoracic cage compliance. Therefore TLC remains unchanged (GIBSON et al. 1976; KNUDSON et al. 1977; TURNER et al. 1968), an important distinguishing observation from emphysema where TLC is increased.

Summary. FEV1 and VC fall with age and RV, FRC, and RV/TLC ratio increase. The tendency, through loss of recoil, for lung volume to increase is offset by stiffness in the chest wall and reduced muscle power so that TLC remains unchanged.

III. Airway Closure and Distribution of Ventilation

In normal young subjects there is preferential ventilation of the dependent parts of the lung. This is explained by the gradient of pleural pressure from base to apex and by the shape of the pressure volume curve. Thus the apical lung units are more distended and ventilation is greatest at the lung base, which is situated on a more compliant part of the p-v curve. When pleural pressure exceeds airway pressure, then the airways close, resulting in gas trapping. Elderly subject lose elastic recoil

and therfore closure of airways occurs in the tidal range at the bases where pleural pressure is higher. EDELMAN et al. (1968) showed that, in the tidal range, ventilation was less uniform in old than in young men but that uniformity increased with deep respiration. Thus, they reasoned, the lungs of old men were more prone to localised alveolar collapse. Similarly, regional studies with xenon-133 (HOLLAND et al. 1968) confirmed poor distribution of ventilation to the bases during tidal breathing. These two studies show that the elderly have the same distribution of ventilation on deep breathing as young people but reduced basal ventilation during quiet tidal breathing.

The maximum expiratory flow volume curve is the result of plotting flow against volume simultaneously during a forced expiration. Studies of the flow volume curve have suggested reduced flow at low lung volumes in the elderly (GIBSON et al. 1976; KNUDSON et al. 1976). Forcible expiration results in compression of the airways and it has been suggested that in addition to loss of lung recoil with age there is increased susceptibility of the airways to dynamic compression (PRIDE et al. 1967).

Summary. The distribution of ventilation becomes dependent on the depth of breathing. Ventilation at the bases is reduced during quiet breathing but becomes normal on deep breathing. It is not necessary to postulate uneven distribution of age changes in the lung to explain this phenomenon.

IV. Ventilation Perfusion Matching: Blood Gases

Ventilation-perfusion studies using xenon-133 show significant impairment during quiet breathing in the elderly (HOLLAND et al. 1968) with areas of low ventilation perfusion ratio at the lung bases. If taken in conjunction with the reduction in cardiac output with age (BRANDFONBRENER et al. 1955), this may explain the increase in alveolar-arterial (A-a) difference from about 1 kPa at age 20 years to about 2.7 kPa at age 60 years. This was also the explanation offered by SORBINI et al. (1968), who noted the now well-recognised fall in arterial PO_2 (PaO_2) with age. [PaO_2 mm Hg = 109 – (0.43 age).] They observed a fall of 20 mm Hg between the age of 30 (94 mm Hg) and 60 (74 mm Hg). There was no change in observed $PaCO_2$.

V. Gas Transfer

Transfer of carbon monoxide declines with age but the observed changes (MCGRATH and THOMPSON 1959; ANDERSON and SHEPHARD 1969) are unlikely to account for the observed fall in PaO_2. This decline occurs both for transfer factor (TLCO) and transfer coefficient (KCO) (COTES 1979; VAN GANSE et al. 1972). Between the age of 20 and 60 years TLCO may fall by 25% (COTES 1979).

VI. Exercise

It is well recognised that exercise capacity declines with age (CANDER and MOYER 1964; COTES 1979; BATES et al. 1971). Many exercise studies (SPIRO 1977; JONES et al. 1975) require considerable expertise and equipment, so for a simple assessment

of the subject's exercise capacity the 12-min walk test described by McGavin et al. (1978) is a useful alternative, particularly in the elderly. In this test exercise tolerance is measured by the distance walked in 12 min in a level corridor at the subject's own pace and regardless of stops.

The factors that determine the breaking point of exercise and what gives rise to the sensation of breathlessness are complex, to say the least. The relationship between the subject's exercise ventilation and the maximal breathing capacity (MBC) is important and breathlessness will arise as the ventilation on exercise approximates to the MBC. Exercise ventilation can be measured and MBC derived indirectly from the FEVI (Freedman 1969). Any factors which serve to increase the drives to ventilation or reduce the bellows capacity of the lung will cause the breaking point of exercise to be reached sooner. Neurogenic factors which contribute to the sensation of breathlessness, although less easily studied are of equal if not greater importance and very variable. Campbell and Howell (1963) drew attention to the importance of the relationship between the force applied to the lung and the movement to which it gives rise; they used the analogy of a person assessing the extensibility of a rubber band by stretching it intermittently and coined the phrase "length-tension inappropriateness." The relationship is likely to be disturbed if the resistance or compliance of the thorax changes or the frequency of breathing is increased.

Muscular power decreases with age and poor muscular coordination results in greater energy expenditure for a given load. Physiological dead space increases (Cotes 1979) and so total ventilation increases and with it the likelihood of breathlessness. The maximal oxygen uptake falls progressively with age (Von Dobeln et al. 1967) from an average value of 3.17 litres/min to 2.29 litres/min between the ages of 35 years and 65 years. A reduced cardiac output (Brandfonbrener et al. 1955), lack of physical fitness (Saltin et al. 1968) and changes in the peripheral vascular bed result in the earlier onset of anaerobic metabolism at lower levels of energy expenditure. This results in lactic acid formation which creates a greater CO_2 load to be excreted and increased H^+, thus representing a potent drive to respiration.

Summary. The reduction in exercise capacity with age is dependent on the cardiac output, circulatory factors and skeletal muscles as well as on pulmonary function. Among the many factors contributing to breathlessness it is worth remembering how much the subject has to breathe (exercise ventilation) in relation to the bellows capacity of the lungs (MBC). In old age a number of variables increase ventilation and reduce MBC and therefore increase the liklihood of breathlessness during exertion.

C. The Appearance of the Chest Radiograph in Old Age

Mayer et al. (1958) described a radiographic appearance of "senile lung" with a spongy or lacy pattern of the lung fields with increased peripheral lung markings and enhanced contrast of these. They noted that the accepted changes of emphysema were seen in few old people but Edge et al. (1964) first attempted to quantify

these observations using objective criteria for the radiographic diagnosis of emphysema (SIMON and GALBRAITH 1953). They examined the radiographs of 100 persons aged 75 or over who had no clinically severe respiratory disease or heart failure, and compared them to radiographs of 70 young persons aged between 20 and 40 years. They noted that in over 80% of elderly females and under 20% of males the cardiothoracic ratio exceeded 50%, a commonly accepted figure for the upper limit of normal size, but that on direct measurements of transverse diameter of the heart there was little difference from that of the younger subjects. The average diameter of the chest was, however, strikingly reduced in old women and rather less so in men. Hence the increase in cardiothoracic ratio is due to contraction of the thoracic cage, and crude assessment of cardiac enlargement on the basis of 50% ratio is of no value in the aged. Applying strict criteria for the radiographic diagnosis of emphysema, they observed that the diaphragm was rarely low or flat, that the retrosternal space was not measureably enlarged in spite of significant kyphosis in the majority of subjects, and that hilar vessels were of normal size. Isolated localised bullae were seen in a few subjects without evidence of generalised emphysema. Finally, although they did not see the "lace-like pattern" described by MAYER et al. (1958) they explained the common observation that vessel shadows are relatively more conspicuous in radiographs of the elderly by the lower density of the rib shadows. Calcification of the trachea, main bronchi or both was seen in 37% of radiographs of old people.

SAGAL et al. (1974) examined the value of routine screening chest radiographs in over 10,000 patients of all ages who were admitted to hospital for a variety of non-respiratory reasons. A serious abnormality was seen on none of the radiographs of 500 patients under 20 years of age but in 16% of 6,000 examinations of those of 40 years or older. Of 1,850 patients who were over 60 years of age, serious abnormalities were suspected from examination of the radiograph in 678. This justifies the routine chest radiograph of all elderly patients admitted to hospital for any reason. The same workers also examined the value of a lateral radiograph and found that of 678 serious abnormalities suspected from inspection of PA radiographs of those over 60 years of age, the lateral projection confirmed or clarified the findings in 392 and that the abnormality was seen in the lateral projection only in 22. Thus in this age group a lateral view is probably justified whenever a chest radiograph is carried out.

D. Infection of the Respiratory Tract in Old Age

I. Upper Respiratory Tract Infection

Little is known of the true incidence of upper respiratory infection in the elderly. Such information can be obtained only from community studies and FRY (1953), analysing consultations in a General Practice near London, found that of all his patients, those in the over 65 year age group had the lowest rate of consultations for colds or sore throats. It seems that these infections are not more likely to lead to illness or complications in the elderly but healthy than in younger adults. Doubtless the situation is different for the ill or very debilitated, or for patients with

chronic bronchitis or severe heart disease, who may develop acute bronchitis in response to infections with viruses which rarely cause more than trivial illness in healthy adults of a younger age.

II. Influenza

In all epidemics in the last 30 years, at least tree-quarters of the total deaths have occurred in persons over the age of 55 (STUART-HARRIS and SCHILD 1976) but this was not always so for 85% of deaths in the pandemic of 1918 occurred in those under 55. Interesting variations in attack rate in successive years of infection with the same virus were described by FRY (1969, 1974).

Thus during the early years of the Asian influenza outbreak (1957 to 1959) attack rates were highest in children and young adults, but by the end of the decade (1967 to 1968) the incidence was highest in those over 60. In a detailed study of an earlier epidemic FRY (1959) found that one-third of those aged 60 to 70 and three-quarters of those over 70 developed chest complications from influenza, whereas the risk of such complications in young adults was only 1 in 20. TYRRELL (1952) in a detailed study of an influenza epidemic found that many deaths amongst the elderly were apparently from heart failure.

There is no unanimity about the value or practicability of immunising the elderly against influenza. Large scale immunisation would be difficult to organise for the elderly in their homes but has been advocated for geriatric units or other organisations housing large numbers of old people. STUART et al. (1969) showed good protection in retired persons who received A.2 vaccine for 2 years before an epidemic caused by that virus, as compared with a comparison group who had received a B vaccine. D'ALLESSIO et al. (1969), however, found that the antibody response to repeated vaccination of elderly people was poor and that no protection was obtained. Whether or not this poor response was solely the result of age is uncertain. Live attenuated influenza vaccines have been prepared and widely tested but seem to be more effective in inducing an antibody response in young subjects, who have little or no previous antibody, than in the elderly who have acquired a range of influenza antibodies during their long and repeated exposure to different strains of influenza virus.

III. Pneumonia

Secondary bronchopneumonia is a frequent and often serious complication of any prolonged or debilitating illness and probably represents a combination of hypostatic oedema, retention of bronchial secretions, aspiration, and secondary bacterial infection. Infection may, however, be absent or play only a minor role and successful treatment therefore depends on more than choice of an appropriate antibiotic. Lung damage is presumably from a number of chemical, enzymatic, toxic, and infective insults. The frequency and importance of anaerobic infection had been recognised in recent years (BARTLETT and FINEGOLD 1974), the source of pulmonary infection presumably being aspiration of infected material from the mouth or pharynx and this may occur more frequently in the sick and elderly than has previously been recognised.

Primary pneumonia (pneumonia attacking previously healthy, though elderly, lungs) may occur at any age and the pathological processes are probably the same at all ages, although clinical and radiographic features may differ in the elderly. *Streptococcus pneumoniae* is the commonest cause at all ages but in the elderly may produce a more patchy consolidation than typically occurs in the younger. This is reflected in a mottled appearance on the chest radiograph (ZISKIND et al. 1970) and in the frequent absence of such classical physical signs as bronchial breathing. It may be difficult to isolate the organism and BARRETT CONNOR (1971) has demonstrated that cultures of the sputum may be misleading and that blood culture is superior as a measure of isolating *Streptococcus pneumoniae*. Staphylococcal pneumonia is virtually never seen except during epidemics of influenza.

Pneumonia due to Mycoplasma pneumoniae is not uncommon in the elderly (MUFSON et al. 1967), usually occurring at the time of community outbreaks, although the elderly may be more likely than the young to develop pneumonia when infected by the organism (BALASSANIAN and ROBBINS 1967). Diagnosis is confirmed by demonstrating rising titres of complement-fixing antibody in acute and convalescent sera, tests for cold agglutinins being less reliable. The commonest radiographic appearance is unilateral lobar or segmental consolidation. Recognition of *Mycoplasma pneumoniae* as the cause of pneumonia is important because the organism is insensitive to the antibiotics such as penicillin, ampicillin, and cotrimoxazole which are frequently chosen for treatment of pneumonia. Tetracyclines and erythromycin are active against the organism in vitro but may in practice have disappointingly little effect on the course of the illness (WATSON 1967).

Primary pneumonia caused by *Gram-negative bacteria* is uncommon but carries a high mortality at all ages (TILLOTSON and LERNER 1966). A high proportion of those with epidemic or sporadic *Legionnaires disease* have been elderly (FRASER et al. 1977; JENKINS et al. 1979). The mortality is high during epidemics and it is not yet clear how effective antibiotic therapy will prove to be. Serological studies have demonstrated that sporadic infection is not uncommon and seems to be much less dangerous.

IV. Unresolved Pneumonia

JAY et al. (1975) showed that radiographic resolution of pneumococcal pneumonia may take 8–10 weeks and is generally slower in the elderly. In practice a distinction must be drawn between mere failure of radiographic resolution and persistence of symptoms, although both may be of clinical importance. Persistent or increasing radiological abnormalities in a patient who is clinically improving after antibiotic therapy will arouse suspicion of tuberculosis or, if the shadowing is of lobar or segmental distribution, of bronchial obstruction, usually by a carcinoma. Slow resolution with loss of volume and ultimate fibrosis seems to occur more frequently in the elderly and in the right upper lobe (BOYD 1975). Persistence of symptoms and of radiological abnormalities may be due to abscess formation, often beyond an occluded bronchus. Increasing readiness to perform fibreoptic bronchoscopy in the elderly and ill permits a proximal tumour to be recognised or discounted and may aid drainage of the abscess (WANNER et al. 1973). A tendency to delay submitting the old and ill to proper radiological examination or to take only anterior films

can result in overlooking an empyema, which may superficially resemble pneumonia both clinically and radiographically. The pleural nature of an opacity should be recognisable on good AP and lateral radiographs and the value of ultrasound examination in detecting pleural fluid and distinguishing fluid from solid lesions has recently been demonstrated (LIPSCOMB and FLOWER 1980). If in doubt about the nature of an opacity, attempted needle aspiration carries less risk than failure to recognise and hence treat an empyema.

V. Tuberculosis

With the rapid decline of new infection in developed countries, the elderly form an increasing proportion of newly diagnosed cases of tuberculosis, reflecting reactivation of infection which had been acquired early in life. Thus 40% of the male and 25% of the female newly diagnosed cases of tuberculosis in Scotland in 1968 were over the age of 55 (HEFFERNAN et al. 1975). Among the elderly there still remain many with long standing "quiescent" tuberculosis of bone, joints, spine or kidneys, and, like pulmonary lesions, these may reactivate as age increases.

It is now recognised that activity of pulmonary tuberculous lesions cannot reliably be assessed from a chest radiograph and that patients with apparently stable calcified lesions may have tubercle bacilli in their sputum if these are searched for and may be the source of outbreaks of disease in the community or in an institution. Recognition of tuberculosis is often delayed in the elderly because of the frequency of respiratory symptoms due to smoking, heart disease or other causes and the reluctance of doctors to arrange radiographic examination or examination of the sputum in an old person who is apparently well apart from relatively minor respiratory symptoms. PRODUFOOT (1971) has described a form of tuberculosis which is particularly difficult to recognise ("cryptic disseminated tuberculosis"). Fifty-seven percent of his patients were over the age of 60 years. Onset is insidious with malaise and weight loss, maybe for several months. Fever is commonly present, possibly with mild anaemia but the chest radiograph may be normal and the tuberculin test negative. Diagnosis may be possible by biopsy of liver or bone marrow but may rest on the response to a therapeutic trial of antituberculous chemotherapy.

Diagnosis of pulmonary tuberculosis rests on demonstration of bacilli in the sputum. When sputum cannot be obtained and the diagnosis of tuberculosis seems probable, or exclusion is important, fibreoptic bronchoscopy can permit aspiration of secretions, biopsy of lesions and irrigation of bronchi with little risk or discomfort and this or similar methods of confirming the diagnosis are now preferred to the previous practice of embarking on antituberculous chemotherapy on nothing more than suspicion of the diagnosis. The diagnostic value of the tuberculin skin test may diminish in the elderly. About 10% of all patients with active pulmonary tuberculosis have been found to have a negative tuberculin skin test to 10 TU, the proportion increasing after the age of 65 (JOHNSTON et al. 1963).

Modern antituberculous chemotherapy is highly effective and a cure rate of nearly 100% can be achieved if the chemotherapy is correctly prescribed and taken. Bacilli resistent to the main drugs are uncommon in patients who have not previously received antituberculous therapy. Rifampicin, isoniazid, and ethambutol are

the widely used drugs, all three being given for the first 2 or 3 months followed by isoniazid with one of the others to complete the course. Nine months has been shown to be sufficient duration of treatment with these drugs (BRITISH THORACIC and TUBERCULOSIS ASSOCIATION 1976). Patients are, for practical purposes, infectious only if sufficient organisms are present in the sputum to be visible on microscopic examination of a suitably stained sputum smear and they lose infectivity rapidly after starting chemotherapy (ROUILLON et al. 1976). Hospital treatment, if needed at all, may be for only a few weeks and emphasis is placed on ensuring that the drugs are taken regularly at home. Supervision may be required particularly in the elderly and forgetful, and good results have been obtained with regimens of twice weekly oral therapy, which are readily supervised (SINGAPORE TUBERCULOSIS SERVICE and BRITISH MEDICAL RESEARCH COUNCIL 1977).

A nationwide review of deaths from tuberculosis in the United Kingdom (BRITISH THORACIC and TUBERCULOSIS ASSOCIATION 1971) showed that the commonest causes were failure or delay in making the diagnosis, and errors of management when the diagnosis has been made. Of those who died, 70% were over the age of 60.

Prevention of tuberculosis in the elderly rests largely upon effective case detection. Alcoholics and the impoverished seem to be at particular risk and there is much to be said for routine chest radiographs for the elderly, particularly those living in institutions. People with extensive fibrotic lesions on radiographs should be considered for chemotherapy *before* reactivation occurs (JOINT TUBERCULOSIS COMMITTEE 1973) and those with proven tuberculosis should receive energetic treatment supervised by physicians who are experienced in the management of this disease and in the use of modern drugs. Treatment by non-pulmonary physicians was shown to produce inferior results due to inappropriate treatment in over half of one series of patients (BYRD et al. 1977).

E. Conditions Associated with Airways Obstruction

I. Chronic Bronchitis and Emphysema

Attempts have been made in the last 2 decades to clarify the definition and improve recognition of chronic bronchitis and emphysema, which so frequently coexist. The MEDICAL RESEARCH COUNCIL (1965) definition of chronic bronchitis as a condition characterised by cough, with production of sputum on most days during at least three consecutive months for more than two successive years, has been widely accepted for clinical purposes but the definition of emphysema (CIBA GUEST SYMPOSIUM 1959) remains based on pathology, which is less useful to the clinician who seeks a clinical diagnosis. The earlier confusion whereby the same condition tended to be labelled "chronic bronchitis" in Britain and "emphysema" in the United States seems largely to have been resolved (FLETCHER et al. 1964). No doubt remains about the primary role of cigarette smoking in causing these diseases. Demonstration of a deficiency of alpha 1 antitrypsin in serum of patients who develop severe emphysema early in life (HUTCHINSON 1973), often with a family history of this condition, has stimulated research into other causes although even in these

deficient subjects the disease occurs earlier in smokers. The role of infection has been reviewed by STUART HARRIS (1968) and it is generally conceded that whereas infection plays little part in initiating the disease, viral, bacterial, and mycoplasma infections are implicated in causing exacerbations. The finding that continuous antibiotic therapy somewhat reduces the duration but has no effect on the frequency of exacerbations (MEDICAL RESEARCH COUNCIL WORKING PARTY 1960) and the demonstration of virus infection preceeding some exacerbations (e.g. LAMY et al. 1973) lends weight to the view that exacerbations are precipitated by infection, usually viral, and that bacterial infection may follow. LAMBERT and STERN (1972) showed that the viral aetiology of exacerbations differs between adults who live in a household with young children and those who do not.

Breathlessness, the predominant symptom, is a reflection of airway obstruction. Simple and inexpensive methods of measuring airways obstruction such as the peak expiratory flow meter and dry spirometers have led to acceptance of the importance of measuring lung function both in diagnosis and in clinical management. The obstruction in patients with chronic bronchitis improves only slightly after administration of adrenergic bronchodilator drugs but perhaps rather more after atropine-like drugs (CROMPTON 1968). The severity of breathlessness correlates well with the degree of airway obstruction (CAPEL and SMART 1959). Transfer of gases (e.g. of carbon monoxide) is impaired more in emphysema than in chronic bronchitis.

Criteria for radiographic recognition of emphysema have been described (SIMON and GALBRAITH 1953), the more subtle changes in chronic bronchitis reflecting diversion of blood flow from lower to upper zones (SIMON 1978).

FLETCHER et al. (1976) have shown that the rate of decline of lung function (fall of FEVI) is greater in smokers than in non-smokers. They, and also HOWARD (1967) have demonstrated that the rate of decline of FEVI is not related to infection and that sudden falls do not seem to be related to acute episodes of infection. The rate of decline may persist or diminish after stopping smoking. The course and prognosis of chronic bronchitis and emphysema have been studied extensively. Contrasting clinical and physiological patterns of the "blue bloater" with cyanosis, hypoxaemia, elevated arterial carbon dioxide tension, oedema, and pulmonary hypertension and the "pink puffer" with more intense dyspnoea, weight loss and relatively well maintained arterial blood gases have been discussed by many, including FLETCHER (1968). GOTTLIEB and BALCHUM (1973) reported that two-thirds of their patients died within 2 years of their first episode of respiratory failure.

Treatment is based upon attempts to persuade patients to stop smoking cigarettes and efforts to improve airway obstruction by inhaled or oral selective beta 2 adrenergic bronchodilator agents, atropine-like drugs or theophylline derivatives. The rational role of antibiotic therapy was reviewed by MAY (1968) and although many newer antibiotics have been developed since, his principles remain unchanged. Short intermittent courses of "broad spectrum" antibiotics given when sputum becomes purulent are generally preferred to continuous therapy. Bacteriological examination of sputum is not helpful before treatment, MAY having shown that *Streptococcus pneumoniae* or *Haemophilus influenzae* are present in the great majority of sputum samples from patients in exacerbations. Attempts to show that physiotherapy has a beneficial effect on lung function have not always

been successful (NEWTON and STEVENSON 1978). The problems of oxygen therapy in patients with chronic bronchitis were described by CAMPBELL (1960) and the rational use of controlled oxygen therapy is now widely accepted. There is increasing, if cautious, use of long-term domiciliary oxygen therapy following the demonstration that oxygen for much or all of the day can partially reverse hypoxic pulmonary hypertension (STARK et al. 1972) and possibly prolong survival (PETTY et al. 1971). Trials are in progress to assess the value and rational application of such therapy. The development of an oxygen concentrator (STARK and BISHOP 1973) could simplify such treatment and reduce costs.

Management of acute respiratory failure in chronic bronchitis has somewhat veered away from assisted ventilation towards "conservative" methods (SLUITER et al. 1972) and these will generally be preferred in the elderly unless such predictably transient factors such as infection, surgical operations or rib fractures have caused temporary respiratory failure in a patient whose condition beforehand was fairly good.

II. Asthma

BURR et al. (1979) identified asthma in 3% of a random sample of people aged over 70, confirming what chest physicians had long believed – that asthma is not uncommon at this age. Recognition may be difficult as the asthma is often "intrinsic," lacking the features of allergy as so often seen in younger asthmatics and because some of the patients may also have chronic bronchitis from cigarette smoking. Clinical features which suggest the diagnosis of asthma are rapid or sudden development or increase of breathlessness and wheezing, paroxysms of breathlessness and cought at night, a family history of allergy and a personal history of hay fever (LEE and STRETTON 1972). Skin tests are frequently negative but an excess of eosinophils may be found in the sputum. The belief that this necessarily indicates asthma (MORROW-BROWN 1958) has been challenged recently by the finding that eosinophils may frequently be found in the sputum of patients with chronic bronchitis if repeated specimens are examined (TURNBULL et al. 1977). The airways obstruction in this age group may not improve significantly after bronchodilator drugs, and a carefully carried out trial of oral corticosteroids may be required to confirm the diagnosis and to obtain improvement. It is essential that such a trial should be based on frequent measurements of lung function with peak expiratory flow rate recorded several times a day both before and during administration of corticosteroids. Without this precaution and attention to detail an erroneous impression of benefit may be obtained because of a temporary euphoria at the effect of corticosteroids, or a significant improvement of lung function may remain unrecognised if not noticed or reported by the patient.

The response of the elderly to treatment of their asthma is gratifying, although many will require systemic corticosteroid therapy. The introduction of inhaled corticosteroids aerosols and powders has further improved the life of elderly asthmatics.

III. Obstruction of Large Airways

Obstruction of large airways may produce stridor, which can be mistaken for the wheeze of asthma or chronic bronchitis. A predominantly *inspiratory* wheeze

should raise suspicion of narrowing of major airways. The forced expiratory and inspiratory flow volume loop may give valuable confirmation, showing either disproportionate reduction if inspiratory flow or marked impairment of flow in both inspiration and expiration. Bronchial carcinoma is the commonest cause but laryngeal palsies or tumours or an enlarging retrosternal thyroid may also narrow the major airways.

F. Cancer of the Lung

The peak of incidence and mortality from lung cancer remains after the age of 60, and the average age of cases at death seems to be increasing (BELCHER 1975). The distribution of histological types of carcinoma appears to be similar to that of younger patients (BATES 1970; BIGNALL 1958) as does the mode of presentation. In the large series from Brompton and Royal Marsden Hospitals in London the proportion who had local or distant metastases at the time of first examination was approximately the same in all age groups (BIGNALL 1968). The selection of patients for referral to specialist hospitals could, however, obscure any tendency for older patients to present on account of metastases and therefore not be referred to hospital. Information on less selected large series of patients is not available.

Haemoptysis, cough, fever, and pain are the commonest symptoms at onset, of which cough and all but severe pain may be ignored by the elderly, only haemoptysis being likely to lead to early investigation. There has been considerable interest in the less common form of presentation with "paramalignant" metabolic or endocrine syndromes associated with release from tumours of biologically active polypeptides resembling ACTH, parathormone or antidiuretic hormone (ROSS 1972). AZZOPARDI et al. (1970) showed that 16 out of 185 unselected patients with bronchial carcinoma developed endocrine syndromes. The non-metastatic neurological and muscular features have been described by BRAIN (1963) and bronchial carcinoma must be borne in mind as a cause of myopathies, cerebellar lesions, polyneuritis, and syndromes resembling motor neurone disease. It is not uncommon for the first manifestation of a bronchial carcinoma to be from intracranial metastases.

Most, but not all, bronchial carcinomas are evident on a good chest radiograph. A lateral view is essential both to define the characteristics and site of any opacity seen on an anterior view and to avoid overlooking tumours which are not easily seen on the anterior film. Radiological features alone such as erosion of adjacent ribs may permit an almost certain diagnosis of malignancy but it is usually necessary to confirm the diagnosis unless a decision has been made on other grounds not to offer treatment whatever the lesion may be. Expert cytological examination of sputum provides the diagnosis in up to 85% of all patients, the yield increasing as up to four specimens are examined (OSWALD et al. 1971). The advent of fibre-optic bronchoscopy performed with local analgesia has considerably extended the application of bronchoscopy in the elderly, who usually tolerate the procedure well. Lesions seen on chest radiographs can be examined and biopsied through the bronchoscope, or fine brushes or forceps can be passed into a peripheral opacity (ZAVALA 1975). Diagnostic yields of over 80% can be expected. Percutaneous aspiration biopsy of localised peripheral lesions yields excellent diagnos-

tic results with only a small risk of pneumothorax (FLOWER and VERNEY 1979), and subjects the elderly patient to little discomfort or risk. PAYNE et al. (1979) have shown that this method, though excellent for the diagnosis of malignancy, is less reliable for identifying the histological cell type.

Surgical excision remains the treatment most likely to result in cure of lung cancer and is most successful for small peripheral squamous carcinomas. THOMPSON-EVANS (1973) reported that 723 (40%) of a series of 1,800 patients with lung cancer were aged 65 to 94 at the time of diagnosis and that of these only 114 were suitable for resection, a proportion which is similar to that in his younger age group. Postoperative hospital mortality was 20% (compared to 10% for those under 65) but the mortality after lobectomy was only 15% as compared to 27% after pneumonectomy. BATES (1970) and SENSENIG et al. (1966) confirmed the high risk of pneumonectomy and the lower mortality after lobectomy. THOMPSON-EVANS reported a 39% 4-year survival after lobectomy.

Many different regimens of chemotherapy are under trial and in expert hands can provide palliation of many symptoms but, as yet, little prolongation of life. In inexpert hands these powerful and toxic drugs can produce greater distress than the malignant process which is being treated. Radiotherapy remains the best method of rapidly relieving pain from localised tumour or metastases, and neurosurgical techniques of pain relief have advanced considerably in recent years. The management of malignant pleural effusion has been reviewed by FRIEDMAN and SLATER (1978). DURRENT et al. (1971) and LAING et al. (1975) have compared a policy of no immediate treatment for inoperable carcinomas with irradiation or chemotherapy.

Malignant pleural mesothelioma (ELMES and SIMPSON 1976), an invariably fatal tumour, seems to be becoming more common possibly as a result of widespread use of asbestos fibre, although recognised contact with asbestos may have been slight, transient and many years earlier. The commonest presentation is with a blood-stained and painful pleural effusion. Diagnosis is difficult in the absence of obvious asbestos exposure, and repeated aspiration or pleural biopsy carries the risk of encouraging tumour to grow along the track of the needle to involve the chest wall. The tumour often spreads as a thick cuirrasse round one or both pleural cavities causing extreme pain and breathlessness. Metastases may occur both in and outside the chest but rarely produce troublesome symptoms. No treatment has been found to alter the inexorable course of this disease.

G. Pulmonary Fibrosis and Alveolitis

I. Cryptogenic Fibrosing Alveolitis

In 1944 HAMMAN and RICH described "acute interstitial fibrosis" of the lungs since when a variety of synonyms have been used both for the acute condition and for the more common and more chronic form of pulmonary fibrosis. Cryptogenic fibrosing alveolitis (SCADDING 1974) is uncommon but not rare and as the mean age of presentation is about 55 years, many patients develop the disease in older life. Dyspnoea on exertion without wheezing is the commonest first symptom and may

develop suddenly or gradually and may be accompanied by a dry cough, often precipitated by effort or by attempts to take a deep breath. Bilateral widespread crackles (crepitations) are heard over the lungs, most markedly at the end of inspiration. Curiously these tend to disappear or move to the front of the chest if the patient bends forward. Clubbing of the fingers occurs in about 60% of patients (TURNER-WARWICK 1972). The chest radiograph shows changes ranging from a fine "ground glass" haze, often in the lower zones, to extensive coarse irregular shadows. These abnormalities are bilateral and persistent but may be asymmetrical. Spirometry shows a restrictive defect of ventilation with proportional reduction of FEV1 and vital capacity with impairment of gas transfer and arterial hypoxaemia on exertion, if not at rest.

The cause of this condition is unknown but features such as presence of either circulating antinuclear antibodies or rheumatoid factor in about two-thirds of all patients, the not infrequent occurrence of arthralgias and the association with rheumatoid arthritis, chronic active hepatitis, and possibly other "connective tissue disorders" suggest an abnormality of immunity (TURNER-WARWICK 1978).

Diagnosis may be possible on the basis of the features described but it is essential to exclude conditions of known aetiology which can produce similar clinical, radiographic, and physiological appearances. Persistent left ventricular failure and bilateral bronchopneumonia can usually be excluded on clinical and radiological findings and on their response to appropriate therapy. Foremost among other conditions to be considered are inhalation of organic dusts (see later), inhalation of inorganic dusts such as coal, silica or asbestos, reactions to drugs such as busulphan (BURNS et al. 1970), bleomycin (LUNA et al. 1972), and nitrofurantoin (NICKLAUS and SNYDER 1968). TURNER-WARWICK (1978) lists other known causes of widespread pulmonary fibrosis. PEARSON and WILSON (1971) describe extensive bilateral fibrosis in six elderly patients who had hiatus hernias and suggested chronic aspiration as the cause.

Biopsy of the lung may be necessary to confirm the diagnosis or exclude other conditions. Although open surgical biopsy provides the largest sample of lung it would rarely be justifiable in the elderly and transbronchial biopsy through the fibreoptic bronchoscope under local analgesia (STABLEFORTH and CLARKE 1977) or percutaneous high speed trephine biopsy (STEEL and WINSTANLEY 1969) will be preferred.

The more acute forms of the disease, termed "desquamative insterstitial pneumonitis" by LIEBOW et al. (1965), usually responds readily to systemic corticosteroid therapy but the response of the more chronic forms is less predictable. Fifty-nine of the 96 patients reported by STACK et al. (1972) died, with a mean survival of 4 years. The main factor influencing survival was the response to corticosteroid therapy. The patients with most severe dyspnoea, poorest tests of lung function and arterial hypoxaemia had the worst prognosis.

II. Extrinsic Allergic Alveolitis

A condition somewhat similar to cryptogenic fibrosing alveolitis can result from inhalation of a variety of organic substances (TURNER-WARWICK 1978). Many of these illnesses, such as farmers' lung, bagassosis, mushroom workers' lung, are re-

lated to specific occupations and are perhaps less likely to be seen amongst the elderly than those which result from domestic exposure. The commonest variety of allergic alveolitis in Britain is due to inhalation of protein from droppings of pet birds, especially budgerigars (parakeets). A survey of 1,000 consecutive attenders at an outpatient clinic (HENDRICK et al. 1978) detected 117 current owners and 296 previous owners of these birds! Thirty-eight patients came into contact with pigeons and 50 lived or worked on farms; hence only 38% of the sample had no exposure to any species of bird. The clinical features (HARGREAVE et al. 1966) are similar whatever the cause, with breathlessness without wheeze on exertion or at rest, which may be acute or slowly progressive. The acute reaction which occurs within 4–8 h of exposure to birds (as in pigeon fanciers who occasionally visit the pigeon loft), may be associated with fever, myalgia, and leucocytosis and may simulate influenza, pneumonia or pulmonary oedema. Patients with a less acute onset with slowly progressing dyspnoea are less likely to report their symptoms and by the time they are first seen may have advanced and extensive fibrosis, often of the upper lobes, resulting from many years of daily exposure to their pet birds. Clubbing is less common than in cryptogenic fibrosing alveolitis, crackles are heard over the lungs and cyanosis may be present. Radiographic changes range from a fine haze to extensive nodules or upper zone fibrosis. The diagnosis is confirmed by the demonstration of precipitins against avian serum and if need be by carefully carried out bronchial challenge tests. Response to corticosteroid treatment is excellent in the early stages but less good when fibrosis has developed and treatment is of course based on permanent avoidance of contact with birds of all types.

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Rehabilitation

Rehabilitation – Physical and Clinical Aspects

J. RUSTEMEYER

In memory of Bernhard Steinmann

A. Definition

The world "rehabilitation" is derived from the Latin and can be roughly translated as "restoration of a capability or faculty." It has become the accepted term for a broad concept, namely provision of the best possible help to people handicapped by disease or disability, this help covering every sector of their lives which is involved. According to WIEDEMANN'S (1977) definition, rehabilitation is the endeavor "to implement the idea of the best conceivable coordination of the interests of society and the individual," and though *restitutio ad integrum* may not always be feasible, *restitutio ad optimum* can and must always be the goal.

It is obvious that this ideal cannot be achieved by medical measures alone and that it calls for an interdisciplinary approach. Among the other sciences involved are sociology, psychology, and educational theory.

In the following chapter the main emphasis will be placed on medical considerations, but an attempt will be made to demonstrate the importance of cooperation with supplementary nonmedical professions.

B. The Importance of Geriatric Rehabilitation

The enormous upsurge in rehabilitation in the last 3 decades has had several causes, among which were the new ideas which arose during the Second World War and the growing importance of measures designed to preserve working capacity. In West Germany for the first 15 years after the Second World War little or no effort was directed toward the rehabilitation of people beyond working age, though in other European countries and in the United States considerable experience in geriatric rehabilitation had been accumulated and encouraging results had been achieved. The pressures exerted by the steadily growing proportion of old people in the population and the increasing numbers of pensioners in need of rehabilitation, many of whom, because of the progressive restructuring of family patterns and the shift from large to small families with segregation of the older generation, could no longer be cared for within their families, led to the creation of institutions designed for rehabilitating elderly people. The illimitable demand for institutional places and the overwhelming social pressures have encouraged these endeavors, and from the social and political standpoint their most important goal is to sustain or restore the capacity of ageing citizens to look after themselves.

The experience gained and the successes achieved have favored these developments. The outcome has been a steady growth in the range of rehabilitation measures carried out in people over 65 years of age (BRONISCH 1975) and in facilities for geriatric rehabilitation.

C. Legislative Background and Costs

Recent statutory regulations and decrees have expanded the potential for rehabilitative measures, which are now available to all citizens irrespective of age (SCHOLZ 1980). This is not the place to discuss the administrative details of the law governing rehabilitation (see appropriate specialist literature, such as JUNG 1975; SCHOLZ 1980).

Who pays the costs? This depends on various factors, notably the nature of the rehabilitative measures, the place in which they are carried out and the person who initiates them. In principle, the major public insurance companies, and under certain conditions the trade or employers' associations, are responsible, but for people over the age of 65 the main burden is carried by statutory and private sickness insurance funds. Details will be found in the relevant specialist literature (STROEBEL 1975 and elsewhere).

The aim of all these endeavors is the "coordination of the interests of society and the individual" or, in other words, the best possible compromise between improving the quality of life for the individual into old age and at the same time minimizing social burdens and obtaining the best possible value for money expended. However, to what extent the "equality of opportunity" proclaimed from the political platform is in fact attainable for the elderly citizen in need of rehabilitation is a question which depends not so much on statutory regulation as on the inherent biological limitations of old age, some of which are discussed below.

D. Biological Factors Governing Rehabilitation in Old Age

I. Physiological Characteristics of Senescence: Diminished Adaptive Capacity and Exaggerated Interindividual Variation

Rehabilitation programs follow more or less the same fundamental concept irrespective of age. However, in the involution phase there are certain special features which distinguish the ageing body and mind, and they are indeed so pronounced as to call for special consideration in connection with most rehabilitation measures. For this reason there is a need for suitably organized educational centers from which the specialist knowledge necessary for geriatric rehabilitation can be disseminated (STRAX 1979).

A detailed survey of the special physiological characteristics of elderly people is not feasible in a chapter on rehabilitation. I shall therefore confine myself to mentioning two relevant peculiarities of fundamental importance: the impoverishment of adaptive capacity and the exaggeration of interindividual variation.

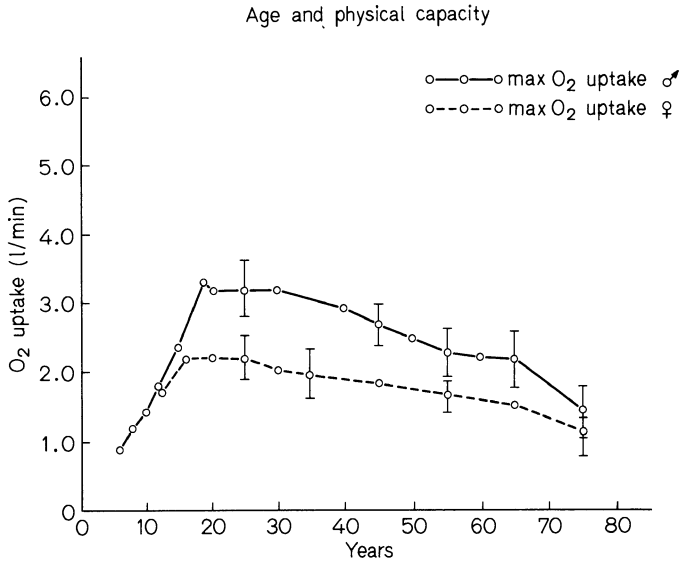

Fig. 1. Changes in max. O_2 uptake/min in healthy males and females during life ($n=2{,}834$). (HOLLMANN 1980)

Old people generally display some degree of biological deficit as compared with younger people (STREHLER 1959). This deficit is in part the result of a development which many authors ascribe to the characteristic diminution in adaptive capacity typical of senescence; this has indeed been emphasized as a characteristic feature of ageing (VERZÀR 1965; BOURLIÉRE 1948; LORENZ 1965; SHOCK 1962; BRONISCH 1975).

A decrease in the powers of adaptation is a fundamental attribute of every ageing organism and, in the same way as ageing itself, it is a function of time. Adaptive capacity denotes the power of any organism successfully to adjust its life-supporting internal demands (internal milieu, homeostasis) to the exigencies of the environment (external milieu). In all higher organisms it is the resultant of numerous and, in some cases, competing factors, e.g., on the one hand the decline in functional efficiency and on the other the compensatory mechanisms developed as the result of accumulated experience. In human beings involutionary and degenerative processes predominate from the 5th decade onward and indeed to such an extent that the loss of adaptive capacity, when plotted as a graph, follows an ever-steepening downward curve (ERBSLÖH 1969).

The degree of impairment of adaptive capacity at any given time, projected in relation to the relevant environmental conditions, determines the magnitude of the individual's need for rehabilitation and also the potential response to rehabilitation. Among other factors, it determines exercise capacity – the most important criterion for physical rehabilitation.

The decline in the general performance curve becomes steeper and steeper as the functioning of various organs deteriorates and compensatory mechanisms become less and less effective. In "healthy" ageing the curve is relatively flat (Fig. 1),

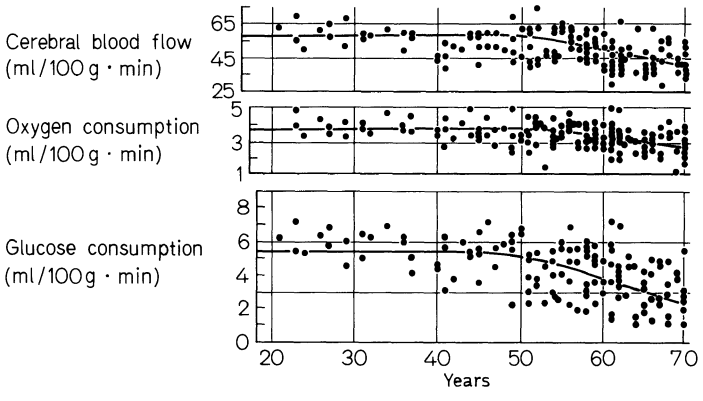

Fig. 2. Cerebral blood flow, oxygen supply and glucose consumption in healthy subjects at different ages. (GOTTSTEIN 1967)

but as the ageing process borders upon the abnormal or actually enters that zone, the curve turns more steeply downward. As age advances, the twilight zone between normal and pathological becomes more and more hazy.

For this reason alone it is far from easy to assess the potential for rehabilitation in elderly handicapped people, and the task is made even more difficult by the exaggerated interindividual variations typical of senescence. This variation is reflected in the steady broadening of the scatter of all normal and abnormal parameters with advancing age (VERZAR 1965; WELFORD 1958; GOTTSTEIN et al. 1963; THOMAE 1980). As will be seen from Fig. 2, physiological performance in old age follows the general decline in the performance curve, but certain individuals display performance figures far above or far below the mean. Any attempt to assess the exercise capacity of elderly candidates for rehabilitation may be extremely difficult. Figures for normal values in advanced age are questionable, because of the enormous variation and because of the indistinctness of the boundaries between normal and abnormal. Most investigations terminate at the age of 65 or 70 and figures for higher age groups are obtained by extrapolation. This means, for example, that the formula for estimating the maximum attainable and tolerable pulse rate (200 minus the age in years) may be of limited validity in old people.

It is often stated that rehabilitation measures involving exercise training carry considerable risks in old age. These risks can be minimized by careful medical supervision, with accurate measurement of *individual* exercise limits, using suitable techniques such as exercise ECG and spiroergometry, *before* each session of exercise treatment and by close clinical supervision *during* treatment.

1. Methods and Indices for Assessing Physical Capacity in Old Age

The available space permits only a short outline of some of the current techniques and indices which have proved of value in appraising the performance range of elderly people. Measurements of maximum O_2 uptake in healthy subjects show a decline of approximately 50% between the ages of 20 and 80 years (Fig. 1). On the

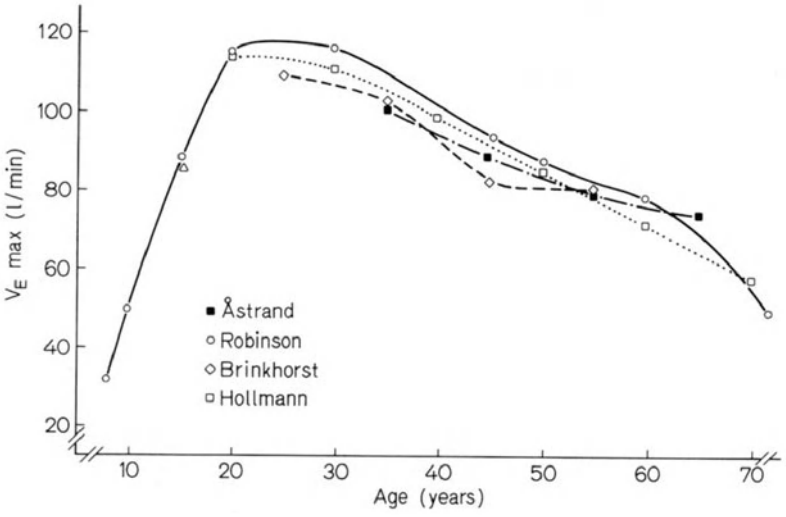

Fig. 3. Changes in maximum ventilation during maximum dynamic work by large muscle groups in healthy persons of various ages. Comparative results from various investigators. (HOLLMANN 1978)

cardiac side this decline results from the decrease in maximal cardiac output, which is in turn limited by the steady decrease in maximal stroke volume and by the reduction in maximal heart rate (which is given by the rule of thumb already quoted: maximal heart rate = 200 minus age in years). On the pulmonary side, mention should be made of the decline in maximal ventilatory capacity (Fig. 3), which likewise amounts to aproximately 50% between the ages of 20 and 70 years. It is due to the progressive loss of elasticity in the lung tissue and the bony thorax, changes which are also registered in the maximum breathing capacity. (Further details will be found in the special chapters of this volume and in the relevant specialist literature, e.g. HOLLMANN et al. 1978).

II. Pathophysiological Characteristics: Variation of Clinical Symptoms Typical of Ageing and Multimorbidity; Extent and Consequences

The high incidence of mishaps during the physical rehabilitation of old people is well known and is not solely due to the difficulties in assessing their exercise limits. The exaggerated variability typical of ageing is also reflected in the extraordinary multiplicity and inconstancy of the change which takes place in the ordinary and well-known symptoms of disease in middle age. All symptoms may apppear in accentuated shape or may be less clearly defined than usual; they may assume a totally unfamiliar guise or they may be completely absent; the older the subject the more frequent and variable are these deviations.

Of special relevance in the sphere of physical rehabilitation is the high incidence of asymptomatic myocardial infarction, e.g., during medical gymnastic treatment. The usual symptoms and signs signaling danger, e.g., those of physical overstress, may be absent or so atypical or attenuated that they are misinterpreted or even en-

tirely disregarded (SCHULZ 1975). Some of the sudden deaths which occur during physical training in geriatric patients are undoubtedly due to this cause.

However, the main factor which sets limits to the possibilities of rehabilitation in old age is the multimorbidity characteristic of senescence (SCHUBERT 1975). As age advances, concurrent diseases increase continuously in number and in severity (RUSTEMEYER 1968). In a study extending over several years we found an average of 4.5 concurrent illnesses among our own patients, a figure which corresponds to most of the reports in the literature (BROCKLEHURST 1980). Furthermore, the pattern of pathological changes is commonly of such nature that its deleterious effects on the response to rehabilitation are not merely additive, but potentiated: e.g., cardiac failure may be combined with abnormal limitation of breathing capacity, obesity, and severe osteoarthrosis of the hips and knee joints (see frequency scale of diseases in persons over 65 years of age, Federal German Statistical Bureau) (RUSTEMEYER 1968). The dire effects of such combinations are obvious.

In the everyday practice of geriatric rehabilitation it is therefore taken for granted that any course of treatment must be preceded by suitable measures to expand the patient's rehabilitation potential or even to create it *ab initio*. Some 84% of our patients were completely or predominantly bedridden on admission. Sixty-two percent had one or more decompensated illnesses (the commonest being decompensated heart failure), so that their first need was conventional hospital treatment to restore compensation. It must, however, be emphasized that rehabilitative measures, in suitably modified form, can and should be initiated during the decompensation phase, and indeed even during intensive treatment, though acute diseases where absolute rest is essential naturally constitute an exception. In many cases, such as hemiplegia due to cerebral infarction, neglect of early treatment by passive and active movements may lead to the immobilization syndrome (ZILLI 1980). Such neglect may seriously compromise the ultimate response to rehabilitation or even make it impracticable, e.g., owing to uncorrectable joint contractures or deformities. These considerations are valid at all ages, but they are of special relevance in geriatric rehabilitation because in no other age group does the discrepancy between the need for exercise and the willingness to take exercise have such grave and fateful effects on the outcome. The incidence of joint stiffness or ankylosis after fractures, pareses, etc., rises steeply in patients over 60 years of age. Early mobilization is therefore one of the essentials of geriatric rehabilitation.

III. Exercise Tolerance and the Demands of Training

Physical rehabilitation in geriatrics presents yet another dilemma, which can be outlined as follows: any rehabilitation measure which involves physical exertion will carry difficulties and risks and therefore calls for great caution and a guarded attitude toward treatment. Nevertheless, experience shows that unless exercise therapy is pushed close to the limits of exercise tolerance the outcome of rehabilitation will not be satisfactory and will not justify the time and trouble expended. Training which falls short of the limits of exercise capacity sticks in the ineffective zone and fails. Exercise to two-thirds of the limit, which is the generally accepted rule in rehabilitation, must in the light of recent findings in elderly patients be revised to three-quarters of the limit. The relatively poor improvement achieved in

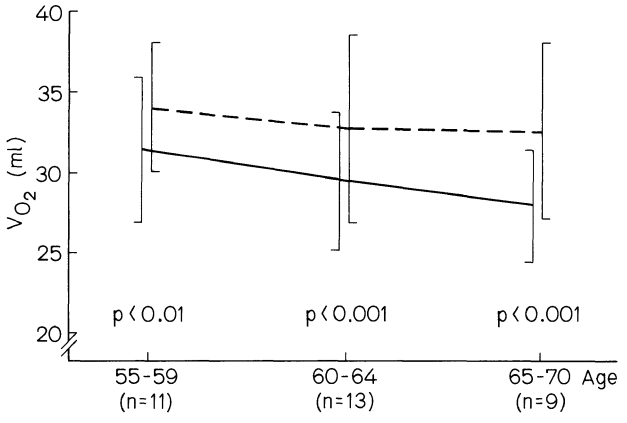

Fig. 4. Changes in maximum O_2 uptake (ml/min · kg) before (——) and after (- - - -) 10 weeks endurance training in persons 55–70 years of age. (From LIESEN, cited from HOLLMANN 1980)

many rehabilitation units despite prolonged treatment is partly attributable to exercise training of inadequate intensity. However, it is only the careful and experienced physician who has the incentive and the justification to encourage his elderly handicapped patients to undertake effective exercise.

IV. The Response to Training in Old Age

The picture of geriatric rehabilitation as outlined so far may well make a negative impact on the reader, but there are certain positive aspects which must be considered. The overall physical capacity of the ageing body, though reduced, is by no means negligible. The capacity to respond to training by an improvement in performance is usually retained into advanced age – provided there are no insuperable disease states – and this is true of the body as well as the mind. Basic research has demonstrated this fact in experimental animals, as for example in the impressive experiments of VERZAR (1965) in old and very old experimental animals after physical and psychological training. HOLLMANN (1980) has demonstrated that physical training capacity persists up to the age of 80. This work involved several investigations and a variety of physiological parameters (Fig. 4).

The preservation of mental training capacity, e.g., the maintenance of learning and memory power into old age, and the fact that even then it is still capable of enhancement, have been demonstrated by numerous workers including THOMAE (1973, 1980) and LEHR (1972, 1975).

The fact that training capacity persists into old age is among the general experience of doctors engaged in geriatrics and is one of the fundamental justifications for encouraging rehabilitative measures even in advanced age.

V. Methods of Training for Elderly Handicapped Patients

In view of the variety of individual features which demand attention during the rehabilitation of the elderly patient, it is impossible here to go into practical details. All that can be done is to discuss certain points of general validity.

When performing physical rehabilitation it is essential to avoid any exercises which demand maximal or submaximal muscular exertion for short periods (prolonged maximal exertion is by its very nature impossible in old age). This prohibition applies both to active exercises (e.g., running or stair climbing) and to isometric muscle contraction exercises. The reasons lie partly in the (patho) physiology of the ageing muscle itself (the adverse effects of a purely anaerobic muscle energy supply, etc., HOLLMANN 1980), and partly in the overproportional rise in systolic blood pressure which accompanies severe physical exertion in old age. The resulting cardiac stress and the reactive rise in pulse rate may lead to an unacceptable oxygen deficit in the myocardium with consequent infarction. Overenthusiastic endurance training may easily overstress the untrained subject (KRAUS 1978). The most suitable approach is through harmonious, rhythmical movement sequences which conform to the natural mode of movement of elderly people and which are in keeping with the physical capacity of the handicapped individual. The more muscles and muscle groups that can be brought into the exercise routine, the more effective the treatment will be. Swimming in warm water constitutes an ideal form of physical exercise, even in old age. All exercise routines should be so devised that they are easily grasped and understood. Overstrain must be avoided. It is often necessary to select the most important measures so as to achieve correctly apportioned concentration on the main problems (see Sect. E.III). These points can be summarized as: moderate active muscular exercises, compatible with the two-thirds to three-quarter loading of the cardiovascular system referred to above, should be carried out in conformity with the principle: "little and often" (RUSK 1977). If the physician remembers the basic guideline of geriatric rehabilitation: "maximum effect and minimum risk," he will usually arrive at the best attainable training.

E. Indications for Rehabilitation in Old Age

I. General Principles

The selection of patients for rehabilitation is based on the definition given at the beginning and on the aims set out under the heading "Rehabilitation" (see Sect. A). In principle the indications in old age are the same as those in all other age groups. With increasing age, however, "fitness for employment" fades into the background and "fitness for self help" takes its place.

Rehabilitation measures are in general a benefit provided by society as part of its duty toward the individual in need of care. It is therefore logical that, when considering whether rehabilitation is indicated, the interests of society must rank equally beside those of the individual. The reconciliation of these two interests usually presents no difficulties provided that, when considering the interests of the community, the physician also gives due weight to the interests of the individual and vice versa, as is in practice nearly always the case. During working life there is no conflict: preservation of fitness for work is in the best interests of society and individual alike. So far as pensioners are concerned, the chief interest of society is in averting, minimizing, or postponing the handicapped individual's need for nurs-

ing care (BENNETT 1980). As the need for nursing care nearly always implies serious loss of independence and self-determination, and may even mean that the individual has to leave home, the interests of the community and the individual are usually at one. In late senescence, however, there may be some divergence between the interests of society and the individual and the physician may be faced with difficult decisions. However, when considering the indications for geriatric rehabilitation, the physician must be primarily guided by the physical and mental needs of his elderly patient.

To what extent should *age* be considered a limiting factor in decisions regarding rehabilitation measures? Chronological age is less important than biological capacity (SHOCK 1962). As already stated, capacity for training is retained even into advanced age and rehabilitation is still feasible and effective. It is therefore unjustifiable to set any arbitrary age limit. Whatever the patient's age, his requirements must be individually assessed.

In the light of general experience it may be said that the following life situations represent three typical sets of circumstances where geriatric rehabilitation is required:

1. The patient who has survived an *acute illness* may require help to return to his former mode of living (e.g., in his own home). This is termed "curative rehabilitation."
2. For the patient with a *chronic illness or handicap* rehabilitation may achieve some actual improvement or may at least prevent further deterioration (e.g., it may be possible to enable the patient to continue to live in his own home). This is termed "conserving rehabilitation."
3. When the patient's state of health *threatens to deteriorate* rehabilitation may ward off the deterioration (e.g., the patient whose capacity for selfhelp is at risk). This is known as "preventative rehabilitation" (STEINMANN).

II. Assessment of the Need for Rehabilitation

The first step must be to estimate the dimensions of the patient's need for rehabilitation. Adequate assessment is often far more difficult than in younger people. The physician must ask himself how long life expectancy is likely to be. Extreme old age and severe mental impairment inevitably lead the assessor to adopt a guarded attitude.

Several aspects have to be taken into account. The dimensions of the need for rehabilitation should invariably be synoptically assessed in terms of:
The individual
The social (personal) environment (family, available nursing help) and living accommodation (home circumstances)
The interests of society.

Assessment must be based on careful medical appraisal and detailed analysis of the patient's social circumstances.

In the medical appraisal of the patient the following questions must be answered:

1. How great is the existing impairment?
2. How serious is the associated functional disability?
3. How troublesome is the resulting handicap in everyday life?

4. How great is the physical and mental suffering caused by the overall handicap and its repercussions?

Analysis of the patient's social circumstances must comprise, inter alia, the following points:

1. How seriously are the people in contact with the handicapped person (the people to whom he or she relates) affected by the consequences of the handicap?
2. How great is the discrepancy between the demands of the existing external life *situation* (e.g., in the patient's own surroundings) and the limitation of the patient's ability for self-help?

In the interests of the community, any assessment of rehabilitation need must take cost-effectiveness into account.

It is impracticable to draw up universally valid guidelines for assessing the rehabilitation needs of the elderly. Categorization of the degree and urgency of need must inevitably depend on the subjective judgement of the assessor. The two dimensions already referred to are the crucial factors:
The extent and severity of objective pathological abnormalities and handicaps and
The severity of the subjective suffering which they impose on the handicaped person and/or those looking after him.

Searching examination will reveal physical disabilities in need of treatment in most elderly people. However, it is neither feasible nor necessary to treat or rehabilitate every minor handicap, as many functional deficiencies are spontaneously compensated. But when the disability becomes so severe as to threaten the health or social integration of the handicapped person, rehabilitation becomes necessary. In estimating the appropriate level of rehabilitative measures and in evaluating any contraindications the physician will be guided, inter alia, by his assessment of the potential response to rehabilitation.

III. Assessment of the Potential Response to Rehabilitation

When assessing the *need* for rehabilitation the physician must look at the situation from the opposite direction and must consider the *potential response* to rehabilitation, measured primarily in terms of the patient himself or herself (for potentialities, see Sect. F). To appraise the potential response we must turn once again to the medical assessment:

1. How large are the remaining "reserves," both organic and functional (rehabilitation potential)?
2. If this rehabilitation potential is fully exploited, what degree of restoration or improvement of function can be expected?
3. To what extent is any improvement in quality of life thus attainable, if only by alleviation of suffering?

This leads on to social questions:

1. Can rehabilitation relieve the ill-effects on the patient's social environment or at least reduce them to an acceptable level?
2. Bearing in mind the expected residual handicap, would it be possible to adapt the remaining potential for living to the existing (modified if necessary) living accommodation available to the patient?
3. Is the necessary expenditure reasonably commensurate with the expected benefit?

Reference has already been made in Sect. D.I to the serious impairment of physical efficiency and exercise capacity which exists even in healthy elderly people and in Sect. D.II to the multiple pathology characteristic of old age. It is not necessary to explain in detail that the potentialities of rehabilitation in old age are a priori limited and it is enough to estimate to what extent the present prospects of rehabilitation are already diminished.

Evaluation of the potential response to rehabilitation in view of the *rehabilitation maximum* is made by setting the overall total of physical shortcomings (impairment, disability, and handicap) against the rehabilitation potential.

When dealing with people of working age the physician will usually strive toward the rehabilitation maximum, but when treating elderly people it is usually neither practicable nor sensible to aim at the theoretically attainable maximum. When considering what rehabilitative measures are indicated the physician should critically review all the features which characterize the special situation of the elderly person. The first obstacle to maximal rehabilitation in old age is the multimorbidity: in the face of four or more concurrent illnesses or handicaps it is often impossible to treat every treatable disability without overburdening patient and therapists alike (to say nothing of the available resources of time and money). It is much more sensible to set a few main objectives, so that efforts can be directed toward the most important disabilities while the less important points are left in abeyance. The best guides for ascertaining the main objectives are the criteria used for determining the individual's rehabilitation goal: the physician should select for treatment those handicaps the alleviation of which will offer the patient the largest improvement in quality of life.

The patient's social environment is also involved, and here too it is often impossible to find a perfect solution for every problem. The main objectives must be carefully chosen and effort must not be dissipated on inessentials.

By this pathway of scrutiny, weighing up, and selection, the physician will arrive at the rehabilitation *optimum* for each individual. Not every doctor has the wide knowledge of sociology and psychology necessary for making an assessment. He can draw on the resources of appropriate specialist agencies such as the social work organizations or he can seek advice from the team in charge of a geriatric rehabilitation clinic. However, the general practitioner familiar with the personal, family, and domestic circumstances of his patient will usually be able to recognize the rehabilitation objective toward which he must aim.

IV. Criteria Which Exclude Rehabilitation

The chief criteria which exclude any prospect of successful rehabilitation are:

1. Irreversible somatic changes (e.g., the terminal stages of inflammatory, degenerative, or posttraumatic joint affections, in cases where mobilization is no longer possible and surgery has nothing to offer)
2. Irrecoverable mental changes (e.g., irreversible brain damage such as senile dementia)
3. Lack of motivation

Re 1: In such cases the impossibility of rehabilitation applies solely to the somatic changes in question. In all other respects the patient may be fully capable of rehabilitation, e.g., by compensation training.

*Re 2:*Deterioration of mental powers beyond a certain point very frequently sets limits to the feasibility of rehabilitation in old age, because rehabilitation is predominantly a learning process. If a patient is no longer capable of understanding and carrying out instructions and incorporating them into his own routine, it is generally the case that the limits of rehabilitation potential have been reached. However, the decision to regard mental impairment as irreversible should not be taken until the patient has undergone careful internal and neurological examination. It is not uncommon to find that the cause of cerebral decompensation is some remediable condition, usually in the sphere of internal medicine, as for example decompensated cardiac failure with cerebral hypoxia, wide deviations from normal blood pressure, uncontrolled diabetes mellitus, renal failure, anemia, or even some inflammatory condition of the respiratory or urinary tract, etc. On the other hand, when the primary cause is cerebral, drug therapy has not a great deal to offer.
Re 3: Lack of motivation need not be regarded as ruling out the possibility of rehabilitation unless it is really insuperable, e.g., if it is due to irreversible mental changes. On his first meeting with an elderly handicapped patient, the rehabilitation therapist frequently encounters rejection. This is due to an attitude of resignation which has arisen as the result of the (often prolonged) confrontation of the sufferer with his own helplessness and his passive acceptance of the role of the "feeble old man." A sensitive and understanding explanation of the present day possibilities of help will nearly always succeed in implanting motivation, provided that the patient retains sufficient insight. Experience shows that it is often beneficial to encourage patients who lack motivation to participate as spectators in rehabilitation exercises and to talk to those who have undergone rehabilitation.

There are of course some unmotivated patients who are unwilling to surrender their role as recipients of aid and attention. Any attempt to impose rehabilitation on such subjects is doomed to failure, because handicaped people of this kind invariably relapse into their old role (or are pushed back into it by their relatives).

F. Resources and Methods of Geriatric Rehabilitation

I. Human Resources: The Rehabilitation Team

The task of rehabilitation is carried by all the people professionally involved in carrying out rehabilitation procedures. When they are working in direct cooperation, as in a rehabilitation clinic, they are known as the rehabilitation team.

In conformity with the concept of modern rehabilitation, which has as its objectives the comprehensive improvement of the *overall* situation of the patient including his social milieu, the rehabilitation team must be of interdisciplinary composition. This necessity is underlined by the special conditions of *geriatric* rehabilitation, in particular multiple pathology and the high incidence of social problems.

The members of the rehabilitation team are doctors, physiotherapists, occupational therapists, speech therapists, specialists in physical medicine, social workers, psychologists, and nurses.

In certain spheres of rehabilitation the team has other important members. First among these is the priest or pastor, who can make an important contribution to the patient's spiritual rehabilitation. Other specialists include art and music

therapists, dieticians, and educational experts, and also "second line rehabilitation helpers" such as opticians, hearing aid specialists, dental technicians, truss makers, and artificial limb and appliance fitters. As regards somatic geriatric rehabilitation, however, the professional groups discussed below constitute the essential elements of the team.

1. The Geriatrician

The order in the above listing does not imply any hierarchy. However, the responsibility for leadership devolves upon the medical profession. The physician decides whether rehabilitation is indicated, carries out most of the diagnostic work, and lays down the rehabilitation plan (in conjunction with the team). He coordinates the practical implementation of rehabilitation (SCHOLZ and JOCHHEIM 1975), organizes the activities of all other members of the rehabilitation team, and – above all – it is he who carries the responsibility.

The center of medical activity should be a doctor or group of doctors experienced in rehabilitation, both general medical and geriatric. In addition – in keeping with the interdisciplinary approach – he must have access to a circle of consultants in all specialities, in particular orthopaedics and neurology.

The center, however, is the converging point of all the threads that make up the web of rehabilitation. It is the center which receives, processes, and transmits all the information without which effective teamwork is impossible. It is the doctor who decides how much physical stress is permissible for each individual patient. He must be the motivator of his rehabilitation patients and his rehabilitation team alike in the unending struggle against resignation and weariness of soul. The success or failure of geriatric rehabilitation depends on his enthusiasm more than on any other factor.

His diagnostic, therapeutic, and – last but not least – administrative activities cannot be even outlined here. He must possess a broadly based knowledge of rehabilitation in all its branches and aspects. However, the wide scope of present-day rehabilitation increasingly requires an interdisciplinary team of specialists available to assist the geriatrician with information and action when required.

As regards the size of the medical establishment necessary to staff a rehabilitation center, it is difficult to lay down precise figures. The number of doctors required depends on many factors such as the nature and severity of the handicaps and diseases requiring treatment, the extent and intensity of the rehabilitative activities, the mean duration of stay, etc. For this reason any figures must be tentative and uncertain, especially for part-resident institutions. For institutions comprising ward accommodation the German Hospital Association (Deutsche Krankenhausgesellschaft 1974a) has provisionally suggested the following establishment figures, and in my opinion they ave proved their value:

Geriatric hospitals for acute care (specialist geriatric rehabilitation clinics and departments):

1 doctor: 12.0 patients.

Establishments for long-term care (rehabilitation clinics for long-stay patients and long-stay hospitals):

1 doctor: 19.6 patients

2. Physiotherapy[1]

Modern rehabilitation recognizes the superiority of active exercises carried out by the patient as opposed to the previously favored passive measures such as massage, packs, and baths, to which the patient is subjected. Physiotherapy has thus assumed a leading position among the procedures of somatic rehabilitation. In my own experience it is employed in some 80% of patients undergoing physical geriatric rehabilitation and in over 90% of patients in active geriatric rehabilitation clinics.

Before starting teatment, the therapist must ask for details of the patient's living conditions (including any problems of his home environment such as stairs, etc.), and the affected parts of the body must be carefully examined, the requirements of the physiotherapist being kept in mind. The practical deployment of physiotherapy begins as early mobilization. Elderly bedridden patients are at special risk of lethal complications (thromboembolic conditions, pneumonia) and lasting disabilities (restriction of joint movement, deformities, contractures), all of which are encouraged by the immobility of old age (see also Sect. D.II), and for these reasons every effort must be made to achieve early mobilization in such patients.

Next comes the major task of *progressive exercise therapy*, which should be carried out in conformity with the principal tenet of geriatric rehabilitation: consistent orientation toward the individual's rehabilitation objectives.

In contrast to the younger handicapped, in whom nonspecific exercise such as group gymnastics, unassisted swimming, etc., can achieve the predetermined objective, successful rehabilitation of the elderly calls for specific problem-oriented measures tailored to individual needs. The older the patient, the greater is the need for such specificity. If the goal of rehabilitation is to be the maintenance or restoration of self-care capacity, then the entire physiotherapeutic rehabilitation programme must be directed toward that objective (BUCHWALD 1952). This presupposes that the physiotherapist is adequately acquainted with the relevant problems of the handicapped individual. Such knowledge can be obtained by personal interrogation of the patient and by close cooperation with and careful assessment of information from other members of the rehabilitation team. In this connexion the patient's personal life-style and the existing domestic situation should so far as possible be respected and kept intact.

This is usually the lengthiest phase of therapy and requires various exercise appliances including walking aids such as walking chairs, walking frames, and parallel bars. Other types of apparatur – usually confined to rehabilitation centers – are used for exercising major functional units of the locomotor system. Among them are the "resistance bench" and the "rowing boat" (Fig. 5; for details see RUSTEMEYER 1980). Physiotherapy strives to be highly practical in its approach to geriatric rehabilitation, a claim which may be exemplified by the functional exercise staircase. This device has movable steps which can be adjusted to match the height of the steps at the entrances and exits of the buses and streetcars in the locality. The task of accustoming patients to prostheses and orthopedic appliances, and of training them in their use, also comes within the purview of physiotherapy.

1 Also termed "physical therapy" in the English language literature (RUSK 1977)

Fig. 5. The "rowing boat"

Anyone undertaking physiotherapy for elderly people must understand and make allowances for their diminished adaptive capacity, and all the consequences which this implies. These problems are instructively reviewed by H. BEINEKE (1978).

The final outcome of reintegration by physiotherapy is to restore the handicapped person to his everyday life and to enable him to cope with it. His capacity to meet these demands must be verified. For this purpose indoor treatment should if possible be supplemented by outdoor physiotherapy with walking exercises in the open air (RUSK 1977), preferably (as in properly equipped rehabilitation centers) in a special walking exercise area. When necessary and feasible, training in traffic discipline and the use of public transport should also be given (see Sect. G.III). The relatives or other persons caring for the patient should if necessary be asked to attend, so that they can be familiarized with any residual disabilities, shown (and perhaps trained in) the correct methods of giving aid, and, where possible, encouraged to take part in the continuing treatment of the elderly patient, either acting as assistants or giving treatment themselves. Special attention must be directed to safety in the home and any hazard which makes walking dangerous should be put right.

The results which can be achieved in old people are often limited. However, geriatric physiotherapy also means a systematic compensation training to minimize the effects of any irremediable handicaps. For example, wheelchair training will enable the invalid to make the best possible use of his remaining living space.

Any attempt to lay down the number of physiotherapists required in rehabilitation centers is subject to the same difficulties as in the medical sector (see Sect. F.I.1). Many of the estimates of establishments for physiotherapists and occupational therapists in hospital geriatric units (CLEMENS 1979) are too low for geriatric

rehabilitation. In my experience the following formula ils appropriate for acute care in rehabilitation clinics:
1 physiotherapist: 12 patients
(up to one-third of these can be students). In other geriatric rehabilitation units the numbers required will depend on the intensity of physiotherapeutic activity and may be twice or even three times (long-stay hospitals) as great.

3. Occupational Therapy

The tasks and working areas of occupational therapy, according to the Worlf Federation of Occupational Therapy (W.F.O.T.), are:
1. Functional exercises designed to improve mobility, strength, and coordination
2. Self-help training:
   a) basic self-help training intended to maintain or restore the basic skills needed for independent living, such as eating and drinking, dressing and undressing, washing and shaving, and using the lavatory
   b) advanced self-help training including the skills needed for tasks such as preparing meals, coping with domestic life (using kitchen and bathroom), and, if appropriate, shopping.
3. Instruction in well conceived, useful, creative, and mentally stimulating activities such as handicrafts and even games.

Training in the use of prostheses, ortheses, and other appliances also comes under this heading.

If occupational therapy is to be successful, it will be necessary first of all to question the patient about his living conditions such as the domestic problems of self-help and self-maintenance, insofar as these are relevant to the proposed occupational therapeutic measures.

In geriatric rehabilitation occupational therapy is the direct and indispensable partner of physiotherapy. Fully effective cooperation demands a free interchange of information regarding the state and progress of therapy and in hospital daily contacts should be the rule.

In my own experience, occupational therapy is employed almost as extensively as physiotherapy, namely in 60%–65% of patients undergoing somatic geriatric rehabilitation and in 70%–80% of patients in geriatric rehabilitation clinics. It must be started at the earliest possible moment, as soon as the patient's condition allows, the aim being early mobilization. Treatment should begin with simple measures such as limb exercises designed to restore function and with basic self-help training (JORDAN 1968). In conjunction with the physiotherapist, the occupational therapist must strive to mobilize the bedridden patient as quickly as possible.

When beside occupational therapy has been completed, it must be followed by functional exercises. In rehabilitation units these are carried out in treatment rooms equipped with therapeutic appliances which supplement the physiotherapeutic devices already mentioned, such as the flexor-extensor and abductor-adductor looms (Figs. 6, 7). Advanced self-help training should be started at about the same time. At this stage, even more than in the case of physiotherapy, it is essential to take account of the patient's personal circumstances, the help available in the home (does he or she live alone?), living accommodation, and financial resources.

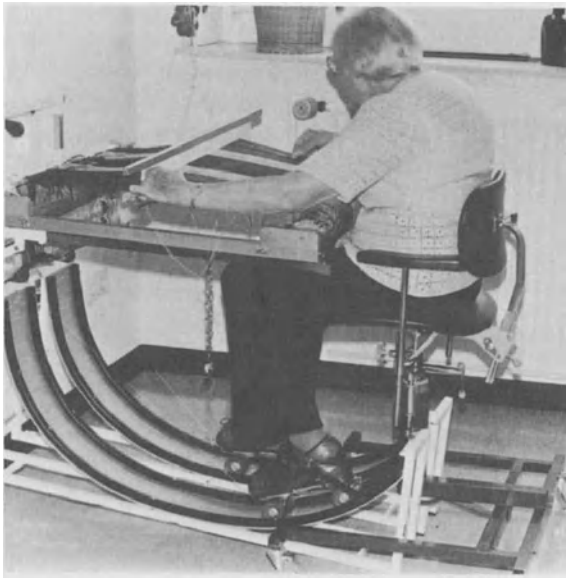

Fig. 6. The "flexor-extensor loom"

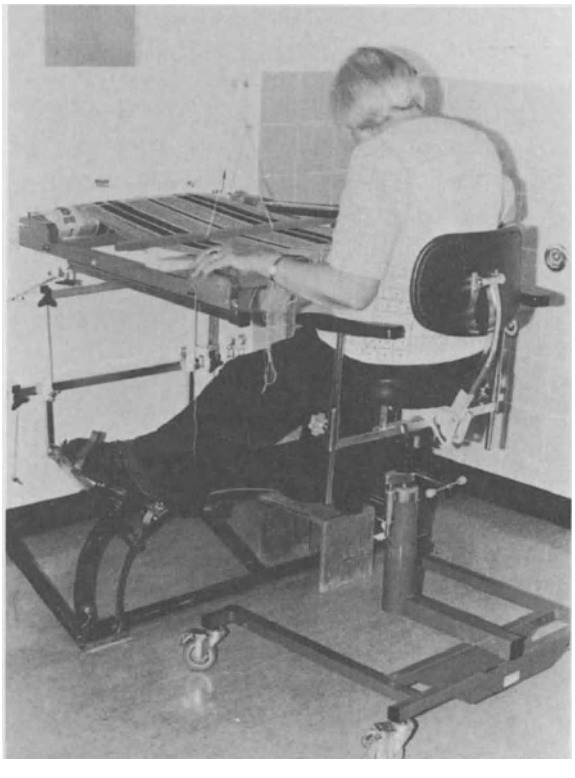

Fig. 7. The "abductor-adductor loom"

Ambulant rehabilitation means that training is carried out in the handicapped person's home, special attention being directed to the problem areas (kitchen, bath, lavatory), while in rehabilitation centers there are practice rooms set aside for the purpose (see Sects. F.II.2.a and G.II). When the handicap is very severe it calls for a high level of experience, resourcefulness, and skill on the part of the occupational therapist, but even in such cases, by exploiting compensatory mechanisms and making full use of remedial aids, the goal of self-help can be attained. Toward the conclusion of treatment, occupational therapy, like physiotherapy, must be aimed at reintegration in the full meaning of the term, i.e., transition to independent life at home. Another measure of value in suitable patients is "shopping training" (see Sect. G.III), and it may also be desirable, as in the case of physiotherapy, to recruit relatives and other persons caring for the patient so that they can be taught the correct way of coping with the patient and if necessary instructed in rendering aid and given further training. When a patient who has undergone hospital treatment with the aim of reintegration into the community still needs further occupational therapy at home, the hospital therapist will get in touch with the community therapist to ensure that correct treatment is continued in the patient's home, especially in the problem areas. She also has the task of procuring aids for self-help – from a self-help aid depot or elsewhere (see Sect. F.IV.1) – and of training the patient in their use. (Any necessary medical prescriptions should be provided by the hospital doctor and the general practitioner, working in conjunction.)

The special rehabilitative value of occupational therapy lies in the fact that in every procedure it combines *mental* training with physical exercise – in particular training in the power of concentration and recent memory. This aspect of occupational therapy is of greater significance in geriatric rehabilitation than in any other sphere.

As to the *numbers* of occupational therapists required, guidance will be found in the corresponding paragraph on physiotherapists (Sect. F.I.2). In my own experience the appropriate ratio for acute geriatric hospitals is

1 occupational therapist : 15 patients

The figures given in Sect. F.I.2 can be used as a guide to the proportion of student therapists and the staffing ratios for other hospital rehabilitation units.

a) Mobile Occupational Therapy

The services of a mobile occupational therapist have proved useful in the management of severely handicapped patients. When hospital treatment is well advanced an occupational therapist belonging to the team at the rehabilitation center (e.g., a geriatric rehabilitation clinic) assesses the patient's home and reports any important points bearing on the handicap, so as to enable the rehabilitation team to plan treatment to overcome any foreseeable problems. At the same time the mobile occupational therapist ascertains whether the existing disability calls for any alterations or improvements in the home (alterations in the lavatory, washbasin, or bath; fitting handgrips, grabrails, etc.). Where necessary she suggests changes and discusses them with the patient, the patient's family, and, if need be, the patient's landlord. She also takes charge of the implementation of these changes herself, should this be required. Shortly before the end of the hospital treatment she checks

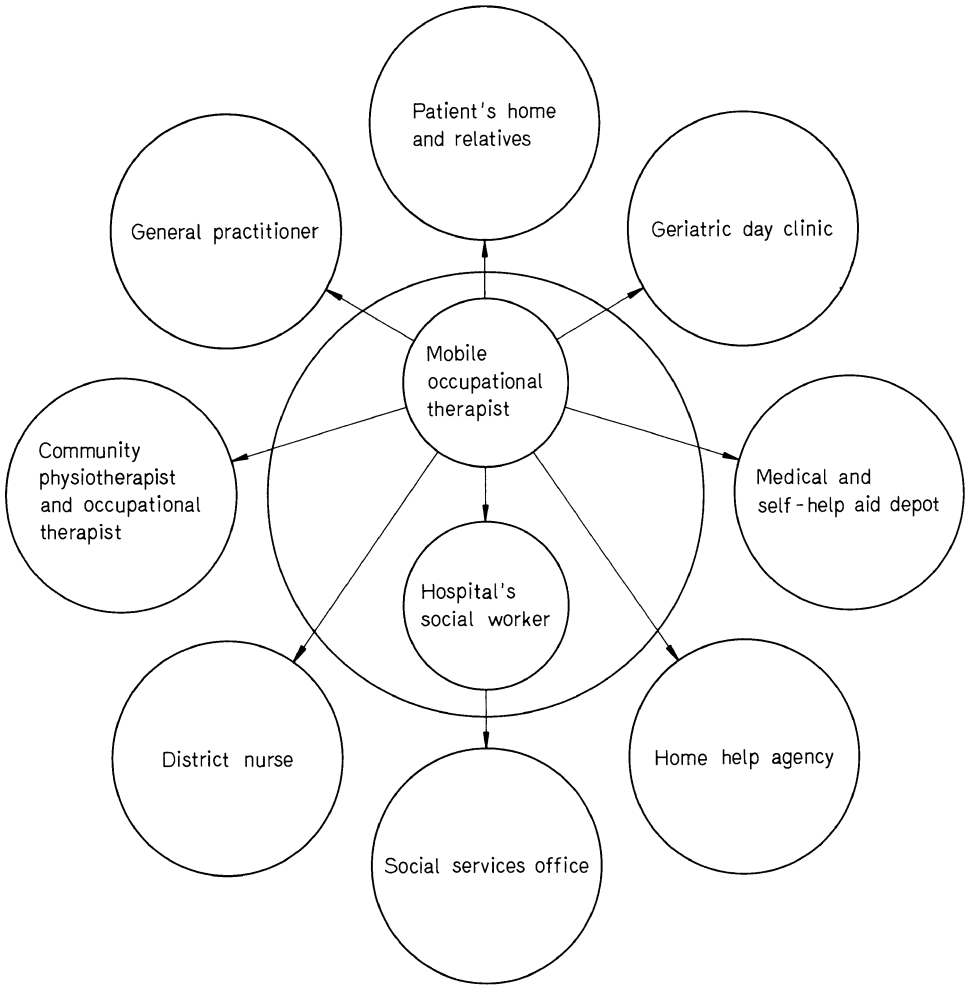

Fig. 8. Cooperation between the mobile occupational therapist and other agencies

all the functional activities of the patient by means of a trial lasting several hours in the patient's home, and/or she visits the patient 1–2 days after the patient's discharge. She continues to visit the patient until she is certain that the reintegration has succeeded; alternatively, after agreement with the family physician, she leaves the patient in the hands of a local occupational therapist. She will cooperate with the local social workers (or the social work office), the district nurse, and the organizers of social services (such as meals on wheels, home helps; see Sects. F.IV.2 and F.V; Fig. 8). If the patient is still in need of self-help aids after his return home she will obtain these (as available) from a self-help aid depot (see Sect. F.IV.1) or will arrange for them to be supplied (on the doctor's prescription or otherwise). It is also part of her duties to make sure that such appliances are used correctly. In the light of current experience an appropriate ratio is
1 mobile occupational therapist: 100–150 hospital patients.

4. Logopedia

If the patient has an acquired and treatable speech handicap (in old age the commonest cause is a cerebrovascular accident) speech therapy should be tried. If possible it should be given by a trained specialist, as aphasias of primarily cerebral etiology require careful diagnostic investigation and appropriate therapy (WEPMAN 1967). In most cases the work is laborious and time consuming, but loss of the power of making oneself understood is one of the most distressing afflictions that disease can bring, and any progress toward regaining speech, though it may take months to achieve, is of enormous value to the patient (CAMPICHE 1976). Treatment should be carried out in close cooperation with the rehabilitation team, in particular the occupational therapist, and may if necessary be continued on an outpatient basis after discharge from hospital.

Estimates of the numbers of logopedists required in geriatric rehabilitation centers are almost impossible to make, because the numbers of patients referred for speech therapy vary enormously from one establishment to another. As a rough guide it may be useful to note that in my own experience approximately 25% of patients with the after effects of cerebral infarcts require speech therapy. CLEMENS (1979) suggests that the complement of logopedists in inpatient geriatric institutions should be 21%–24% (i.e., the percentage of all therapeutic procedures carried out). From this it may be assumed that a ratio of 1 logopedist: 70–75 patients will be appropriate for a geriatric rehabilitation clinic.

5. Physical Medicine

Physical medicine comprises the use of heat, cold, light, water, massage, and electricity. Although all these modes of treatment are also employed in physiotherapy, when applied to the *passive* patient they come within the domain of the masseur and the balneotherapist. In geriatric rehabilitation it is of value principally in giving support to exercise therapy. For example, electrotherapy, heat therapy, and hydrotherapy can be of great help in the management of chronic inflammatory and degenerative joint conditions and cervical and lumbar syndromes due to degenerative lesions of the vertebral column. Space is not available to enumerate or describe the indications and applications in detail, and there seems little purpose in so doing, because the same guidelines apply in geriatric practice as in younger patients. However, it should be remembered that all these forms of treatment require special caution, with avoidance of extreme temperatures and careful observation of the elderly patient's reactions. It is often best not to apply packs and baths to the whole body, but only to one part at a time. A warning must be given against the uncritical prescribing of such treatments, as is often done at spas. The treatment of elderly handicapped people calls for adequate knowledge of geriatric medicine on the part of those engaged in physical therapy. As regards the *establishment* of staff needed for physical therapy in geriatric rehabilitation centers, this is inversely related to the number of physiotherapists (remedial gymnasts). A ratio of 1 masseur or balneotherapist: 50 patients will be appropriate in the majority of instances.

6. Social Work

Because of the exceedingly numerous social problems which arise in old people in need of medical rehabilitation, the task of the social worker is of special importance. Even at the assessment stage, when the need for rehabilitation is still being considered, detailed acquaintance with the social situation of the elderly handicapped person is indispensable. Without the social worker, the doctor would be hard pressed and would miss the expert knowledge which he (she) contributes. Social work is of special value in the reintegration of aged patients undergoing rehabilitation.

It has proved useful to attach social workers to rehabilitation centers so that they can become members of the rehabilitation team. Among the functions of the social worker are to supervise the transition phase (preparations and arrangements for discharge) and subsequent care at home. This is done in close collaboration with other members of the hospital team (in particular the mobile occupational therapist) and the community services such as local authority homes and relief services, as set out in Sects. F.IV.1, F.IV.2, and F.V, and in Fig. 8.

The *complement* of social workers required depends on the average age of the patients and the average severity of their handicaps (both factors are usually related to the degree of social need) and to the average duration of stay in hospital for rehabilitation. The demand for the services of social workers fluctuates much more widely than the need for therapeutic procedures, and it is therefore exceedingly difficult to arrive at an estimate of the numbers required. Technical and numerical details should therefore be sought in the relevant literature.

7. Psychology

Experience has revealed the need for a psychologist as a member of the rehabilitation team. Young patients are generally optimistic about the outcome of their disease, but the elderly handicapped patient often suffers much more severely from his disability and from the associated feelings of permanent helplessness and hopelessness. He needs more help from outside to enable him to come to terms with his future. Without such help there is a far from negligible risk of suicide. By virtue of his broad range of activity, the psychologist relieves the burden on the doctor and enhances the effectiveness of the rehabilitation team. (Information on the value of psychology in rehabilitation in old age will be found in the relevant literature, including LEHR 1975.)

8. Activating Care

At one time nursing care was exclusively passive, but the current doctrine is "activating care." Its objectives can be summarized in two sentences:

1. "Never do anything for the patient he can do himself"
2. When you *do* help, do it in such a way that the help you give is also training the patient in self-help

The correct implementation of activating care for the elderly handicapped demands a knowledge of rehabilitation medicine, exercise therapy, and the physiol-

ogy and psychology of old age. It also calls for persuasiveness and patience. One of its tasks is to participate in the work of the physiotherapist and occupational therapist – especially during self-help training – and to reinforce and continue this by reciprocal arrangement (STEINMANN 1976; HACKLER 1976). In one example, during early mobilization the occupational therapist was carrying out dressing and undressing training for a patient as a means of basic training in self-help. After the patient had made good progress the nurse responsible for the patient attended the training sessions, took over the training technique, and continued the dressing training, first at weekends, and then daily until the patient became independent of help and the nurse's role became merely supervisory. This example may appear elementary, but in serious handicaps instruction in the correct technique for the patient requires broad knowledge which can be imparted only by specialists.

Postgraduate education should be among the duties of doctors, occupational therapists, and physiotherapists in every major rehabilitation unit, and, thanks to the partial realization of this ideal, there is now a growing number of nurses with postqualification training in activating care. Working in rehabilitation units and from community and local authority homes, they are already capable of independently carrying out valuable rehabilitative functions. If this movement achieves wide acceptance the disciples of activating care will exercise a missionary function in geriatric rehabilitation.

Numerical estimates of the complement of nurses in hospitals can be based on the figures given by the German Hospital Association (Deutsche Krankenhausgesellschaft 1974b). These are founded on a ratio of 1 nurse: 2.79 patients. This ratio is seldom attained, but in my experience a ratio of 1 nurse: 3 patients is acceptable and – depending on the proportion of patients needing intensive nursing care – appropriate for most geriatric rehabilitation units.

II. Institutional Resources: Rehabilitation Centers

One prerequisite for the ideal rehabilitation of elderly people is a graded series of institutions offering facilities for full and partial inpatient care in accordance with the needs of the individual. Only by providing a suitably graded structure against the background of an integrated medical care system is it possible to create optimal conditions for rehabilitation and to reconcile the needs of the elderly handicapped with the demand for the utmost economy.

1. Part-time Inpatient Care: The Geriatric Day Clinic

The objective of the geriatric day clinic or day ward is to carry out treatment for those geriatric patients who no longer need full inpatient care but for whom ambulant treatment is impracticable because of the nature of their disease or handicap and/or for social reasons. The term "part-time inpatient care" denotes that a day clinic cannot undertake all the functions of an ordinary hospital, the limitations being mainly temporal. The patient in a geriatric day clinic spends the evenings and nights – and usually the weekends – at home and attends the clinic during the daytime only. This means that he must not be bedridden and that regular transport

to and from the clinic must be available. (Many clinics have their own vehicles for the purpose.)

Efficient day clinics have at their disposal the services of a complete rehabilitation team and all the therapeutic facilities necessary for physical rehabilitation (BROCKLEHURST 1964, 1979). For appropriate patients they are hence just as valuable as inpatient rehabilitation centers (COSIN 1954), and they combine high efficiency with great economy (for example, they require to be staffed for *one* shift of 8 h only). They have other advantages: the elderly patient need not be separated from his familiar surroundings and the relatives who look after him at night can follow their occupations during the day (HUBER 1974). For reasons similar to those discussed in connexion with geriatric rehabilitation clinics (Sect. F.II.2.a) it has been found best to situate the day clinic in proximity to a fully equipped hospital.

These part-time inpatient institutions can undertake short-term and medium-term rehabilitation as well as long-term care. Their range of indications follows logically from their intermediate position between inpatient and ambulant treatment facilities. Attached to most day hospitals is an outpatient advisory center, available to general practitioners for advice and for carrying out geriatric rehabilitation treatment. The optimal *number of places* is given as 30–50.

Mention should also be made of so-called geriatric day centers. As opposed to day clinics, their main emphasis is on care and their primary purpose is to look after the elderly handicapped person who is not capable of any significant improvement, to avert or postpone his admission to an old people's home, and to enable his relatives to go to work during the day. Many day centers offer a limited range of rehabilitation facilities, and in view of the call for "conserving rehabilitation" this seems entirely appropriate. In such centers the employment of nurses trained in activating care (Sect. F.I.8) is of particular importance. Day centers, like day clinics, are organized for short-term, medium-term, and long-term care.

2. Inpatient Facilities

a) The Geriatric Rehabilitation Clinic and the Department of Geriatric Rehabilitation

If the proposed rehabilitation requires to be carried under *inpatient* conditions, a geriatric rehabilitation clinic will be appropriate, provided the necessary rehabilitation can be accomplished or substantially improved in a short- or medium-term course of treatment (i.e., within 6–12 weeks) (BROCKLEHURST 1980).

Inpatient rehabilitation can indeed be undertaken in general hospitals, but the outcome and success rates show that special geriatric institutions are better. Ordinary hospital wards cannot provide the facilities required for rehabilitation of elderly disabled patients. General wards are attuned to acute treatment, and to the management of the acute threat posed by illness. They are more concerned with the preservation of life as a biological phenomenon and less with the value and content of that life. They offer nursing attention only and have no way of providing transitional care or aftercare in the home.

An efficient rehabilitation clinic should be planned as an independent organization, though it should work in the closest possible cooperation with a general

hospital in which the major specialties are available, or alternatively it should be located in a general hospital as an independent and fully competent special department (WSI Study 1975) with its own therapeutic team of specially trained workers under the leadership of an appropriately qualified and experienced doctor.

The patients admitted to the clinic are not usually in need of emergency or intensive therapy. They should be accepted for the purpose of clinical rehabilitation and not merely for nursing care. As the doctors who request their admission or transfer do not always fully understand the proper indications, it is always advisable for a doctor from the rehabilitation clinic or department to discuss the problems in detail and if possible to carry out an assessment of the patient. For the purpose of assessing patients sent in from "outside" it has proved useful to have an outpatient clinic in the rehabilitation clinic.

In addition to a competent rehabilitation team the clinic should possess all the resources necessary for its manifold tasks. The basic items are the *diagnostic* facilities of a general hospital with special emphasis on the realm of internal medicine. However, as geriatrics is an interdisciplinary subject, transcending narrow specialties, it is necessary that all the major consultants and all the diagnostic facilities of a major hospital should be accessible without exposing the patient to the fatigue of long journeys. The same applies to the basic *therapeutic* facilities; in addition to the normal resources of internal medicine, all other therapeutic facilities must be available. Beyond this is the specific equipment and furniture for rehabilitation medicine such as exercise implements and apparatus for physiotherapy, occupational therapy, and logopedia; these should not be restricted to the conventional range of equipment but should be supplemented by the special apparatus required for geriatric rehabilitation. Among these are appliances which can be used even by very aged and tottery patients to carry out exercises which conform to the practical needs of elderly people (e.g., the reattainment of self-help capacity), and training rooms which meet the domestic needs of the patient, in particular problem zones such as kitchen, bathroom, and lavatory (Sects. F.I.2 and F.I.3). Space is not available even to enumerate and describe the equipment (a few appliances are listed in Sects. G.I–III).

Besides the domestic and self-help training which forms part of the reintegration endeavor, some geriatric rehabilitation clinics undertake extended training in living management, using inter alia the techniques of outdoor therapy already referred to (Sect. F.I.2). This is carried out in a walking exercise ground, a road traffic park, and on the streets outside the clinic. Patients also visit stores and supermarkets near the clinic for shopping training by occupational therapists (Sects. F.I.3 and G.III). Mention has already been made of the assistance given toward reintegration by mobile occupational therapists and social workers (Sects. F.I.3.a and F.I.6). They figure in the synopsis of the activities of the rehabilitation clinic and its cooperation with other agencies depicted in Fig. 9.

Numerical estimates: A bed complement of between 80 and 120 is generally regarded as the best size for a geriatric rehabilitation clinic. The staffing of the rehabilitation team is summarizd in Sects. F.I.1–8.

Average duration of stay: in 1979 I carried out an enquiry in nine geriatric rehabilitation clinics in the Federal German Republic and found that the duration of stay ranged from 5 to 12 weeks, with an average of almost exactly 8 weeks.

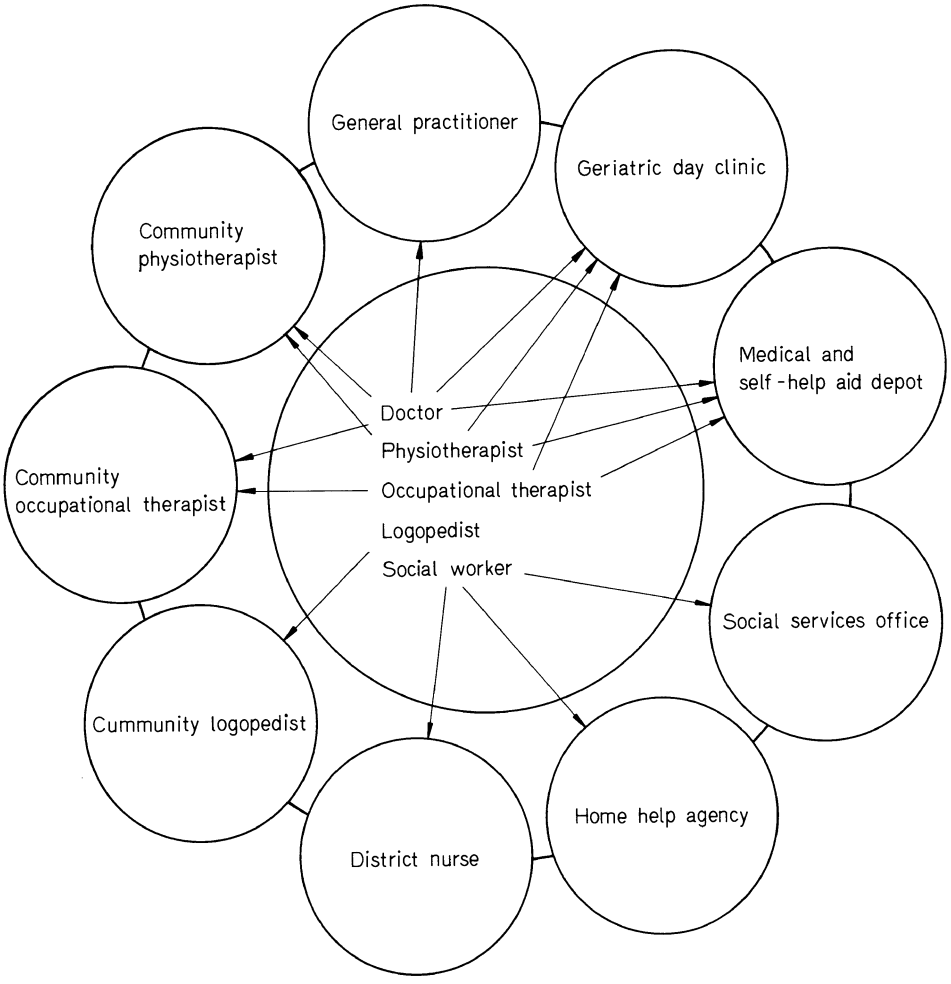

Fig. 9. The geriatric rehabilitation clinic and its cooperation with other agencies

b) The Long-Stay Hospital and the Old People's Home with Rehabilitation Facilities

For patients who require rehabilitation but who obviously need prolonged therapy (longer than 3–4 months) to produce adequate improvement and for whom inpatient treatment is necessary, the best solution is the long-stay hospital which has some facilities for rehabilitation. Such hospitals are primarily suitable for patients who are confined to bed because of some internal disease in need of inpatient treatment. If their bedridden state is due solely to general frailty, an old people's home with rehabilitation facilities is preferable. In either case – if only because their exercise capacity is so small – all that can be offered are minor and limited rehabilitation measures such as passive movements of the limbs, breathing exercises, and basic self-help training, in keeping with the primary aim of "conserving rehabilita-

tion." Nevertheless, even in such cases, efforts should always be aimed at improvement and ultimately, if possible, at discharge from the institution, e.g., by means of the transitional phase in a day clinic or center, provided that relatives are available to care for the patient. Estimates of the most appropriae *bed complement* range between approximately 100 and several hundred. (Staffing plan: Sects. F.I.1–6).

III. Ambulant Rehabilitation Measures

1. Measures Governed by Local Facilities

Before admitting a patient to a rehabilitation center there is one question which should always be settled, namely whether ambulant rehabilitation might still offer prospects of worthwhile improvement. This will depend on the facilities available on the spot, and the doctor must be acquainted with them.

a) The Human Resources

Ambulant rehabilitation demands the same specialist resources as the rehabilitation team described above, e.g., the physiotherapist, occupational therapist, and logopedist in the community, the regional welfare worker, and the nurse trained in activating care and based on the local authority or social security center. The first two specialties are of particular importance for the maintenance or reattainment of self-help capacity in the patient's domestic sphere, especially as they operate in his own home. The general practitioner must, however, issue detailed, problem-oriented directions based on specialist knowledge. Given satisfactory mutual cooperation, it is better to deploy physiotherapy and occupational therapy simultaneously than consecutively (e.g., first a course of medical gymnastic alone and then, after its completion, a course of occupational therapy).

Any available manpower in the home, in particular the patient's relatives, should if possible and suitable be recruited for the task of rehabilitation. Working under specialist supervision (e.g., by the physiotherapist and occupational therapist) they can often make a substantial contribution toward a better ultimate outcome.

b) The Material Resources

The apparatus available for ambulant rehabilitation includes the equipment at the disposal of the physiotherapist, occupational therapist, logopedist in the community, staff from the social services, and district nurses (the latter two should be better equipped for rehabilitation therapy). Valuable reinforcements can be obtained from medical appliance depots including implements for self-help (Sect. F.IV.1); by using their resources the available equipment can be greatly expanded. Another great advantage is that the patient can retain this equipment for long periods. If there is no medical appliance depot within reach, the necessary appliances can be supplied by means of a doctor's prescription (with or without support from the Sick Fund).

2. Measures Governed by the Patient's Circumstances

Assessment of the indications for ambulant rehabilitation is governed primarily by the overall circumstances of the patient himself, both medical and social.

The criteria used to differentiate cases suitable for ambulant rehabilitation from cases in which prehospital or hospital rehabilitation is preferable can be summarized by the following battery of questions:

1. Are the existing handicaps and (associated) diseases (if any) such that they can be effectively benefitted by ambulant measures?
2. Is the patient's exercise capacity high enough for physical training, or is there any hint that physical training might constitute a risk which calls for clinical assessment and/or follow-up?
3. Are the available human and material resources sufficient in numbers and quality for the ambulant management of the case in question?
4. While the patient is undergoing ambulant treatment, is there anyone who can look after him at home in case of need?

The correct decision can be reached only by careful consideration of all four questions. Evaluation of the first three questions requires a certain degree of relevant experience which the assessing doctor may not always possess. In such circumstances consultation with a colleague who works in the outpatient or rehabilitation clinic and is familiar with local circumstances can be helpful.

There is no doubt that large numbers of old people who need rehabilitation and are capable of benefit from ambulant measures are not treated at all or are treated too late or unavailingly, simply because the necessary therapeutic resources are lacking. Especially, there is a deficiency of well-trained community occupational therapists and logopedists and of experts in activating care. In particular there is a wide and still largely unexploited field where preventive rehabilitation offers great possibilities (STEINMANN 1978). Its importance is also apparent from the studies of WILD, NAJAK and ISAACS (1981) and GRYFE, AMIES and ASHLEY (1977). In consequence, countless elderly people have to endure avoidable handicaps in old age (HUNT 1980) and another result is the overwhelming demand for places in hospital geriatric rehabilitation centers and old people's homes, to say nothing of the heavy burden on the social budget. Every effort should be made to remedy this situation by appropriate supportive measures.

IV. Other Therapeutic Ancillary Facilities at the Service of Geriatric Rehabilitation

1. The Depot of Medical and Self-help Aids

During ambulant rehabilitation and during reintegration after hospital or prehospital rehabilitation treatment a depot of medical and self-help aids can assist in treatment and can enhance its efficiency.

Such a depot stocks all the well-tried remedial appliances which are successfully employed in the commonest physical handicaps of old age to master the problems of everyday living. Among these are aids such as walking sticks, forearm supports, walking chairs and trolleys, reciprocal walking frames, self-propelled wheelchairs

(for one-handed operation if necessary), special adjustable chairs and beds, and other appliances for grasping, washing, dressing, eating, and drinking, and aids to housework such as devices for people who have the use of only one hand, gadgets for holding saucepans, etc., safety precautions for the bath, raised lavatory seats, and so on. All these aids and appliances can be supplied through the doctor or the therapist (occupational therapist, physiotherapist, nurse). In certain model organizations the municipal authority bears the cost (FRIEDRICH and HÖCKER 1974). All these appliances can be issued free of charge and left with the patient until it is clear that his need is not merely temporary and that he will require the appliance indefinitely. Only at this stage is he supplied with his own appliances, some of which will be paid for by the Sick Funds while others he will have to buy himself.

2. Social Services and District Nurses

These organizations can also contribute to the rehabilitation of elderly handicapped people. As already mentioned, the best results are obtained when members of the organization have undergone further training in activating care, and are hence capable of carrying out their nursing duties in such a way as to promote rehabilitation (Sect. F.I.8). Working alone or preferably in conjunction with other members of the team (occupational therapists and physiotherapists) they can make a valuable contribution toward improving the quality of life for elderly handicapped patients (HACKLER 1976).

V. Other Aids and Supporting Services: Meals on Wheels, Shopping Services, and Sheltered Workshops

For the sake of completeness mention should be made of certain organizations which, though not therapeutic in the narrower sense, are nevertheless important components of the geriatric rehabilitation and reintegration endeavor.

The delivery of meals to the home by the "Meals on Wheels" service is in operation in many areas. The menus are varied and offer good value for money; special diets are available in many areas. In addition there is a wide variety of supportive services, such as laundry service and general assistance with shopping; information can be obtained from the local social services and from the head offices of charitable and other welfare organizations (SCHREIBER 1976).

Many of the problems involved in maintaining self-help capacity and independence in old age can be overcome in this way. Mention should also be made of the sheltered workshops which have been set up in some cities. These offer opportunities for a wide range of manual crafts. Old people, healthy or handicapped, can undertake work so far as their disabilities allow. They can choose what they want to do and they can work at their own pace. Some of them engage in hobbies, but others work at a trade and earn extra money. The workshops are invariably under supervision from the welfare department and in part under medical supervision as well. Their main value is that they enable elderly people to regain and continue an active life and to maintain contact with their environment.

Old people's centers and "Darby and Joan clubs" can also contribute towards rehabilitation e.g., by supplying meals, by acting as agencies for aid (including mu-

tual aid), and by offering opportunities for mental and physical activity. These organizations are predominantly charitable or private.

G. The Practical Implementation of Geriatric Rehabilitation as Exemplified by Rehabilitation Hospital Procedures

As already mentioned, somatic rehabilitation follows a common basic concept toward the objectives which were outlined under the definition of "Rehabilitation" (Sect. A). However, owing to the special characteristics of old age dealt with in the foregoing sections, most procedures call for certain modifications in technique and approach (as pointed out in the relevant sections).

The following three points deserve special emphasis:

1. The increased risk of deleterious consequences from physical training in rehabilitation
2. The need for careful selection of the main aims when choosing the procedures to be carried out
3. Concrete orientation of all procedures toward a rehabilitation objective commensurate with individual needs.

The importance of point 1 has been adequately emphasized in the previous sections (Sects. D.T. and D.II). Point 2 and in particular point 3 are discussed in grater detail in the following illustration of clinical rehabilitation in a geriatric rehabilitation hospital.

I. Initial Measures (Early Phase, Bedside Therapy)

Rehabilitation is a dynamic process made up of numerous components which are intimately interwoven and to some extent overlap. It is true that the phases of treatment are arranged in sequence, but it is often impossible or fruitless to attempt to say when one phase ends and the next begins. Diagnostic procedures and the setting of the rehabilitation objective certainly belong to the initial measures, but in accordance with the present-day demand that rehabilitative activities should be commenced as early as possible a start should be made with simple mobilizing therapy, provided that there is no contraindication to movement therapy (including passive movements). In this way it is often possible to start the first procedures before the diagnosis has been finally settled and before a definitive rehabilitation objective has been established. The initial examination of the patient carried out on admission is frequently followed by various supplementary diagnostic procedures which often take several days to complete. During this period of close observation the doctor gradually forms an estimate of the patient's exercise capacity and individual rehabilitation target. Movement therapy and other training are therefore constantly modified as the doctor becomes more familiar with the patient's capacity and the objectives will gradually emerge more clearly.

In my experience the overwhelming majority of patients in geriatric rehabilitation hospitals are bedridden on admission (in my own hospital approximately 90%). For this reason the rehabilitation chart in Fig. 10 begins with the "bedbound

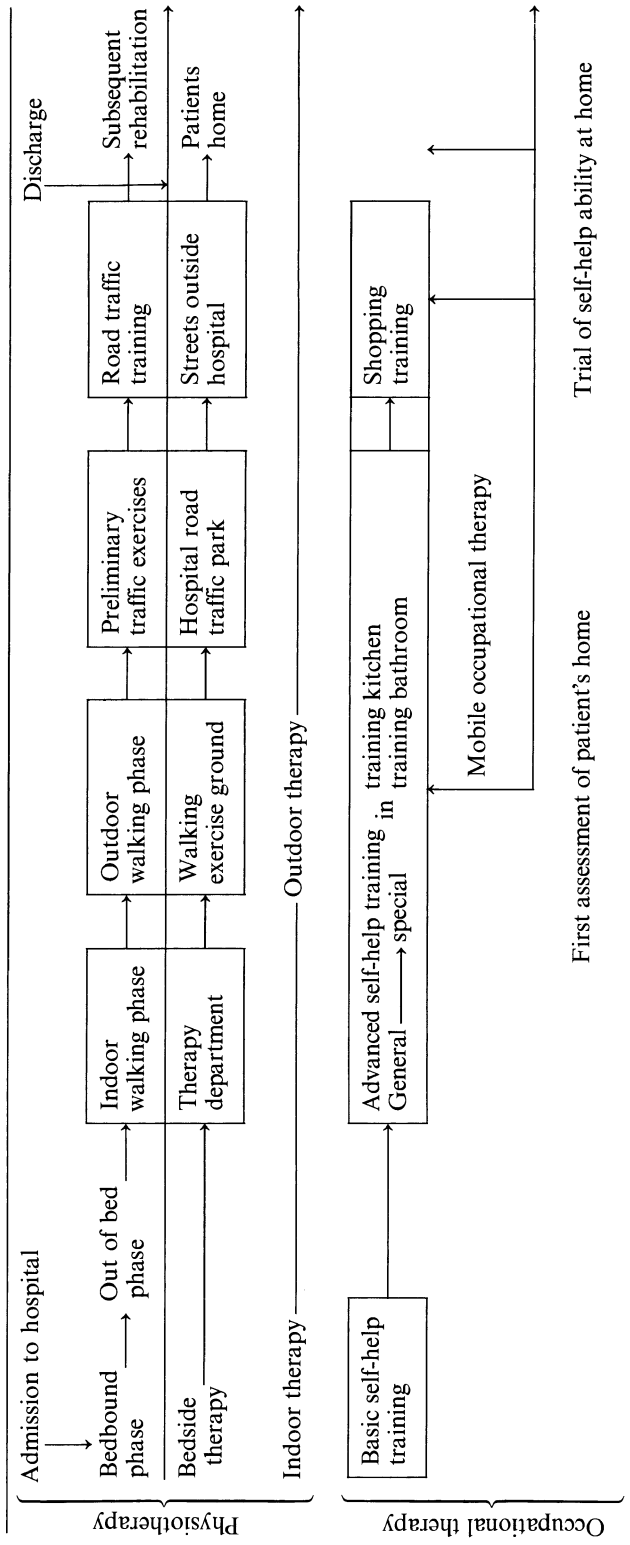

Fig. 10. The treatment phases in geriatric rehabilitation

phase" (no attempt has been made to chart the diagnosis). The choice of therapeutic measures to be carried out obviously depends on the nature of the patient's handicap or illness, and also on the patient's exercise capacity and on the degree of improvement which seems attainable and which has already been attained. (The latter is particularly relevant to outdoor therapy.) In what follows it is therefore possible only to outline the general sequence of rehabilitation without reference to any particular disease and indeed – as will be seen from Fig. 9 – solely in terms of physiotherapy and occupational therapy, because any attempt to present all the professions which cooperate in rehabilitation would exceed the space available. (For further details the reader is referred to the specialist literature, including RUSK 1977; LICHT 1968).

Immediately after the patient's admission a start is made with movements and occupational therapy. In the realm of physiotherapy these include passive and active movement exercises of all limbs carried out as frequently as possible (several times daily). There is incrasing emphasis on active movements, breathing exercises and sitting up exercises, if necessary, in the realm of occupational therapy there are simple functional exercises for the limbs, in some circumstances utilizing light bedside therapeutic devices, and basic self-help training (Sect. F.I.3). These are followed by procedures carried out by both professions, first with the patients sitting up in bed and later sitting unsupported. The procedures include exercise training directed toward reeducation of balance and preparation for standing, and comprise movements against resistance to strengthen the muscles and continuation of basic self-help training.

The standing phase is initiated by brief standing exercises at the side of the bed (two assistants are often needed at the beginning) and continued until the patient can stand unsupported.

The beginning of the walking phase often poses the most difficult demands on therapist and patient alike. Not infrequently, two or even three assistants will be required before the elderly patient can overcome the typical anxiety and muscle tension. It may be necessary to employ walking aids (ranging from a walking frame to a walking stick) and/or ortheses (such as light splintage to stabilize the knee).

II. Indoor Walking Phase

As walking ability gradually returns (first exercises in the sick room) the bedside phase comes to an end. Treatment is then continued in therapy rooms where walking exercises can be carried out with the aid of walking bars or parallel bars. (These should be not less than 6 meters long because elderly people need this distance to "get into their stride").

Once the bedside phase has been surmounted a wider range of therapeutic measures becomes available, especially in the direction of practical everyday exercises. The swimming bath should be used for basic therapy at this stage. It is of great value for the restoration of movements and walking capacity and is much better tolerated, even in advanced old age, than is generally realized. In the realm of physiotherapy, treatment is supplemented by the appliances already described in Sect. F.I.2 for guided exercise of certain functionally connected parts of the locomotor apparatus, e.g., the resistance bench and the rowing boat (Fig. 5). This phase also comprises preliminary exercises for subsequent training in the use of

public transport including the exercise steps with adjustable step heights to suit the entry steps of buses and street cars (Sect. F.I.2).

At the same time as these exercises the occupational therapist will employ equipment which has effects complementary to those of the physiotherapeutic exercises, for example the flexor-extensor and abductor-adductor looms (Sect. F.I.3) used to exercise all four limbs (Figs. 6, 7). Concurrently with indoor therapy the patient begins advanced self-help training, first in the form of general training to enable him to adapt to the altered conditions of life arising from his illness (e.g., stroke) or trauma (e.g., fractures, amputations). After he has made some progress the occupational therapist will visit the patient's home for the first time in order to assess the areas in which the handicapped person is most likely to encounter difficulties (Sect. F.I.3.a). Once provided with this information, the occupational therapists and physiotherapists of the hospital team will be in a position to work together with the patient with the object of overcoming any problems which his home may present, e.g., by using the adjustable practice kitchen in the hospital to imitate the layout of the kitchen in the patient's home.

III. Concluding Phase with Outdoor Therapy

When the patient has learnt to walk safely indoors he can begin outdoor therapy. This is carried out under the guidance of a physiotherapist and begins on the walking exercise ground of the hospital. It consists of footpaths of gradually increasing difficulty progressing from sand to gravel and broken stones or from small cobbles to large stone setts, paths with deliberately ill-laid paving stones, rising and falling gradients, steps without handrails, etc. The aim of this training is to give the elderly patient both the physical skills and the inner confidence which he needs to cope with all kinds of paths and pavements, and so to restore his willingness to go out and to minimize the danger of isolation.

The next step is "preliminary traffic exercises" in the hospital's road traffic park. Patients whose exercise capacity is adequate are given individual training to enable them to use cars, buses trains etc., to overcome their personal handicaps and once again to be able to use public transport – so important in city life. Next comes practical "road traffic training" on the public streets outside the hospital: under the guidance of the therapist the patient learns to use buses and streetcars once again. He is thus reeducated in road usage with due allowance for his handicap.

To complete these exercises shopping training is carried out by an occupational therapist in stores and supermarkets near the hospital. The elderly patients learns once again how to cope with money, purchases, and sales staff, while overcoming any feelings of shyness and regaining self-confidence. At the same time he learns to pay heed to certain points related to his handicap, for example the correct choice of food and clothing.

Before the patient's discharge the mobile occupational therapist visits his home once more to check whether any alterations or improvements are needed to enable him once again to master all his necessary domestic tasks. These duties of the mobile occupational therapist, briefly described in Sect. F.I.3.a, are of particular significance in the reintegration of the elderly handicapped patient. If a mobile therapist is not available the task should be undertaken by a community occupational therapist in cooperation with the hospital rehabilitation team. The supply of means

for self-help from the self-help aid depot must also be remembered at this point (Sect. F.IV.1).

IV. Transition, Aftercare, and Reintegration

The reintegration of the elderly handicapped patient calls for care and specialist knowledge during the preparations for discharge, on the day of discharge, and during the period of aftercare. The hospital rehabilitation team, in particular the doctor, social workers, physiotherapists, and mobile or hospital occupational therapists, make preparations for the patient's discharge and his reinstallation in his home environment. They do this by getting in touch with their cooperation partners (Fig. 9) in good time and – each in his or her specialist field, but constantly in consulation with one another – arranging all necessary forms of aid and assistance for life "outside." In this way it is feasible to review all the existing possibilities and utilize them for comprehensive rehabilitation and reintegration. Experience shows that elderly patients need more careful handling than younger people. It is not always enough to bring the hospital patient to the stage at which he can once again move about freely under the conditions of the rehabilitation center. At home, without the facilities of the hospital, he is frequently incapable of meeting the demands of his everyday life. The outcome is discouragement, resignation, breakdown of domestic arrangements and, as is well known, large numbers of failures (readmissions to hospital) or transfers to old people's homes despite elaborate rehabilitation measures. Such cases may even end in suicide, especially among widowers and widows.

After discharge from hospital no elderly handicapped person should be allowed to remain without supervision and, if necessary, help. This is especially important for people living alone. Aftercare by a mobile occupational therapist, as already outlined, has proved of great value. She has detailed knowledge of the patient's day-to-day problems and visits him regularly at home. If necessary, she can undertake aftertreatment until he is firmly reestablished and as independent as possible, and has recovered the will and capacity to soldier on. She must work in close cooperation with the general practitioner and also, when necessary, with the other members of the team shown in Fig. 8. Here again, the community occupational therapist can undertake the role of the mobile therapist.

Many elderly people do not achieve genuine, i.e., lasting reintegration until all these measures have been applied; only then do they once more return to worthwhile life (SMITH 1979).

H. Results of Geriatric Rehabilitation Measures

It is obvious that only a certain proportion of patients entering a course of rehabilitation will win through all the phases of treatment and reach the ideal goal. With advancing age the success rate naturally drops; however, the therapeutic outcome is primarily determined by the extent and severity of the permanent functional defects.

Although the patients admitted to a rehabilitation clinic invariably represent a negative selection of cases in need of rehabilitation (this is particularly true of

patients transferred from other hospitals), some remarkable successes have been reported in the literature. The published results vary widely, ranging from 46% (HUBER 1970) to 81% (BÖGER 1979). However, it should be noted that the figures from the literature are not truely comparable, first because the series of patients were not identical in age, nature, and severity of disease or handicap, etc., methods of rehabilitation, duration of treatment, etc., and secondly because of differences in the criteria and definitions used to assess the results of rehabilitation. These factors will explain the relatively wide differences between the published figures. Systematic investigations which have recently been started in the German Federal Republic will comprise certain clearly defined areas of geriatric rehabilitation and will be directed toward precisely defined questions and enquiries. It is to be hoped that they will present a clear picture of the value of hospital rehabilitation for 65-year-old patients in groups of comparable numbers.

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Nutrition

Nutritional Characteristics of the Elderly

I. WERNER

A. Introduction

The number of elderly subjects is rapidly increasing in the affluent society. People live longer and better. Positive economic development, improved hygienic standards and access to first-class medical care for practically everybody have been the main contributory factors. The increased percentage of elderly has also brought problems. The demand for socio-medical geriatric care has grown dramatically in many communities and has placed a heavy load on social and individual economy. It has become a practical necessity to investigate the possibilities of creating optimal living conditions for the elderly by preventive measures to enable them to lead a "normal" life at home as long as possible. One obvious measure in this direction is of course to ascertain optimal nutritional facilities for the elderly.

It is a well-known fact that signs of nutritional deficiencies observed on admission to hospital occur much more often in elderly than in young patients and that is the case also in communities where food supply is abundant and economic obstacles are eliminated. It is also well known that elderly subjects in debilitated states sometimes recover after a few weeks in hospital without any other treatment than ordinary hospital food. There are thus reasons to assume that the risk of malnourishment may be higher in higher ages. Physiological and behavioural changes in the elderly, such as reduced body size and reduced physical activity, may be contributory factors. Altered requirements of essential nutrients have been proposed and discussed as well as individual factors such as ignorance and lack of interest in good food. The subject of nutrition in the elderly thus is not only a scientific or medical question, it is also of great socio-economic importance. The interest in what elderly people eat and what they should eat has accordingly increased rapidly during the past decades.

B. Physiological Changes Influencing Nutrition

I. Changes in Body Size and Composition

It is well known that body weight and body height tend to decrease after the 3rd–4th decades. There is a wide range of variation, especially in weight, but after the 6th decade there are few exceptions. There is a loss of muscle mass and bone tissue, and organ weights are reduced. Accordingly, body composition changes continuously with rising age. Body cell mass (BCM) and extracellular fluid (ECF), decrease, while the body fat (BF) content rises (FORBES and REINA 1970; SHOCK 1972;

STEEN et al. 1977b; STEEN et al. 1979; BRUCE et al. 1980). The rate of loss of BCM is higher in males than in females. Changes in the quotient BCM/BF must of course influence the protein requirement calculated on kilogram body weight, as the protein requirement is directly related to BCM. The effect is partially counterbalanced by the simultaneous loss of ECF, reducing the change in the quotient BCM/body weight.

II. Energy Expenditure

There is a gradual decrease in basal metabolic rate with increasing age, the reduction from the 4th to the 8th decade of life amounting to about 10% (SHOCK 1972), and at least partly depending on the decrease in BCM. The decrease in total energy expenditure in elderly subjects is, however, often more than double that which can be explained by the change in BMR. This further reduction, which shows a wide range of individual variation, is due to reduction of physical activity, which to some degree invariably seems to follow aging (MCGANDY et al. 1966; SHOCK 1972).

III. Metabolism

There seem to be no age-related changes in oxidative capacity of the cells, to judge from oxygen uptake studies in tissue slices, homogenates or isolated mitochondria from heart, liver, and kidney (BARROWS 1966). There are, however, changes in the enzymal patterns (cf. WILSON 1973), the most apparent being a reduction of respiratory and an increase in hydrolytic enzymes corresponding to a decrease in mitochondria and an increase in lysosomes.

These changes do not seem to have any serious impact on the metabolic capacity. More important is probably a reduced enzymatic adaptability and inducibility (WILSON 1973). A striking example was presented by ADELMAN (1971). While rats were starved for 3 days the liver glucokinase content decreased by 90%. When the rats were refed, glucokinase levels were restored to normal. The restoration process in young animals took 1 day, in old rats 2–3 days. Observations on drug elimination in elderly patients have also indicated a reduced capacity to metabolize certain drugs (cf. HYAMS 1978). The reduced adaptive capacity may in turn depend on a reduced cellular response to hormones (ADELMAN 1970). The diminished sensitivity, probably due to reduced number of target cell receptors, has been thoroughly studied in the case of insulin (DEFRONZO 1979; PAGANO et al. 1981) and explains the reduced glucose tolerance in elderly people.

Population studies have shown that people over 60 have a higher plasma level of high-density lipoprotein (HDL) cholesterol (HEISS et al. 1980). This might mean a change in lipid metabolism but more probably it is the result of a selective process, low HDL levels being closely related to early death in cardiovascular disease.

Generally, the enzymatic changes in elderly subjects indicate a reduced tolerance for extraordinary metabolic loads and irregularities.

IV. Digestion

Several age-related changes in the digestive tract may potentially contribute to impaired digestion and absorption. The loss of teeth and the fall in salivary volume

means impaired mastication (KAMOCKA 1970). The secretion of hydrochloric acid in the stomach decreases with age and achlorhydria is found in 25%–35% of individuals over 60 (VANZAT et al. 1932; BOCKUS et al. 1932). Pancreatic lipase secretion is reduced (NECHELES et al. 1942; WEBSTER et al. 1976) and bile volume is reduced (BERTOLINI 1969). Signs of villous atrophy in the jejuno-ileal wall have also been reported (WEBSTER and LEEMING 1975).

All these changes seem to have marginal effects, if any, on the digestive capacity. There are no convincing reports on malabsorption in elderly people without digestive-tract disease and the prevalence and degree of obesity is often high (DE-WIJN 1967; WERNER and BERFENSTAM 1974). There is, however, a reduced tolerance to high protein and fat loads (WERNER and HAMBRAEUS 1972). A daily protein intake of 100 g or higher often gave an abnormally high faecal nitrogen excretion. A daily fat intake of 100–120 g was usually well tolerated provided the fat consumption was evenly distributed over the day. When half the amount was given at one meal, there was a mild or moderate steatorrhoea.

To conclude: The reduction of the digestive and absorptive capacity is marginal and should normally play no practical role. To avoid unnecessary digestive discomfort, the elderly should avoid large meals and have the meals reasonably distributed over the day. The reduction of cardiovascular capacity in the elderly (SHOCK 1972) further enforces the importance of such a regimen.

C. Requirements of Essential Nutrients

The possibility of age-related changes in the requirement of essential nutrients has been discussed frequently. Special interest has been directed towards protein and essential amino acids, some of the vitamins, viz. B_6, C, and D, and the minerals iron and calcium. In the case of the other vitamins and common minerals no indications of changed requirements have been observed; in some cases no studies on the requirements of elderly people have been performed or published. This is especially the case for most trace elements.

I. Protein and Essential Amino Acids

Studies on protein and essential amino acid requirements in elderly people are scarce and the results in several respects are contradictory. The number of subjects studied is often small; the techniques and methods applied vary. Critical evaluation and comparison of the studies and the differences of the results are often very difficult.

1. Protein

Especially in early studies the results indicated a considerably increased protein requirement in elderly people (cf KOCH 1911; KOUNTZ et al. 1947, 1948, 1951, 1953). In contrast with these findings ALBANESE et al. (1952) reported a study on elderly women who were maintained in good health on self-chosen diets providing daily protein intakes of 0.6–0.8 g protein/kg body wt. These authors concluded

that the protein requirements of elderly women might be lower than those of young sedentary women. In a later study ALBANESE et al. (1957) found that a positive nitrogen balance was maintained on an average daily protein intake of 0.9 g/kg. Essentially unchanged protein requirements in healthy elderly people were found by ROBERTS et al. (1948), HORWITT (1953), and WATKIN et al. (1965). Other balance studies have shown that some elderly individuals need considerably more protein to maintain equilibrium although the average protein requirement of the elderly may be about the same as that of younger adults (MUNRO and YOUNG 1978; UYAU et al. 1978; CHENG et al. 1978; ZANNI et al. 1979).

Serum albumin concentration and the total albumin pool decrease with increasing age after the 4th decade, the reduction being approximately 10% and 20% respectively in the 8th decade (YAN and FRANKS 1968). ACHESON and JESSOP (1962) found lower albumin levels in subjects with histories of low protein intake and suggested the hypoalbuminaemia was an indication of increased protein requirement in the aged. Most authors, however, have found no consistent relationship between protein intake and albumin levels in healthy elderly people (ANDERSON et al. 1972). An age-related impairment of some mechanism regulating albumin homeostasis and/or synthesis is much more likely to be the causative factor of the reduced albumin content than is a primary nutritive factor (cf. WATKIN 1978; EXTON-SMITH 1978).

2. Essential Amino Acids

TUTTLE et al. (1957) found a considerably higher requirement of essential amino acids in a group of elderly men than in young men. They used a balance technique and the essential amino acids were provided as egg protein or as an artificial mixture according to the egg protein amino acid pattern. In a subsequent paper TUTTLE et al. (1959), using the same technique, observed that the essential amino acid requirement might be related to the total nitrogen intake.

WATTS et al. (1964) found no evidence for higher requirements in older men. They also used a balance technique but provided the essential amino acids as milk or artificial mixtures according to the milk or FAO patterns. They concluded that there was no indication of a higher requirement for men over 65 than for men of 25.

The differences between the results of the TUTTLE group and the WATTS group may possibly be explained by the differences in techniques and especially by the different amino acid patterns used in the experiments.

TUTTLE et al. (1965) also found indications of a higher need for lysine and methionine in elderly men. The raised methionine requirement could possibly be due to decreased ability to convert methionine to cystine. WATTS et al. (1964) observed no signs of an increased need for methionine in a group of elderly men. A beneficial effect of lysine on the nitrogen balance in some elderly women had earlier been reported by ALBANESE et al. (1957).

The three essential questions, once beautifully summarized by MUNRO (1972) – (1) do the elderly have an increased protein requirement? (2) Do they have an increased requirement of one or more essential amino acids? And (3) are there special relationships between the two characteristic for old age? – still wait their def-

inite answer. From our present-day knowledge we can reasonably conclude that eventual increased requirements of protein and amino acids in the elderly must be small or moderate in magnitude. Any reduction of the requirements seems highly unlikely. From the practical point of view the existence or nonexistence of minor differences may not be of very great importance. Minimum protein and essential amino acid requirements are usually determined under more or less artificial, optimal conditions in perfectly healthy subjects. The values obtained are then translated to normal food and living conditions. This "translation" naturally involves assumptions and approximations and thus is very inexact. The risk of underestimation of the real requirements must be specially big in the case of elderly people. The health is often not perfect, the digestive capacity is often reduced and so is the metabolic adaptability (cf. above).

The elderly subject is a low-calorie consumer and has often an insufficient caloric intake, which means an impairment of the protein equilibrium, especially at a low level of intake. The "healthy" elderly person is usually not as healthy as the healthy young adult (cf. above). There are thus a number of conditions and factors pertinent to the recommendable protein intake of the elderly, all of them potentially impairing the effective utilization of the protein consumed. SCRIMSHAW (1976) has pointed out that the prevailing recommended daily allowances (RDAs) for elderly people, 50–60 g/day for men and 45–50 g/day for women, i.e. 0.7–0.8 g/body wt., are really too low. There are good reasons for making the recommendations for elderly more generous in the future.

II. Vitamins

1. Vitamin B_6

Studies on plasma levels of pyridoxal phosphate (the biochemically active form of pyridoxine) have shown decreasing values in elderly subjects (RANKE et al. 1960; HAMFELT 1964; WALSH 1966; JACOBS et al. 1968). The low plasma pyridoxal level was also coupled to an abnormal tryptophane breakdown (normally a pyridoxine-dependent process) and a low degree of pyridoxal phosphate saturation of aspartate-aminotransferase (RANKE et al. 1960; HAMFELT 1964; JACOBS et al. 1968). Supplementation with dietary pyridoxine normalized the plasma levels and the enzymatic defects disappeared.

There is thus good reason to assume that elderly subjects may have an increased requirement of vitamin B_6.

2. Vitamin C

Low blood levels of ascorbic acid – plasma, leucocytes, and whole blood – seem to be characteristic for elderly people (KIRK and CHIEFFI 1953a; KATARIA et al. 1965; BOWERS and KUBIC 1965; ANDREWS et al. 1969; LOH and WILSON 1971; MILNE et al. 1971). The reduction is small in women but quite considerable in men, about 40% in the 8th decade compared with 40-year-olds. The age changes have been found in individuals on low or moderate ascorbic intake but not in individuals on very high or very low intakes. Daily supplementation of the intake with 100 mg ascorbid acid normalized the blood values (KIRK and CHIEFFI 1953b), which quick-

ly returned to initial levels when supplementation was stopped. The authors suggested that decreased ascorbic acid content in blood is an age-related physiological change in the elderly. The fact that elderly men have a lower blood ascorbic acid than elderly women caused MORGAN et al. (1955) to suggest that men over 50 had an increased requirement of vitamin C. Studies of ascorbic acid requirements by "saturation" techniques have not given any clear indications of increased demands in elderly people, however (BOWERS and KUBIC 1965; O'SULLIVAN et al. 1968; MITRA 1970). Attempts to relate the low ascorbic acid levels in blood in elderly people to clinical signs of scurvy have not yielded convincing evidence for such a relationship (ANDREWS and BROOK 1966; ARTHUR et al. 1967; ANDREWS et al. 1969).

To conclude: There might be an increased requirement for ascorbic acid in elderly people, especially in men. No real evidence for such an increase has been presented thus far and circumstantial evidence is far from conclusive. It must be borne in mind, however, that present-day techniques for determining requirements of vitamin C are unsatisfactory.

3. Vitamin D

The vitamin D deficiency leading to osteomalacia in elderly subjects with normal gastro-intestinal function observed in nutritional surveys (see below) is most commonly caused by insufficient dietary intake (cf. EXTON-SMITH et al. 1966) or, sometimes, by a reduced exposure to sunlight (STAMP and ROUND 1974). DENT (1969) suggested that there might be an increased physiological requirement of the vitamin in the elderly. The assumption has been supported by the findings of GALLAGHER et al. (1979). They observed lower serum levels of 1.25-dihydroxycholecalciferol in elderly than in young adults. This lowering might be due to impaired conversion of 25-hydroxyvitamin D by the aging kidney gradually losing nephrons. The results of some therapeutic attempts may also be interpreted in the same direction (LUND et al. 1975; GALLAGHER et al. 1979).

III. Minerals

1. Iron

There seems to be no report in the literature of direct attempts to determine the daily iron requirements of elderly people.

BONNET et al. (1960) studied the percentage of ^{59}Fe absorbed from a test dose and found that it decreased with age. They concluded that iron absorption is impaired with advancing age. Criticism must be raised against the material used for study, as 36 of the 41 subjects were between 21 and 34 years.

FREIMAN et al. (1963), using a similar technique, studied 45 healthy subjects aged 69–87 and compared them with a group of younger adults. They found absorption values well within normal ranges. Women had a higher absorption than men and there were no significant age group differences. Similar results were reported by BRÜSCHKE et al. (1967), who studied 38 subjects, 62–99 years old. JACOBS and OWEN (1969) reported a tendency to decreased absorption of inorganic but not of organic iron with increasing age. The number of subjects studied was small.

The iron content of the bone marrow usually rises after the 5th decade (BENTZIE 1963) and so does the serum-ferritin level (WAHLBERG et al. 1976). The blood haemoglobin concentration shows no age-related changes in healthy adults after 50. Thus, there seems to be no reason to assume a decreased iron absorption capacity or increased iron requirements in elderly people.

An interesting study was reported by MARX (1979). Using a double-isotope technique and total-body scanning, he studied the absorption and uptake of iron in different compartments. In subjects with normal haemograms he found perfectly normal values for mucosal uptake, transfer and retention or iron. The erythrocyte uptake after 14 days, however, was significantly lower, 66%, compared with 91% in the young controls. The probable explanation is an age-related ineffectiveness of the erythropoesis. The iron apparently reaches the marrow in normal amounts and is incorporated in erythrocyte precursors normally, but the precursors often develop abnormally and the defect products are trapped in the reticulo-endothelial system and will not appear in the peripheral blood. Thus, a haematological picture may appear that can be misinterpreted as due to iron deficiency/malabsorption.

2. Calcium

Normally there is a loss of bone calcium beginning in the 5th decade (GARN et al. 1967; ALBANESE 1977). In early adult life there is an equilibrium between bone formation and bone resorption; in the latter life resorption predominates. The bone loss is more rapid in women than in men (GARN et al. 1967) and it seems to be more pronounced in those who have a small or light skeleton in the 4th decade. This physiological (?) bone reduction of latter adult life seems not to be related to previous calcium intake nor is it influenced by changes in calcium intake (GARN et al. 1967; GARN 1970).

The picture of osteoporosis can be induced experimentally in animals by a low-calcium diet. The osteoporosis seen in human adults, especially in postmenopausal women, is not related to dietary calcium intake (HEANEY 1965; YOUNG and NORDIN 1967; SMITH et al. 1968) nor can it possibly be caused by the decreasing calcium absorption found in men and women over 70 (BULLAMORE et al. 1979). Treatment of osteoporosis with calcium suplementation may slow down or even stop the progress of the condition (cf. AVIOLI 1977; NORDIN et al. 1980). Reports of cures and restitution of normal bone with calcium therapy have not been convincing with one exception. LUTWAK et al. (1971) reported reversal of the localized osteoporosis in periodontal disease when extra calcium was given.

Several studies on calcium balance in elderly people have been reported. OWEN (1939) concluded that the mean daily requirement for elderly men was about 0.52 g. ACKERMANN and TORO (1953) reported higher figures, about 1 g and so did BOGDONOFF et al. (1953) (0.85 g). OHLSON et al. (1952) found a daily requirement of about 0.9 g for women aged 60–69 but only 0.73 g for women aged 70–79. The daily requirement for women, usually showing greater interindividual variations, was found by ROBERTS (1948) to lie around 1 g, and around 0.9 g by ACKERMANN and TORO (1954). Quite different results were obtained by HEGSTED (1952), who found 0.2–0.3 g daily sufficient for Peruvian male prisoners, and by FUJITANI (1960), who found that elderly Japanese men were in balance on 0.29–0.30 g daily.

MALM (1958) recorded a successful adaptation to diets containing from 0.9 to 0.45 g calcium daily in a study of elderly men.

The disparity of the results is apparent and it is obvious that conventional balance techniques are not very useful for the study of calcium requirements. Apart from the amount of calcium supplied, a lot of factors, dietary, and non-dietary, influence calcium balance, many of them impossible or at least very difficult to standardize and evaluate. Physical activity is of importance, bed rest inevitably leading to calcium loss. Psychic imbalance may lead to negative calcium balance for long periods (MALM 1958). The sex hormones influence calcium absorption and bone formation and the vitamin D status is naturally of utmost importance, and so is the degree of adrenal activity. The adaptability of the organism to considerable reductions of the calcium intake is apparently not lost in high age (MALM 1958) and must also be taken into consideration. Two dietary factors deserve special attention in a discussion of calcium requirement in the elderly. One is the long well-known fact that caloric insufficiency – not infrequently observed in the elderly – in itself tends to impair calcium balance (GAMBLE et al. 1923). The other is the influence of the protein intake. JOHNSON et al. (1970) and LINKSWILER et al. (1974) found that young men on a daily calcium intake of 500 mg went into a negative calcium balance when the protein intake was kept at 95 g a day or higher. They concluded that "borderline" or low-calcium intakes combined with high dietary protein might involve a risk of long-term loss of calcium.

To conclude: The loss of skeletal calcium regularly found in elderly as well as postmenopausal or "senile" osteoporosis is not primarily caused by dietary calcium deficiency. The calcium requirement of elderly people is not known. It seems to be of the same magnitude as that of younger adults, at least up to the 7 th decade, i.e. varying from 0.2 to 1 g/day. There is a considerable interindividual variation and the ability to adapt to reduction in the calcium supply is, at least partly, retained. After 70 there may be a fall in calcium requirements.

D. Food Consumption and Nutritional Status of the Elderly

Our knowledge of the nutritional status of elderly people is still rather scanty and also geographically unevenly distributed. Thus, we know practically nothing of the nutritional status of elderly people in Africa, the Asian continent or South America and the essential knowledge is based on observations from Western Europe, North America, and Japan. A number of nutritional surveys of elderly people in the Western world have been reported during the last decades, several of them quite extensive. GILLUM and MORGAN (1955) studied elderly people in California, DURNIN (1961, 1966) in Scotland, and EXTON-SMITH and STANTON (1965) in London. MCGANDY et al. (1966) reported from a Baltimore study, DIBBLE et al. (1967) from Syracuse, and DEWIJN et al. (1967) from Holland. There is a report from the Department of Health and Social Security (1972) from the UK and the Ten-State Nutrition Survey (1972) from the United States. WERNER and BERFENSTAM (1974) reported from mid-Sweden, STEEN et al. (1977 a) from Western Sweden, GARCIA et al. (1975) from Iowa, and STIEDEMANN et al. (1978) from Colorado.

There are naturally differences in investigative methodology and techniques, regional differences in cultural habits, economy and climate as well as highly variable non-response rates in the population studies, which make attempts of detailed analysis and comparison of the figures reported meaningless or at least very difficult to evaluate. The principle observations of the studies, however, show a strikingly high degree of uniformity.

All studies have shown that elderly people, even those in good health, consume less than younger adults, the reduction from the 5th to the 8th decade of life being in the average order of magnitude 15%–25%, somewhat higher in men than in women. In spite of this reduced intake the prevalence and degree of obesity seems to be about the same at 70 as at 50 (DEWIJN et al. 1967; DHSS 1970; WERNER and BERFENSTAM 1974; STEEN et al. 1977a, b).

Another general observation is that elderly people choose their food according to tradition and former habits, i.e. they eat the same as they used to eat but less. Apart from situations of real poverty, economic considerations do not influence the choice of food of the elderly more than that of young adults, i.e. at least they are not aware of it (EXTON-SMITH and STANTON 1965; BROCKINGTON and LEMPERT 1967; Ten-State Nutrition Survey 1972; WERNER and BERFENSTAM 1974; STEEN et al. 1977a).

With few exceptions the average consumption of essential nutrients has been found satisfactory. The interindividual variation, however, often is very wide and a certain percentage of the elderly have deficient intakes of one or more essential nutrients according to accepted standards. Symptoms of deficiency, clinical or "sub-clinical" (chemical), are also much more common in elderly people than in young adults. This is of course to be expected, as a reduced total food intake in itself must mean increased risk for insufficient intakes of one or more essential nutrients unless the food has unusually high nutritional quality (nutrient concentration). The symptoms of deficiency practically always depend on low dietary intake, which in the majority of cases is due to physical disability and/or disease. In the remaining cases, however, other causes are found, the most important of which seem to be ignorance, indifference, social isolation, psychic insufficiency and/or extremely low total caloric intakes (EXTON-SMITH and STANTON 1965; WERNER and BERFENSTAM 1974; STEEN et al. 1977a; EXTON-SMITH 1978). Ignorance, concerning basic nutritional knowledge as well as cooking, is probably the main reason for the high prevalence of vitamin deficiencies observed in widowers and elderly men living alone. Social isolation, "loneliness," probably plays an important role for corresponding phenomena observed in elderly women. Psychic insufficiency, a diffuse concept, covers lack of initiative, not infrequently observed in the elderly but also mild to moderate depression, which of course tends to aggravate a developing malnutrition. All four causative factors have in common that they are easily accessible by simple socio-medical efforts: (1) identification of individuals at risk, (2) information and (3) social visiting and provisional activities (e.g. DURNIN 1978; EXTON-SMITH 1978; BROCKLEHURST 1978; MUNRO 1980).

Some observations of malnutrition show certain regional differences. The prevalence of obesity seems to be much higher in Holland and Sweden than in the UK and United States (DEWIJN et al. 1967; WERNER and BERFENSTAM 1974). Signs of vitamin D deficiency, apparently not uncommon in the UK (EXTON-SMITH et al.

1966; ANDERSON et al. 1966; CHALMERS et al. 1967), were not observed at all in western Sweden (STEEN et al. 1977a); the same is also true for riboflavin. The deficiencies most commonly observed or suspected among the elderly in most studies are folate deficiency (HERBERT 1967) and ascorbic acid deficiency (Ten-State Nutrition Survey 1972, DHSS 1972).

E. Conclusions

Elderly people eat less and need less food than younger adults because of an age-related reduction of energy expenditure. They usually do not change their dietary habits much, eating the same food as before, but less.

The daily requirements of essential nutritients are largely unknown but, perhaps with a few exceptions, no evidence of essential differences between young adults and elderly has been brought forth so far. The reduced total caloric consumption implies an increasing risk of nutritional deficiencies, however, unless the nutritive quality of the food consumed is augmented.

The most common form of malnourishment in elderly people in the affluent world is obesity. Signs of malnutrition deficiencies are not common but found much more often in elderly than in young adults. The deficiencies can almost invariably be traced back to insufficient dietary intakes, the primary cause of which are manifold: disease, physical or psychic disability, ignorance or lack of interest in the individual and negligence from the surrounding society.

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The Role of Nutrition in Human Aging

W. O. CASTER

A. Introduction

Over 40 years ago MCCAY et al. (1935, 1939) excited the imagination of nutritionists and gerontologists with reports that when the diet of the weanling rat was restricted by 30%–60%, the rat would grow correspondingly smaller but that its life span was lengthened two-fold. Some work on food restriction still persists, but much of the zeal departed when it was found that these long-lived rats were apathetic and slow to mature, had a low metabolism and body temperature, had a low resistance to stress or infection, and showed decrements in intellectual and neurological performance.

In human experience, early dietary restrictions have tended to produce physical and mental retardation, a low resistance to infection, and high infant death rates from kwashiorkor and marasmus, but the life span has typically been shortened rather than lengthened. Restricting the diet of the infant, therefore, has not appeared to be a practical way of lengthening the life of the human. Nutritional gerontology has thus had to look in other directions.

More recently, attention has turned to the study of the aging process itself, which is an inherently multifaceted process. The question, then, became one of searching for possible relationships between diet and each of the many physiological and functional changes that constitute measurable parts of the overall aging process.

B. Multifactorial Nature of the Aging Process

Some signs of aging are easily recognizable. Ask any beginning actor to play the part of an aged person and you can expect to see the slumped posture, unsteady gait, shaky hand, and high-pitched voice. Increasing age is associated with progressive decreases in strength, vigor, and agility.

I. Physical Performance

Trained athletes can expect to see their greatest strength and endurance records achieved around their 30th year. LEHMAN (1951) summarized the achievements of thousands of professional and Olympic athletes, and found their best performances were given during their ages of 23–35. The best skiing times were observed at about 31 years of age (NORDEN 1979). Championships in many sports were won

by contestants whose ages ranged between 28 and 36 years. MILES (1950) and BURKE et al. (1953), using a hand dynamometer, measured the grip strength of over a thousand men and women at different ages. The maximum strength was observed at about age 30, and there was a slow progressive decrease until age 60–70, at which time strength declined more rapidly.

BURKE et al. (1953) measured maximum grip strength and grip endurance in 311 male subjects aged 12–79 years. In the age range 12–25, there was a linear increase in performance. In the age span 25–65 there was a slow, linear decrease in most measurable abilities. The total change amounted to a 20% decrease in maximum strength but a 50% decrease in endurance. Beyond age 65, the rate of decline was much more rapid with both measures.

BRANDFONBRENER et al. (1955) measured the decrease in cardiac output with advancing age. HODGSON and BUSKIRK (1977) measured the maximum oxygen transport capacity of the body during periods of heavy exercise. They found a progressive and linear decrease in maximal aerobic capacity from ages 20 to 90. The trained athlete had a greater transport ability, but the slope of this decrease with age was the same for the athlete as for the moderate worker or the sedentary individual. NORRIS et al. (1956) studied pulmonary function in both younger (20–30 years) and older (80–90 years) subjects. The vital capacity decreased with age. With mild exercise the older subjects started to breathe much more rapidly, but with increasing work rates their maximum rate of breathing was lower and was reached at much lower rates of work output.

Athletes have strong and varied opinions concerning diet. In general, however, there is a long-standing preference for a high-protein diet during training and a high-carbohydrate diet prior to performance (ASTRAND 1973). One of the few instances in which diet composition is reported to have a markedly deleterious effect on physical performance is to be found in the data of KROGH and LINDHART (1920). They found that when the work level was sufficiently severe, athletes consuming a high-fat diet performed with greater difficulty and became tired more rapidly. Performance was much better on a high-carbohydrate diet.

There is no evidence to show that special diets of any type can assure physical vigor in old age. To achieve this goal, it would seem more effective to enter the later years with a well-developed body, and continue some pattern of reasonable exercise.

II. Changes in Energy Metabolism

With age there is a progressive decrease in the ability to use glucose and an increased tendency to store fat.

ANDRES (1971) has indicated that on the average "there is a progressive deterioration of performance, decade by decade of life, on all commonly used diagnostic tests for diabetes." One standard test consists of administering a test dose of glucose and measuring the rate at which this glucose disappears from the blood stream. As age increases beyond 30 years, there is a progressive decline in the rate of glucose disappearance (UNGER 1957; SILVERSTONE et al. 1957; HAYNER et al. 1965) and at the same time there is a progressive increase in the prevalence of diabetes and in the death rate from diabetes (U.S. DEPARTMENT HEW 1970).

An examination of public health data demonstrates that there is as much as a five- to ten-fold difference between the prevalence of diabetes in different population groups living in the same area. In all cases, however, these groups have very different economic status and quite different eating habit patterns (BRUNNER et al. 1964; U.S. DEPARTMENT HEW 1970). No simple cause and effect relationship has been established between diet and the onset of diabetes, though there are some bits of evidence that suggest that the type of fat (CASTER et al. 1975) and the amount of sucrose (REISER and SZEPESI 1978) in the diet could be important factors.

From the teenage years there is a progressive increase in the tendency to deposit fat. This is seen in the continual increase in skinfold thickness (MAYER 1968) and in the increase in total body fat (BROZEK et al. 1953). From the teen years onward there is somewhat more body fat on the female than on the male. KEYS et al. (1972) describe the average weight changes beyond age 20 that are observed in the United States and other "developed" countries. If the average weight at age 20–29 is taken as 100%, then the average weight of the male during the years 30–39 is 5.4% greater and for the years 40–59 is 8.0% greater than this. For the female the average weight at ages 30–39 is 7.1% greater and at 40–59 is 13.7% greater. In all cases the lean body mass decreases with age, so the net increase in fat is even greater.

Because of the linear increase in body fat with the passage of years, it is easy to correlate death rates, degenerative disease rates, and a variety of health problems with the amount of fat present. The more fat in the body, and the older age, the higher the death rate and the higher the incidence of degenerative disease. It is also true that the maturity-onset diabetic tends to be overweight and is highly susceptible to diseases of the kidney, heart, and vascular systems. Elimination of these and similar considerations from the health data leaves one with the conclusion that, within reasonable limits, body weight has little or no measurable influence on health (COSTA et al. 1978; KEYS 1955, 1967; KEYS et al. 1972; WEINSIER et al. 1976). Indeed, it appears (NATIONAL DAIRY COUNCIL 1979 b) that the older person whose weight is between 100% and 130% of "ideal weight" has lower morbidity and lower mortality rates than is seen in either the underweight individual or the one who is grossly obese.

It is the popular view that overweight is usually the direct result of gluttony. There is reasonably convincing evidence, however, to indicate that this is not the case (ROSE and WILLIAMS 1961; KEYS 1967, 1970; MILLER and MUMFORD 1967 a, b; SIMS et al. 1973; DUBOIS et al. 1979). In the typical case, other factors, including exercise and genetic controls, may be more important than the amount or type of diet consumed over the course of years. Where gross obesity is involved, this is another matter (discussed elsewhere in this volume).

III. Lipid Metabolism and the Cardiovascular System

There is a tendency for plasma lipid levels to increase with advancing age and for this increase to be correlated with a tendency toward atherosclerosis and coronary heart disease. These factors are interrelated and tend to increase in prevalence beyond the age of 40. PINCHERLE (1971) studied 700 businessmen in 1964–1969 and measured their plasma cholesterol levels. Several correlations were noted. The cholesterol tended to be elevated for those in jobs involving a substantial amount

of "mental stress." Furthermore, whenever the cholesterol was elevated, there was a tendency for the iliac artery to be calcified and for the blood uric acid to be elevated.

KRITCHEVSKY et al. (1973) studied male rats at 2 months, 12 months, and 24 months of age, and noted that there was a systematic increase in the activity of certain enzymes within the aorta of these rats with increasing age. Over the period studied, there was a 79% increase in the concentration of those enzymes that tend to esterify cholesterol. At the same time, however, there was more than an 11-fold increase in the activity of those enzymes that tend to hydrolyze cholesterol esters. The net result was a marked increase in lipolytic activity of the artery with increasing age. One might expect this metabolic change to be associated with a progressive increase in the deposition of cholesterol in the aorta with advancing age. This observation is of particular interest because the rat is a species quite resistant to atherosclerosis.

YAMAMOTO and YAMAMURA (1971) studied the cholesterol metabolism of the rat. With increasing age, they found a lower rate of conversion of acetate to cholesterol in the liver, together with a lower rate of cholesterol catabolism, and a lowered rate of biliary and fecal excretion of cholic acid derivatives. With increasing age there was also a decreased rate of absorption of cholesterol from the gastrointestinal tract. BIERENBAUM et al. (1970), in a 5-year experiment, found that weight loss had no influence on serum cholesterol levels.

GLUECK et al. (1977) studied the blood lipids of 22 octogenarians and found that a majority of them had an elevated level of alpha-lipoprotein with a lowered level of beta-lipoprotein in their plasma. This suggests that certain alterations in lipid metabolism may be correlated with increased life span.

The relationship of this group of problems to the lipid content of the diet will be discussed elsewhere.

IV. Nervous System and Sensory Changes

The brain reaches its maximum weight at about age 20–30 (BONDAREFF 1959). From age 30 to 60 there is a progressive decrease in brain weight and decrement in nervous system performance. NORRIS et al. (1953) measured the maximum conduction velocity in motor nerve fibers of the human ulnar nerves, and found a maximum response at ages 30–40, with a decrease thereafter. These decreases in velocity paralleled the 4%–13% reduction in observed performance tests. BIRREN and BOTWINICK (1955) measured the reflex response times observed in the finger, jaw, and foot following an auditory stimulus. The comparison was between 32 subjects aged 16–36 years and 32 subjects with ages ranging from 61 to 91 years. There was a 20%–30% slowing of reaction rate seen with age. KNOWLTON and BRITT (1949) reported a progressive decrease in knee jerk reflex time and decrease in jerk amplitude beyond 40 years of age.

SIMONSON (1975) reported a progressive decrease in cerebral blood flow and in flicker fusion frequency from age 20–70. These decreases were similar to the decreases in muscle strength and endurance, and the decrease in maximal oxygen transport ability of the heart.

Steven (1946) and McFarland and Fisher (1955) reported a progressive and linear decrease in dark adaptation (final rod threshold) from age 20 to 60. Robertson and Yudkin (1944) studied 758 factory workers and found a progressive decrease in final rod threshold over the age range 14–71 years. The rate of decrease was somewhat greater after age 50 than it was prior to that time.

Botwinick (1973) described the decreases in auditory abilities that occurred beyond age 25. The decline with age was relatively slight in the tone frequency range 250–1,000 Hz, but marked for sound frequencies above 4,000 Hz. The deficits were progressive and more rapid beyond age 50–60.

Orma and Koskenoja (1957) reported that 81% of the men and 91% of the women over age 65 coming into a Helsinki clinic were troubled with dizziness. Typically, this was a momentary postural dizziness coming with sudden movements of the head or the whole body. Many patients were also troubled with a sense of buzzing or murmuring in the ears. The authors further indicated that 8% of the patients reporting dizziness later suffered a stroke, but that there were no strokes among patients not experiencing dizziness.

Botwinick (1973) discussed the measurable drop in IQ test scores (Wechsler-Bellevue test) seen in the period just prior to death.

All of these factors are critical to the physical performance and general well-being of the older person; however, no preventive or curative diets are known. The nutritional literature tends to couple deficits in dark adaptation with vitamin A deficiency (Rodriguez and Irwin 1972). However, there is no evidence that vitamin A supplementation can prevent the visual changes characteristic of old age, and there is some evidence that factors other than vitamin A can be critical in relation to night blindness (Wittkower et al. 1941).

V. Hormonal Changes

Beyond midlife there are well-defined changes in sexual function, an increase in the tendency toward diabetes (Sect. B.II) and a number of changes that might best be interpreted in terms of changes in neurotransmitter or neurohormonal activity. Finch (1973) reported a progressive decrease in the concentration of dopamine as measured in certain brain structures of the mouse with increasing age. There were also reduced rates in the conversion of tyrosine and dopa to catecholamines in four regions of the brain. There was a slowed rate of catabolism for norepinephrine in the hypothalamus.

Marx (1979) summarized conference reports suggesting that many of the changes seen during later life in relation to sexual activity, sleeping cycles, insensitivity to insulin, and some of the changes following menopause, may best be understood in terms of the changes in production and balance of the neurohormones. Samorajski (1977) suggested that changes in the sleep-wake cycles and the decrease in REM-sleep pattern, as well as the changes in feeding and drinking habits, the reduction in sexual function, and the changes in personality (aggression) may be attributed to changes in central neurotransmitter substances with age.

The pattern of change with respect to age is not well established for most of these hormonal changes and related behaviors. In the case of sexual performance of the male, it is well known (Kinsey et al. 1948) that the maximum activity occurs

around age 20, and there is a progressive and nearly linear decrease until age 60 or 70. Many of the other hormonal changes are most evident beyond age 65.

DAYAN (1971) made histological studies of the brains of 47 species of vertebrates, but in none of these were there aging changes seen that are characteristic of the changes seen in the aged human. Biochemical studies of experimental animals may provide more insights, however. Many of the neurotransmitter changes that give rise to behavioral effects (SMITH J. E. et al. 1976) can be related to amino acid metabolism, and those related to serotonin (APRISON and HINGTGEN 1972) can sometimes be produced by feeding diets high in corn protein (LYTLE et al. 1975). Some of these same changes are also seen under conditions of diminished kidney function.

VI. Kidney Changes

SHOCK (1957) reported a progressive and linear decrease in renal plasma flow (as measured with diodrast) from ages 20–90. There was also a decrease in tubular reabsorptive capacity and in the tubular transport maximum, as well as a decrease in kidney response to a standard dose of pitressin.

Chronic renal failure is routinely associated with substantial changes in amino acid metabolism (GULYASSY 1970; MCGALE et al. 1972) of a type known to influence neurotransmitter metabolism. Renal disease produced behavioral changes (TYLER 1970) reminiscent of those seen with alterations in neurotransmitter metabolism (BUNNEY and DAVIS 1975; SMITH J. E. et al. 1976). These data suggest a marked interaction between protein nutrition, kidney metabolism, and neurohormonal effects.

VII. Skeletal Changes

There is a progressive demineralization of the skeleton starting around age 30–40 and becoming increasingly rapid in later years. Osteoporosis is a common problem in older women. MARX (1980) reported that as many as 190,000 hip fractures and 100,000 broken wrists were caused each year by osteoporosis. SMITH et al.(1975) suggested that this effect is common to all women and does not represent a specific disease entity causing selective losses in only certain women. EXTON-SMITH (1972) suggested that the best protection against osteoporosis is to enter later life with a well-developed and massive skeleton.

DRAPER (1964) studied the mineral balance of laboratory mice at different ages and with different diets. When low-calcium and low-magnesium diets were given for a 10-day period, it was found that older animals lost calcium more readily and in larger amount than did younger animals – and thus were more susceptible to decalcification of the skeleton. BIRGE et al. (1967) studied skeletal decalcification in older humans and found osteoporosis was frequently associated with lactose intolerance. About half of the osteoporotics had low levels of intestinal lactase and a low rate of lactose digestion. This, in turn, was usually associated with a low milk consumption, and hence a low calcium intake.

HOWELL (1917) has shown that the thickness and weight of leg bones in the dog are highly dependent upon the amount of exercise (and the amount of stress ap-

plied to the bone). ZUCKERMAN and STULL (1969) indicated that the strength of the knee joints and ligaments are highly dependent upon the amount of exercise given to experimental animals. ASHER (1947) has discussed the dangers of inactivity that occur as older people become bedridden. These effects include a marked calcium loss leading to disuse osteoporosis and a stiffening and painful action in the joints.

DEQUEKER et al. (1969) studied 140 women aged 30–94 in a psychiatric hospital. Over most of the age span studied, there was a progressive decrease in body height (either standing height or body length measured in a supine position). This decrease amounted to 1.3–2.2 cm per decade.

There have been attempts to control or reduce the calcium loss in the aged by changing the diet. It has been suggested that increasing the intake of fluoride could harden the bone mineral and delay the process of demineralization (CASS et al. 1966; COHEN and GARDNER 1966). This fluoride treatment has now come into routine use in some quarters; however, the success of this procedure has been questioned (MARX 1980). Alternatively it was suggested that the calcium intake be greatly increased (MARX 1980). GARN et al. (1967) studied the relationship between bone density and age in populations with quite different calcium intakes, and found that the age response was independent of calcium intake. This suggests that, in normal populations, the negative calcium balance seen with age may not be easily reversed by simply increasing the calcium intake. It still seems probable, however, that a calcium deficient diet might speed the loss of calcium from the body.

SILBERBERG and SILBERBERG (1957) found that the deterioration of joints and the development of osteoarthritis in mice was promoted by feeding a high-fat diet. Since excess, unabsorbed fatty acid tends to be excreted in feces in the form of their calcium salts, a high-fat diet may be roughly the equivalent of feeding a low-calcium diet.

SMITH D. M. et al. (1976) found that the rate of bone mineral loss in women varied by as much as five-fold in different age periods beyond 50. The greatest rate of loss was in the immediate postmenopausal years. There was no correlation between calcium loss and physical activity, and no correlation with changes in muscle strength. MCCONKEY et al. (1963) points out that bone matrix is a connective tissue, and that osteoporosis of old age may be thought of as a generalized connective tissue disorder. This suggests that the problem may be related to protein nutrition and protein metabolism as well as to mineral metabolism. He further pointed to a significant correlation between osteroporosis and the development of "transparent skin."

VIII. Skin Changes

Though the subcutaneous fat pads may tend to increase with age, the skin itself becomes thinner and more susceptible to damage. MCCONKEY et al. (1963) reported that the mean skin thickness, as measured over the fourth metacarpal, was 1.8 mm for the normal adult, but was more typically in the 1.0–1.6 mm range for subjects beyond the age of 70. The authors refer to this condition as "transparent skin," and indicated that it was best visualized by infrared photography. During the 6th decade of life, 4% of the males and 6% of the females were characterized

as having transparent skin. During their seventies this percentage rose to 8% and 12%, respectively. In the eighties 13% and 35% were observed. Associated with the deterioration of skin is the tendency for the skin to become dry and easily irritated. JOHNSON (1975) has discussed the problems of itching skin commonly seen in the geriatric patient.

LETO et al. (1976) fed mice a high-casein diet (26%) or a low-casein diet (4%) for life, but did not find that this altered the age-related changes in the collagen structure or the collagen content of skin. They did find, however, that the mice fed the low-casein diet lived longer (28 months) than did the rats with the high-casein diet (23.5 months). JACKSON (1964) studied the collagen extracted from skin of young and older animals, and could not find anything chemically abnormal about the collagen present in aging skin.

It is clear that systematic and progressive changes occur in skin with increasing age. However, biochemical studies have not yet been able to define the chemical nature of these changes.

IX. Gastrointestinal Tract Changes

There is a progressive decrease in digestive and absorptive capacity of the gastrointestinal tract beyond about age 30. BALACKI and DOBBINS (1974) noted a progressive atrophy of the gastric mucosa, along with a decrease in the production of hydrochloric acid, pepsin, and intrinsic factor. The low pH of gastric juice is important in providing bactericidal action. As the pH rises above 4.0, bacterial contamination becomes a chronic problem. With increasing age, there was a progressive decrease in pancreatic secretion and bile flow. Associated with these changes, were progressive decreases in xylose absorption and the absorption of other test substances. A decrease in intrinsic factor is specifically associated with a decrease in the absorption of vitamin B_{12}.

A general decrease in absorptive abilities can be further compounded by the ingestion of alcohol or certain drugs (particularly carthartics, mineral oil, or diphenylhydantoin). Characteristic endocrine changes, and some of the changes associated with the degenerative disease of old age, further decrease digestive abilities. BALACKI and DOBBINS (1974) concluded that "aggressive supplementation with vitamins, minerals, and calories is necessary to compensate for nutrients lost through maldigestion and malabsorption."

There is a progressive decrease in the mechanical action of the intestinal tract. On usual (low-fiber) diets there is a progressive tendency toward diverticulitis and constipation. DOBROWOLSKI (1971) found a linear increase in the frequency of diverticulitis from age 40–90. The incidence at age 40 was about 10% whereas at age 90 the incidence was in excess of 60% in the population studied.

In addition to normal aging effects, there are a variety of pathological effects, and the effects coming directly from therapeutic actions that cannot be ignored in individual cases. DONALDSON (1977), for example, has described the effects of radiotherapy. When the radiation field included the abdomen, the results included enteritis, vomiting, nausea, diarrhea, and weight loss. In such cases impairment of digestive function with aging may be even more profound.

X. Generalization

Taken together, these data suggest that aging is best viewed as a melange of degenerative changes that can occur simultaneously in all parts of the body. Starting by age 30, the rate of change is modest in most cases until about age 60, but at some point beyond that age, degenerative changes can occur more rapidly, even in the absence of any easily defined disease process. Beyond age 80 it is probably not worth asking the cause of death.

One may picture the entire life cycle as being composed of three distinct stages. Following the early growth period, there is an adult period (roughly ages 20–60) in which degenerative changes are present but the rate of change is relatively slow. The age at which the rapid degeneration of senesence begins is higly characteristic of the individual. In some malnourished populations it may begin in the thirties; whereas, in a few select populations there is no rapid decline until well after the 100th year. Herein lies one of the basic problems in gerontology. Aging cannot be adequately described in terms of chronological age. Yet, too many studies of "aging" have been carried out on subjects who have passed a specific birth date – with no other parameter defined. In some studies subjects have actually been picked so as to be as free as possible of all degenerative changes characteristic of old age. As MARX (1979) has indicated, the results of such work may have only minimal value when applied to a broad cross section of the elderly population. This is particularly true in terms of any effort to define the role of nutrition in human aging. Some consideration must be given to a wide variety of problems, and particularly to the common degenerative diseases of old age.

From evidence available thus far, there does not seem to be any magical diet that can prevent or retard the general effects of old age. It is in relation to the common degenerative diseases of old age that dietary controls seem to be most useful.

C. Degenerative Diseases and Diet

Most of what we know about "normal" human nutrition comes from controlled studies with young, rapidly growing laboratory animals, or from studies designed to increase the efficiency of feeding for farm animals. In neither instance is there much interest in the problems of gerontology or in the relationship between diet and the degenerative diseases characteristic of old age. By contrast, most of the nutritional knowledge that is uniquely important to the older person comes from the experience of the clinician and dietitian and reflects their experience in working with older patients. Many of their conclusions relate to those specific food items or food groups which should be avoided in certain chronic disease conditions. It is difficult to overestimate the importance of medical advice in determining what goes into the mouth of older persons, both in the way of food and drugs.

HOWELL (1963) studied the autopsy records of persons living beyond their 90th birthday. Bronchopneumonia was the most commonly cited cause of death, but autopsy examinations revealed that each had a wide variety of metabolic and pathological problems. Indeed, 498 separate lesions were identified in 40 subjects, or an average of more than 12 pathological problems per person. Had all of these

conditions been diagnosed during the life of the patient, a formidable array of drugs and dietary modifications could have been suggested for the management of many of these conditions. The best records in relation to drug intake of older persons comes from hospitals and nursing homes. MELMON (1971) indicates that the average hospital patient receives six to ten drugs simultaneously. Many older persons also take suplements of vitamins and/or minerals and certain nonprescription remedies. It is quite reasonable, therefore, to picture that the typical older person finds himself with quite a collection of dietary restrictions (superimposed upon those already present due to economic circumstances and culturally determined eating habit patterns) and that he may be spending much of his limited cash on a handful of pills that must be taken each day.

I. Common Dietary Restrictions

Among the persons who have passed their 60 th birthday, most are lacking an adequate number of their natural teeth to allow them to do an efficient job of chewing food. Many have had dentures for some years – and in all too many cases these dentures no longer fit as well as they should. This inability to chew efficiently has direct implications relating to the type of meat and the varieties of fresh fruits and vegetables that these older persons can eat.

Most have a tendency toward maturity-onset diabetes, or at least have an elevated glucose tolerance curve (SILVERSTONE et al. 1957). They have been advised to avoid sugar, sweets, fresh, and canned fruits, and root vegetables. Most of the older persons have high blood presssure and/or elevated plasma cholesterol levels and have been advised to avoid salt in their diet and to remove all products containing animal fat (milk, meat, and eggs) from their diet (COUNCIL ON FOOD AND NUTRITION 1972).

Not infrequently the removal of a gall bladder will make it necessary to avoid fatty foods. A tendency toward gout can eliminate organ meats (and purine nucleotides used as flavor-enhancing agents in soups and gravys). Difficulty with a kidney stone can result in the removal of milk products from the diet and the prescription of an acid-ash diet that minimizes the plant products in the diet.

Frequently the physician will look at the bodily proportions and the amount of subcutaneous fat on an older person, and suggest that he would do well to reduce his body weight. The health significance of this advice may be open to question (KEYS 1955; KEYS et al. 1972; WEINSIER et al. 1976; COSTA et al. 1978), but the advice is frequently given, and may include the suggestion to cut down on the amount of bread, potatoes, and other "starchy products" in the diet.

Rarely if ever is the physician's dietary advice based on any firm data concerning what the patient is already eating or is willing to eat. In concluding his discussion with the patient, the physician may well say, "This diet may not help – but at least if cannot hurt."

II. Health Foods

Once the older patient has left the physician's office and has filled his prescriptions for drugs (and frequently for a vitamin and mineral suppplement), he faces the

problem of preparing the next meal. Given certain combinations of the dietary restrictions listed above, this can be a formidable task. In many cases the patient sees no rational solution. Meanwhile the grocery stores, news stands, and health food stores are well supplied with books, magazines, and handouts providing all sorts of optimistic nutritional advice, complete with assurances and testimonials. The NATIONAL DAIRY COUNCIL (1979a) lists the three basic causes of food faddism as "(a) those in which special virtues of a particular food are exaggerated and purported to cure specific diseases, (b) those in which certain foods are eliminated from the diet due to the belief that harmful constituents are present, and (c) those in which emphasis is placed on 'natural foods."

Many older persons already have some distrust of the medical profession. After this last piece of dietary advice, followed by a chat with the folks at the local health food store, our oldster may now be well on the way to becoming a devoted food faddist and spending a substantial portion of his meager funds on the nostrums and health foods sold in that establishment.

Had the physician been able to visualize this response to his advice it is questionable whether his final words would have been, "– but at least it cannot hurt."

Some of the common effects of the physician's dietary advice may well be to: (a) remove all sources of high quality animal protein from the patient's diet, (b) impress the patient with that fact that diet is critical to health – but give no positive guidance on menu planning, and (c) drive the patient into the clutches of the food faddist and the natural food vendor. The high prevalence of this type of response can be seen in the popularity of "diet" books and health food stores. Some view this response as constituting one of the greatest nutritional problems in the United States today (RYNEARSON 1974).

III. Generalizations

Degenerative disease problems increase with age until the older person finds that medical problems are the major determinants of the daily diet. Nutritional problems may be further compounded by drug effects, radiation therapy, and other medical and dental problems.

For such a patient it becomes essential that all of this medical information be coordinated and brought under positive dietetic guidance. A noncoordinated series of dietary restrictions leaves the older person unable to cope with meal-planning problems, and forces him to seek dietary advice from readily available sources who may have little knowledge or guidance other than that which relates to their own economic interests. Next to outright neglect and starvation, this situation can be designated as constituting the greatest nutritional hazard to which the older person is likely to be exposed.

D. Significance of Diet

Dietary adjustments, preferably with the support of a qualified dietitian, can be important in the successful management of a number of metabolic diseases frequently encountered in old age. Beyond this point, however, it may be appropriate to ask

about the nature of any evidence suggesting that diet has any positive affect on the aging process at all. If malnutrition is a serious hazard to the aged, how widespread is this problem?

I. Nutrition Survey Evidence

For several decades one answer to this problem has been to send survey teams into the field to try and locate cases of scurvy, rickets, pellagra, and other examples of classical nutritional deficiency conditions. It is now reasonably established that a frank deficiency disease is extremely rare, but that anemia is fairly common and "unacceptable biochemical values" can be found in most surveys – particularly those involving poverty populations. When the Ten State Survey (U.S. DEPARTMENT HEW 1972) was completed, its headquarters were in Georgia – a state with over 100 deaths per year from starvation and severe malnutrition (roughly one-third of which were people above age 65), and a large poverty population reporting incidences of maternal and infant death, mental retardation, diabetes and hypertension that were two- to five-fold above the national averages (GEORGIA DEPARTMENT OF PUBLIC HEALTH 1968). Pertinent health data of this type were not reported and seem not to have been considered in this nutritional survey report.

II. Population Differences

As one looks around the world, one cannot help but be impressed with the facts that: (a) there are major differences in eating habit patterns in different cultural groups and in different geographical areas and (b) there are major differences in life span and health data in different parts of the world. In much of the underdeveloped world, the average life span for the "common man" does not extend much beyond the 40th or 50th year. In a few selected areas, such as the Caucasus mountains, there seem to be a substantial number of people whose ages extend well beyond the century mark (LEAF 1973). It was noted some years ago that one of the characteristic items in the diet of these oldsters was a soured milk product. Thereafter, for a time, *Lactobacillus bulgaricus* milk became a favorite fad item in the American dietary.

III. Economic Effects

There are systematic differences in diet and in the nature of health problems observed in different populations with the different diets and different levels of income. FAO has studied the diet of over 80 different populations in different parts of the world. PERISSE et al. (1969) has summarized these data and indicated that there is a nearly linear relationship between annual income and the amount of fat, animal protein, and sucrose in the diet. This general relationship is shown diagrammatically in Fig. 1. At the lower end of the economic scale one finds people living on diets composed of plant products (cassava, rice, other grains). Many of these persons are short of stature, have a short life expectancy, and have a low resistance

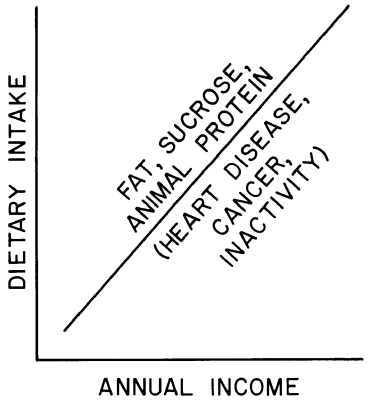

Fig. 1. Diagrammatic representation of the findings of PERISSE et al. (1969), indicating a high positive correlation between the annual income of a population and its average dietary intake of sucrose, fat, and animal protein. In parenthesis it is also indicated that there is a high positive correlation between all dietary variables and the prevalence of cancer and coronary heart disease, and a negative correlation between the dietary variables and physical activity

to infectious disease. Cancer and coronary heart disease are seldom problems. At the upper end of economic scale one finds a diet which is rich in animal products but lacking in crude fiber. The individuals tend to be taller, heavier, and lead a less physically vigorous life. In middle age they tend to develop high blood pressure, and a high proportion die of coronary heart disease, stroke, and cancer.

There are many differences in the way of life, their living conditions, and the industrial pollutants to which the populations at the two ends of the economic scale are exposed. If, however, one looks at populations in the United States that, for reasons of religious belief, tend to avoid meat, coffee, and alcohol, one also finds a decrease in the plasma cholesterol level (WEST and HAYES 1968) and a decrease in the incidence of heart disease (PHILLIPS et al. 1978). It therefore appears that simply by changing to a diet which is more characteristic of a lower economic class, one also can change the pattern of health statistics in a similar fashion.

IV. Transplanted Populations

There are certain mass migrations that have caused substantial diet changes for a defined population within the course of a single generation. HANKIN et al. (1975) studied the diet changes in over 6,000 men of Japanese ancestry who were living in Hawaii and were active in the Honolulu heart and Japanese-Hawaii cancer studies. DUNN (1975) reported that as the Japanese families moved to Hawaii, or other parts of the United States, there was a decrease in the incidence of colon cancer, but an increase in the cancers of the stomach, breast, uterus, ovaries, and prostate. RHOADS et al. (1976) have studied the serum lipids and the incidence of coronary heart disease in the Japanese-Hawaiian population. The study involved over 1,800 men aged 50 to 72 years. The greatest incidence of coronary heart disease occurred among those having high plasma cholesterol levels (either total cholesterol or cholesterol in the beta fraction) and was lowest in those having an elevated alpha lipoprotein level. In comparing the Japanese and Western diets, WYNDER et al. (1969) reported that the Western diet tended to be high in fat. It included more eggs, milk, animal protein, and vitamin A. Associated with the Western diet was an increase in rectal cancer and a decrease in colon cancer.

V. Diet and Cancer

CLAYSON (1975) has reviewed the evidence suggesting that the amounts of vitamin A, vitamin C, copper, iodine, and selenium in the diet can all influence both the probability of cancer and the growth rate of tumors. SUGAI et al. (1962) fed rats both fresh and heated vegetable oils with and without a known carcinogen. Cancer was seen only in those animals fed the heated and oxidized vegetable oil along with the carcinogen. HARMAN (1972) speculates that the addition of antioxidants to the diet could increase the average human life span by 7 years. BURKITT (1973) suggests that the addition of more fiber-containing plant products to the diet would decrease the incidence of large-bowel disease and colon cancer. The effect of cigarette smoking on mortality due to coronary heart disease and cancer is well known (ABRAMSON 1977). There is a current concern about the relationship between nitrite-cured meat products, nitrosamines, and certain types of cancer (LIJINSKY and EPSTEIN 1970; WOLFF and WASSERMAN 1972).

There are a variety of regional health problems that may be related to diet (HIGGINSON 1969; TYROLER 1970; LILIENFELD et al. 1972), but the reasons are not currently known. At the southeastern corner of the Caspian Sea the incidence of esophageal cancer is some 10- to 30-fold higher than in adjacent regions (KMET and MAHBOURBI 1972).

Where heavy metals, industrial pollutants, and aflatoxin are involved, there are a host of studies indicating local health problems (SMITH 1980), and in many cases either drinking water or a specific food had a major responsibility.

VI. Generalization

It seems clear that diet can exert a powerful and controlling effect on health and longevity. In a few cases physiological changes are well correlated with the intakes of specific foods or nutrients, but in most cases the data fail to show whether this relationship is causal or incidental. Much basic work remains to be done in this area of human nutrition.

E. Importance of Diet Components

Some gerontologists (SHOCK 1970) accept the view that aging has little or no effect upon the recommended daily allowance for most nutrients. There are suggestions elsewhere, however, that certain food components may take on added significance with increasing age. While there are very few critical studies of nutrition in older persons that have been carried out under controlled conditions, some insights can be gained by reviewing the health statistics and the indirect evidence relating to specific nutrients and diet components.

I. Crude Fiber

Constipation, diverticulitis, and general sluggish action of the gastrointestinal tract are common complaints among older people. It is now suggested (BURKITT 1973)

that these complaints, as well as other bowel disease problems, can be largely avoided by increasing the amount of crude fiber in the diet. Unfortunately the term "crude fiber" includes a variety of materials ranging from cellulose and hemicellulose to pectins (van Soest and McQueen 1973). As one goes down the list from cellulose to pectin, there is a progressive increase in water-holding ability and the ability to bind mineral elements. The bulk associated with this water-holding capacity is important in determining the volume and consistency of the fecal waste – and also is important in controlling the bacterial flora of the gut (Eastwood 1973). Different fruit, vegetable, and whole grain products have differing amounts and ratios of these different crude fiber components. Some foods may yet prove to have specific significance, but for the time being it is best to suggest that older people should include an adequate variety of these plant products in their diet as a means of aiding and controlling bowel action.

II. Minerals

Hypertension is a common complaint among older persons, and the positive correlation between hypertension and the sodium content of the diet is well established (Meneeley and Batterbee 1976). There is also some suggestion concerning a geographical correlation between hypertension and soft water. Chah et al. (1977) studied the trace mineral content of diet and drinking water and found no relation to coronary heart disease. They further point out that the overwhelming proportion of the mineral intake comes from the foods in the diet. Hence there is little likelihood that water hardness can be a critical variable capable of influencing any aspect of health.

In the treatment of hypertension it is a frequent practice to administer diuretics, and some of these selectively remove potassium, zinc, and perhaps other trace minerals at the same time they are removing sodium and water from the system (Roe 1976). One of the characteristics of this type of treatment is that it frequently continues for many months or years. Thus it becomes quite possible to develop a chronic mineral deficiency unless specific mineral supplementation is provided.

III. Lipids

There is a substantial interest in the relationship between dietary fat and the incidence of hypercholesteremia and/or cardiovascular disease. The correlations are most striking when one looks at the saturated fatty acid components of the diet. Keys (1970) studied over 12,000 men in seven different countries, and his data leave no doubt of the strong positive correlation between saturated fatty acids in the diet and the elevation of serum cholesterol – and the correlation of both of these factors with coronary heart disease.

Which one of the saturated fatty acids, if any, is primarily responsible for this correlation is still uncertain. Keys and Parlin (1966) found that stearate (18 carbons) did not raise cholesterol levels. Moore et al. (1975, 1976, 1977) reported that myristate (14 carbons) from coconut oil was the only saturated fatty acid correlated with atherosclerosis, but their search did not include caproate (6 carbons) which is also characteristic of coconut oil, and thus would be highly correlated with

the same factors that correlate with myristate. CASTER et al. (1975), with controlled animal experiments, demonstrated that, of the eight common saturated fatty acids, only dietary caproate increased plasma cholesterol levels. Neither this observation nor the suggestions concerning myristate have yet been checked in human subjects in controlled experiments using chemically pure lipid supplements.

Other conjectures have related to the effects of the cholesterol content of the diet. A positive effect has been established, but its magnitude seems quite small under normal conditions. About half of the cholesterol in the normal diet comes from eggs. When one egg per day (KUMMEROW et al. 1977) or two eggs per day (FLYNN et al. 1979) were added to the diet of middle-aged men, there was no measurable change seen in serum cholesterol or triglyceride levels. Excessive amounts of vitamin D (TAURA et al. 1978) or unusual dietary lipid components, such as oxidized cholesterol (IMAI et al. 1976) or trans acids (KUMMEROW 1979), have been suggested as possible causes of atherosclerosis and hypercholesteremia.

There is no question that a positive correlation exists between the amount of saturated fatty acid in diet and the incidence of coronary heart disease and hypercholesteremia in populations of middle-aged men that live in the "developed" nations. There is, however, no general agreement concerning the chemical basis for this correlation (REISER 1973; KEYS et al. 1974). This unsatisfactory situation has been further compounded by efforts to replace saturated fatty acids (or animal fat) with polyunsaturated fatty acids (or vegetable oils) in some diets.

In some cases, this substitution appears to have decreased serum cholesterol levels and reduced the incidence of coronary heart disease (but not the total death rate). In some longer studies (ALBANESE and WOODHULL 1967; BERKOWITZ 1973) no clear effects were noted. In addition, some concern has been expressed (PEARCE and DAYTON 1971) about an increase in the incidence of cancer seen among men on a high polyunsaturated fatty acid diet that was intended to lower the serum cholesterol levels. EDERER et al. (1971) combined the statistical results of five different studies and concluded that a substitution of polyunsaturated fatty acids for the saturated fatty acids in the diet really has no measurable effect on any of the human health data that were studied.

In view of the negative results related to all major lipid components, it has been suggested that the increase in coronary heart disease might be due to some other closely correlated factor. YUDKIN and MORLAND (1967) suggested it may be sucrose, rather than fat, that is the main cause of coronary heart disease. KEYS (1971) is not inclined to see this as a credible answer. More recently, MANSON (1978) has suggested that heat-modified milk protein might cause increases in cholesterol levels.

Figure 1 suggests that the amount of lipid, sucrose, and animal protein are all correlated with income and thus with the affluent way of life. One might, therefore, expect that any factor, such as coronary heart disease, that is correlated with any one of these variables would be correlated to some extent with all of the others.

IV. Trace Components

The development of cancer from the ingestion of aflatoxin, PPB, pesticides, radiostrontium, radioiodine, saccharin, or other trace contaminants of food typically

takes many years. It is in the older person that these effects may show up, but because of the long induction period involved, it could be less critical to exclude these items from the diet of the elderly person than from the diet of the young person. The same might be said for smoking cigarettes, although there is evidence (ABRAMSON 1977) that a decrease or cessation of smoking even late in life has helpful effects on a person's health. Where emphysema or other pulmonary problems are evident, it is prudent to prevent any other further irritation to the area. Much the same could be said about the chronic use of alcohol in relation to problems of liver degeneration. A substantial use of alcohol can also lead to a negative magnesium and zinc balance, and impair the utilization of thiamin. In fact, most of the beriberi and Wernecke's syndrome cases that are seen in hospitals in the United States are alcoholic patients.

Many older patients take quite a collection of drugs. Some of these interact directly with vitamin and mineral nutrition. ROE (1976) has summarized interactions of this nature. Methotrexate and purimethamine are folic acid antagonists. Colchicine, potassium chloride, phenformin, para-aminosalicylic acid and a variety of cathartics may result in malabsorption leading to a vitamin B_{12} deficiency. Isoniazid is a metabolic antagonist that can lead to a vitamin B_6 and niacin deficiency. Anticonvulsant therapy with diphenylhydantoin markedly reduces serum folate levels (HAGHSHENASS and RAO 1973), and a combination of phenobarbital and diphenylhydantoin interferes with vitamin D metabolism and leads to hypocalcemia (HAHN et al. 1972). Boric acid can increase the excretion of riboflavin, and aspirin can increase the rate of excretion of vitamin C. Mineral oil, neomycin, and cholestyramine can greatly decrease the absorption of vitamin A and some of the other fat soluble vitamins. Aluminum hydroxide, when given in excess, can greatly decrease the absorption of phosphate and fluoride.

V. Generalization

It is probably wise for all older persons to minimize their intake of sucrose, fat, and salt, and to make certain that their diet contains an adequate amount of crude fiber from various fruit, vegetable, and whole grain sources. Beyond this point the most critical nutrient needs may be those precipitated by chronic administration of drugs.

F. Experience from Surveys and Feeding Programs

Dietary intake data coming from nutrition surveys and from reports of feeding programs, suggest that many older persons have quite satisfactory nutrient intakes, but that some specific individuals have serious nutritional problems.

I. Survey Data

STEINKAMP et al. (1965) studied the diets of 500 persons over 50 years of age in California, and followed these subjects for 14 years (or until death). About 35% of this group reported that they took daily nutrient supplements. However, the authors reported that the diets of half of these subjects were very adequate in all

Table 1. Percentage of persons aged 65 and above reporting 24-h dietary intakes less than the following amounts for selected diet components

Diet component	Less than	Income more than poverty level				Income less than poverty level			
		White		Black		White		Black	
		Male	Female	Male	Female	Male	Female	Male	Female
Energy	30% of RDA	1	1	6	6	5	7	6	12
Protein	40 g	2	5	9	8	7	9	7	15
Iron	4 mg	2	3	4	9	6	9	15	16
Vitamin C	5 mg	4	3	5	9	11	6	20	15
Vitamin B_1	0.4 mg	5	3	3	9	6	2	8	9
Vitamin B_2	0.5 mg	2	2	7	4	3	1	3	4
Niacin	4 mg	2	1	6	3	6	3	5	5

RDA, Recommended Daily Allowance

of the nutrients represented in the supplements that they were taking. Data showed that with increasing age the intake of both calories and protein tended to decrease, but that the total weight of animal protein remained unchanged with time. The most distinct decreases in intake were noted after age 75.

GUGGENHEIM and MARGULEC (1965) studied 115 older men and women in Jerusalem and found that older men living alone consumed less fruits and vegetables (less vitamin C and vitamin A) than those who were living with their spouses. DIBBLE et al. (1967) studied the intake of 214 older persons at different times of the year and found that the carotene and the riboflavin intake was greater in autumn than in spring.

TODHUNTER et al. (1974) studied the food intake of 500 older persons in Tennessee. Major interest was directed toward the identification of those food items which were disliked and those which were readily accepted by this group, but data were also provided relating to the nutrient evaluation of the diets consumed. Diets were considered "satisfactory" for a given nutrient when more than two-thirds of the Recommended Daily Allowance was present. On this basis, three-quarters of the subjects had satisfactory protein intakes; over half had satisfactory intakes of calcium, vitamin A, and vitamin C; and between one-quarter and one-half had satisfactory intakes of thiamin and riboflavin. For iron, 40% of the females and 65% of the males had satisfactory intakes.

The NATIONAL CENTER FOR HEALTH STATISTICS (1979) reported nutrient intake data obtained from a survey of a statistically selected sample of the United States population in 1971–1974. The report includes 24-h dietary intake data from 1,344 persons aged 65 and above. Table 1 summarizes some of these data that relate to the percentage of this population having low nutrient intakes. It is evident that both race and economic status had marked effects upon the intake of several nutrients. These effects were particularly evident in the case of calories, protein, iron, and vitamin C.

II. Feeding Programs

There have been a number of studies related to feeding programs designed to serve older persons. JOERING (1971) found that the total daily intakes of most nutrients was greater when a meal was furnished, and that the daily intake of several nutrients were further increased when juice and milk were specifically provided as a part of that meal. SCHLETTWEIN-GSELL (1971) found that a Meals-on-Wheels program in Switzerland did not increase the total nutrient intake of subjects when compared to other older persons who were preparing their own meals. GOODMAN (1974) studied over 500 older persons in Pennsylvania and found that a food program had no influence on the nutrient intake of more affluent participants, but did increase the vitamin C and vitamin A intakes for those with the lower incomes. The intakes of protein, iron, and total calories were most directly influenced by the amount of food produced in home gardens.

III. Economic Considerations

What older people eat is highly dependent upon their economic status. JORDAN et al. (1954) studied the dietary habits of 100 persons over age 65 who were living in

Westchester County, New York. No economic data were given, but 8% ate regularly at restaurants and another 14% ate out at least once per week. The authors could find little problem with their dietaries except for a lack in green and yellow vegetables (which they did not care for) and a lower amount of dairy products and citrus fruit than might have been desirable. Where there had been changes in eating habit pattern, the subjects reported that these were largely due to medical advice rather than economic necessity. Only 4% reported that problems with their dentures in any way modified their food choices. Some 44% were taking vitamin pills (29% by physician's prescription) and 55% frequently took laxatives.

KELLEY et al. (1957) studied 97 white women and 104 black women in suburban Michigan. This was a follow-up to a study carried out nearly 10 years before, and over half of the subjects had been studied previously. The authors reported that 95% of the subjects had dietary intakes that were less than 80% of the Recommended Daily Allowances, and a number had less than 40% of the Recommended Daily Allowances for a number of nutrients including vitamin A and vitamin C. Among the group that had poor dietaries, there was a much higher incidence of death, unexplained tiredness, joint pain, and shortness of breath.

MORGAN (1975) reported laboratory work done on 93 acute geriatric admissions to a hospital in Yorkshire, United Kingdom. It was found that 29% of the laboratory tests gave abnormal results, and for 22% of the patients, over half of the tests showed abnormalities. The most common low test values were in relation to vitamin C, vitamin E, carotene, niacin, and serum albumin.

OHLSON et al. (1948) studied groups of women in several parts of the midwest in the United States that were in the age range 40–78, and contrasted those that were in "good health" with those that were in "poor health." They found that those in poor health had dietary protein intakes of 41–48 g/day on average while those in good health had an average protein intake of about 56 g/day.

A British housing project in Stockton-on-Tees was moved to provide newer and better housing units. These units were also somewhat more expensive. Within the next few years here was a 30% increase in death rate (MCGONIGLE 1933). Since most of the group were on a fixed income, it has been suggested (BENDER 1974) that a net decrease in their food money might have had a greater effect on their health and well-being than could be compensated for by the better housing conditions.

BATCHELDER (1957) reports dietary data from 2,800 women and 250 men ranging in age from 40 to 80. It was found that the average caloric intake decreased by 100 kcal/decade (from roughly 1,800 to 1,400 kcal over the 40-year span). At the same time the average protein intake decreased by about 5 g/decade (roughly 63 g at age 40 to 45 g at age 75). This suggests a proportionately greater decrease in protein than in calories.

MAYER (1962) points to data reporting the finding of a number of frank vitamin deficiency cases in the eastern United States. All of these were among elderly people.

MIHELICH et al. (1980) described the food consumption of older people receiving a delivered hot meal at noon on 5 days of the week. Nearly a quarter of the group had a light breakfast and little more than crackers and milk for supper. Many of them did not fare much better over the weekend. For some it was fairly clear that the Meals-On-Wheels program was essential for survival.

SOMMERS and SHIELDS (1979) point out that the United States is rapidly approaching the time at which a majority of full-time homemakers can expect to spend their later years alone and in poverty. They will rely on governmental services for survival, and 20% of them will die in a nursing home.

IV. Generalizations

Beyond the 30th year of life most nutrient requirements do not change appreciably, but the caloric requirement decreases by about 0.5%/year. After age 60–80, as the person becomes less vigorous, the intake decreases more rapidly.

The greatest danger of nutrient deficiency is seen among poverty groups and perhaps among certain cultural groups that tend to limit their intake of certain food items, including those containing high quality protein.

Feeding programs may do little to improve the nutritional status of the affluent and the vigorous aged. Gardening efforts may serve some of these groups more effectively. However, as physical and economic disabilities become more pronounced, feeding programs can play a critical role in delaying nursing home institutionalization. Some rudimentary cooking and meal planning abilities may also be critical to the older person living alone.

The few data that do exist, suggest a negative correlation between nutrient intakes of older persons and the corresponding morbidity and mortality statistics.

G. Conclusions

Beyond age 30, the passage of years has very little influence on most of the nutrient requirements. Any discussion of the role of nutrition and aging, therefore, is centered not on age per se but on the physiological changes and the metabolic and degenerative disease conditions that are associated with aging. It is in relation to these that nutrition can play a crucial role and may be a major determinant of health and survival.

Some of these problems are fairly universal in the "developed" world. This makes it reasonable to suggest that most oldsters should limit their intake of sodium, sucrose, and triglycerides, and be certain that their diets contain enough crude fiber (whole grains, vegetables, and fruits) to assure proper bowel action. Other advice must be specifically related to individual problems.

It is the physician, more than any other single factor, who may determine the diet of many elderly persons. Too often the physician has had minimal instruction in human nutrition and dietetics. He may not even be aware of the nutritional side effects of some of the drugs he prescribes. His dietary advice frequently takes the form of a series of prohibitions. Some may be crucial for health and others may fall in the class of "it can't hurt."

Too often an existing eating habit pattern is disrupted with no positive guidance being given in the direction of providing a satisfactory alternative diet pattern. Without this help, the patient can be burdened with needless or ill-advised vitamin and mineral supplements, and left to fend for himself among the commercial health food advisors and the pulp literature on "nutrition and health" – which frequently

goes out of its way to cast doubt on the validity of professional medical and dietetic advice. If nothing else, this action can place a needless economic burden on a person who already has serious and increasing economic problems.

Where outright starvation and death from malnutrition are found, extreme economic deprivation is usually a primary cause. No nutritional evalution is complete until it provides information on the possible existence of acute economic and health problems that can be a major determinant of diet.

The social planner needs to take a good look at current feeding programs for the elderly. The type of program that is appropriate and effective for a given person is highly dependent upon his health, economic status and living conditions.

The vigorous elderly couple with garden space might use help and instruction on gardening and food preservation. Many will shortly find themselves living alone, and if they do not have rudimentary cooking skills, some instruction in shopping, menu planning, cooking, and food safety could be important. Periodic medical and dental examinations are an important part of any preventive program.

As the person becomes less able, a Meals-on-Wheels program, coupled with collateral social services and a periodical case review, can be a crucial aid to keeping a person in his own home and in delaying institutionalization. Because of the high cost of nursing home care, such a program can be highly cost effective and can be of critical benefit to the older person at an important transition period.

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Protein and Amino Acid Metabolism and Nutrition During Human Aging

V. R. YOUNG

A. Introduction

The maintenance of an adequate content of organ and tissue total protein, as well as a wide variety of individual structural and functional proteins, including enzymes and polypeptide hormones, is necessary for survival and attainment of full health of the organism at all stages of life. Furthermore, the maintenance of the physiological and biochemical processes of tissue and organ cells depends upon the participation of numerous physiologically active, *N*-containing compounds. Substrates for formation of proteins and the *N*-containing compounds are obtained from the digestion and utilization of proteins present in foods that are eaten.

Specifically, the dietary requirement for protein consists of two components: (1) a number of indispensable (essential) amino acids that cannot be made by the mammalian organism at rates commensurate with needs and (2) a source of utilizable nitrogen, usually in the form of the dispensable (nonessential) amino acids (YOUNG and SCRIMSHAW 1978). We will consider in more detail later these nutrition issues, but it would be useful first to begin with an account of the metabolic basis of the dietary protein and amino acid requirement. This will be accomplished by an initial discussion of the changes that occur in body composition during progression of the adult years, followed by a brief review of studies concerned with whole body and tissue protein metabolism in older human subjects. Next, methods and approaches used for determining the dietary requirements for protein and amino acids will be examined and a discussion made of current estimates of the requirements and recommended allowances for these nutrients in adult human nutrition. Finally the reader is encouraged to consult previous reviews to obtain a more complete coverage of the topic of protein metabolism and nutrition in relation to human aging (e.g. YOUNG et al. 1976a, b, c, 1981; UAUY et al. 1978b).

B. Some Aspects of Body Composition in Relation to Aging

Amino acids represent the currency of body protein metabolism (Fig. 1). The major fate of the amino acids that enter the tissue free amino acid pools are: (1) incorporation into proteins; (2) catabolism via transamination and oxidative reactions, leading to their elimination from the body as carbon dioxide, and water and nitrogen, principally as urea and ammonia; and (3) conversion to other physiologically important compounds such as nucleic acids, porphyrins, glutathione, and creatine. The continued breakdown of protein within cells endows a capacity for adaptation

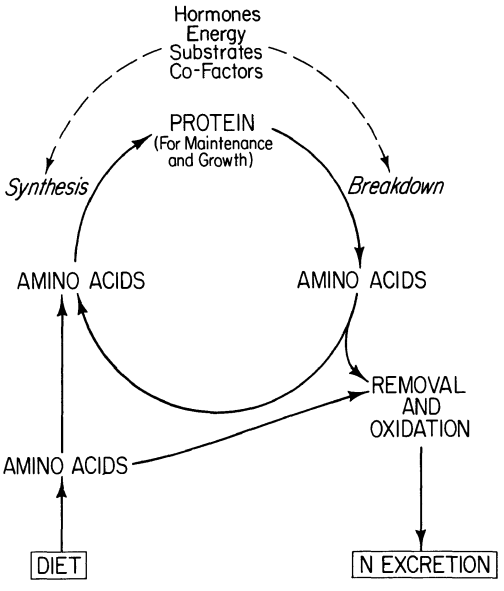

Fig. 1. A schematic outline of the relationship between amino acid and protein metabolism

Table 1. An approximation of total body nitrogen in humans at different ages. (YOUNG et al. 1976c)

Age group	Body nitrogen	
	g	g kg body wt^{-1}
Newborn (full-term)	66	19
Child (10 years)	615	19
Adult (25 years)	1,320	18
Elderly (65–70 years)	1,070	15

to alterations in the internal and/or external environments and the former process contributes to the turnover of proteins. The balance between incorporation of amino acids into proteins and their subsequent release from them via protein breakdown will determine the size of the body and organ protein mass. In turn these rates affect the total daily requirement for protein and amino acids. It is pertinent, then, to consider the changes in the size and distribution of the body protein mass that occur with the advancing adult years.

Briefly, cross-sectional and longitudinal studies have shown that there is a progressive decline in total body potassium (ALLEN et al. 1960; FORBES and REINA 1970; STEEN et al. 1979) as adult age advances in humans. Although the precise physiological significance of this loss of body potassium is uncertain, it is interpreted usually to indicate a decrease in total body protein mass. Therefore, studies of this kind provide an approximation of the body N (protein) content of humans at various stages of life. Hence, as shown in Table 1, body N increases rapidly from birth during childhood and early maturity approaching maximum by about the 3rd decade. Thereafter body N decreases gradually, with the decline possibly oc-

Table 2. Some observations on skeletal muscle weights in old versus young rats and mice. (YOUNG et al. 1976c)

Species	Age comparison	Muscle	Weight change	Fiber number	Reference
Rat	4 months vs 2 years	Soleus		Decreased	GUTMANN and HANZLIKOVA (1966)
Mouse (M)	137 vs 750 days	Soleus	Little change	Little change	ROWE (1969)
Mouse (F)	137 vs 750 days	Soleus	Little change	Decreased	ROWE (1969)
Mouse (M)	137 vs 750 days	Anterior tibialis	26% decrease	No change	Rowe (1969)
Rat (M and F)	200 vs 800 days	Gastro-cnemius	22%–29% decrease		NEUMASTER and RING (1965)
Rat	450 vs 900 days	Gastro-cnemius	Decreased		MCCAFFERTY and EDINGTON (1974)
		Soleus	Little change		

curring somewhat more rapidly in men than in women (FORBES and REINA 1970). These changes in body protein mass have possible nutritional implications, because the physiological requirement for protein is usually considered to be that intake necessary to just achieve a "maintenance" of total body nitrogen content. Although this concept of the protein requirement is rather limited, because amino acids fulfill functions in addition to providing substrate for maintenance of cellular protein content, it follows that these changes in total body N content might lead to the prediction that the total protein needs change during the progression of adult life. This topic will be explored later. An additional comment should be made, however, with respect to the age-related change in body nitrogen (protein) content.

The lower body nitrogen in the older subject may be the consequence of parallel changes in the protein content of many organs or a relatively greater change in only selected organs. Table 2 summarizes some reported observations on differences in the weight of individual muscles in young and aged animals. The degree of morphological (JENNEKENS et al. 1971) and biochemical (BASS et al. 1975) change presumably depends upon the function of the individual muscles. Thus, in old age not only are there decreases in total muscle mass but also marked differences occur in the degree of change among different muscles in the number and diameter of fibers (e.g. ROWE 1969). Although the weight of some muscles is maintained in old age (Table 2), these various studies imply an overall decrease in the size of the skeletal muscle mass. Furthermore, about 85% of total body potassium and 50% of body nitrogen in the adult is located in the skeletal musculature (WIDDOWSON and DICKERSON 1964). Therefore, changes in total body potassium during human aging may be due to atrophy of skeletal muscles.

Data on age-related changes in the mass of muscles of human subjects are limited but as shown in Fig. 2, autopsy studies of hospitalized patients suggest that total muscle mass undergoes a relatively greater percentage decline in old age than does that of other organs, such as the liver and heart. In agreement with this, there

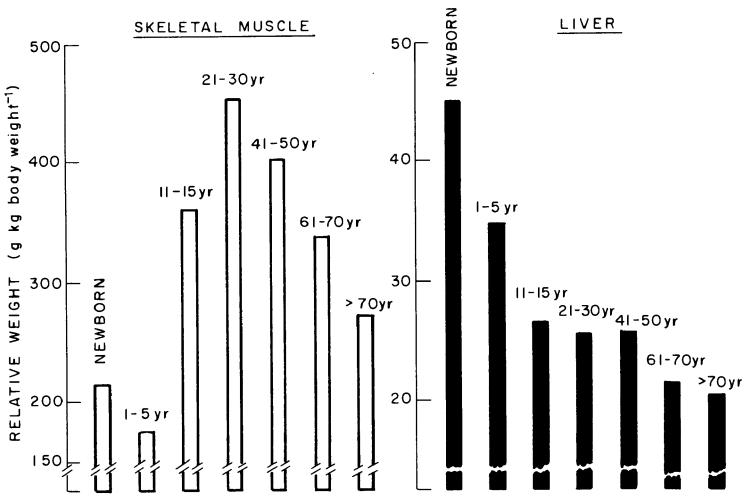

Fig. 2. Contribution of skeletal muscles and liver to body weight at different ages in human subjects. (Drawn from KORENCHEVSKY 1961)

is a decline in urinary creatinine excretion, assumed to be a index of muscle mass (GRAYSTONE 1968) in aged rats. Furthermore, we have observed a correlation between urinary creatinine and body cell mass in adult humans and lower rates of creatinine output in older subjects, again suggesting that muscle atrophy accounts for a major portion of the decline in total body cell mass during aging in humans (UAUY et al. 1978c).

C. Whole Body and Muscle Protein Metabolism

In the context of this review, it is important to examine, in addition to changes in protein mass, the effect of advancing adult age on *in vivo* rates of whole body and organ protein synthesis and breakdown. The report of SHARP et al. (1957) suggests that the rate of whole body protein synthesis is considerably lower in elderly people than in young adults. However, their study was limited to one young adult male and female and two older male and female subjects and they utilized a method that is not reliable for determination of whole body protein synthesis rates. Thus, we have explored this aspect of human protein metabolism with the aid of a continuous isotope administration protocol, which is regarded currently as the best approach for determining rates of whole body protein synthesis and breakdown (WATERLOW et al. 1978). With the aid of leucine labeled with the nonradioactive isotope ^{13}C, the dynamic status of whole body protein synthesis and breakdown in postabsorptive young adult and elderly men and women was investigated. Our results are summarized in Table 3. Under these conditions the estimated rate of protein synthesis, derived from the incorporation of leucine into body proteins in young adults and elderly subjects did not differ markedly, except for a lower rate in elderly females, which appears to be due mainly to the lower body cell mass in this group as compared with younger subjects of the same sex. However, because

Table 3. Rate of protein synthesis and breakdown (expressed as leucine kinetics and estimated with the aid of 1^{-13}C-leucine) in young adult and elderly male and female subjects during the postabsorptive state (ROBERT et al., unpublished data)

	Young adult		Elderly	
	Male	Female	Male	Female
No. subjects	10	5	6	4
Mean age (years)	25	22	75	76
Mean wt (kg)	77	61	74	61
Protein synthesis				
As leucine incorporation				
per kg per h	80±4	99±8	72±8	68±6
per kg LBM per h	136±9	182±18	136±15	134±5
Protein breakdown				
As leucine release per kg per h	101±3	120±8	97±10	85±6

Values for protein synthesis and protein breakdown, are Mean±SEM and expressed as μmol leucine. LBM, lean body mass estimated from total body water by isotope dilution techniques

Table 4. Rates of protein synthesis, as estimated in different ways, in a group of elderly subjects. (Summarized from GOLDEN and WATERLOW 1977)

No. subjects	6	
Age range (years)	66–91	
Body wt (kg)	47–78	
Protein synthesis		
(g protein kg^{-1} day^{-1})		
^{14}C-leucine method		2.67±0.29
^{15}N-glycine method		3.17±0.19

there are fluctuations in the rates of protein synthesis and breakdown throughout the day (e.g. GARLICK et al. 1980; MOTIL et al. 1981) a comprehensive assessment of whole body protein dynamics should include studies that provide a picture of the average rates of protein synthesis and breakdown for the entire 24-h period.

To accomplish this we have estimated rates of body protein synthesis and breakdown using the ^{13}N-glycine method of PICOU and TAYLOR-ROBERTS (1969), which probably provides an integrative estimate of total daily protein turnover. The results of our small series of cross-sectional studies reveal only small, but at times statistically significant, differences in these rates between young adult and older subjects, when the results are expressed per unit body weight (WINTERER et al. 1976; UAUY et al. 1978 b, c; YOUNG et al. 1981). These results are similar to those reported by GOLDEN and WATERLOW (1977) using a similar approach (Table 4).

Because of differences in body composition between young and elderly adults, we have also examined rates of whole body protein synthesis and breakdown in relation to indices of body composition; (creatinine as an index of muscle mass, and body cell mass, determined by whole body ^{40}K). The results of our more recent

Table 5. Comparison of rates of whole body protein synthesis, determined with the aid of ^{15}N-glycine, in young and elderly males. (GERSOVITZ et al., unpublished data)

Parameter	Young males[a]	Elderly males[b]
Age (years)	21 ±1	72 ± 2
Body wt (kg)	77 ±5	69 ± 4
BCM (kg)	37.6±3.3	25.9± 1.4
BCM (% Body wt)	48 ±1	38 ± 1
Creatinine excretion		
g per day	2.1±0.2	1.3± 0.1
mg per kg BCM per day	55 ±0.6	50 ± 1.6
Whole body protein synthesis (g)		
per kg per day	3.1±0.2	3.1± 0.2
per kg BCM	6.5±0.3	8.1± 0.6
per g creatinine	118 ±6	165 ±16
Whole body protein breakdown		
g per kg per day	3.0±0.2	2.7± 0.2

BCM, body cell mass determined from whole body ^{40}K
[a] Mean±SEM for five young males
[b] Mean±SEM for six elderly males

studies are summarized in Table 5 and they show that whole body protein synthesis and breakdown rates, per unit of creatinine excretion, are higher in the elderly than in young adults. Also these rates tended to be higher in the older subjects when expressed per unit of body cell mass. These findings may reflect a lower contribution by muscle to whole body protein synthesis and breakdown in the elderly as compared with young adults.

In order to explore this possibility an estimate must be made of the rate of muscle protein breakdown, in relation to whole body protein breakdown, in the intact human subject. We (YOUNG and MUNRO 1980) have discussed the ways by which this might be accomplished and none are without their limitations. However, the approach that we have chosen is based on measurement of urinary N^{τ}-methylhistidine (3-methylhistidine) excretion. We (YOUNG and MUNRO 1978) have reviewed the evidence indicating that the output of this amino acid serves as index of the rate of muscle protein breakdown in vivo, in both rats and human subjects. This concept is schematically outlined in Fig. 3, emphasizing that the daily excretion of the amino acid is quantitatively related to its rate of release from the myofibrillar proteins in the skeletal musculature. Therefore, the urinary output of the amino acid reflects the breakdown rate of these major muscle proteins. Furthermore, if it is assumed that there is 4.2 μmol N^{τ}-methylhistidine/g mixed protein in adult human muscle (BILMAZES et al. 1978), the daily breakdown of protein within the skeletal musculature can be computed from the measured output of N^{τ}-methylhistidine in urine when subjects consume a flesh-free diet. It is important to be cautious about the interpretation of urinary N^{τ}-methylhistidine data because sources other than muscles, such as skin and intestine, may also contribute to the total daily output of the amino acid. Although the quantitative significance of these

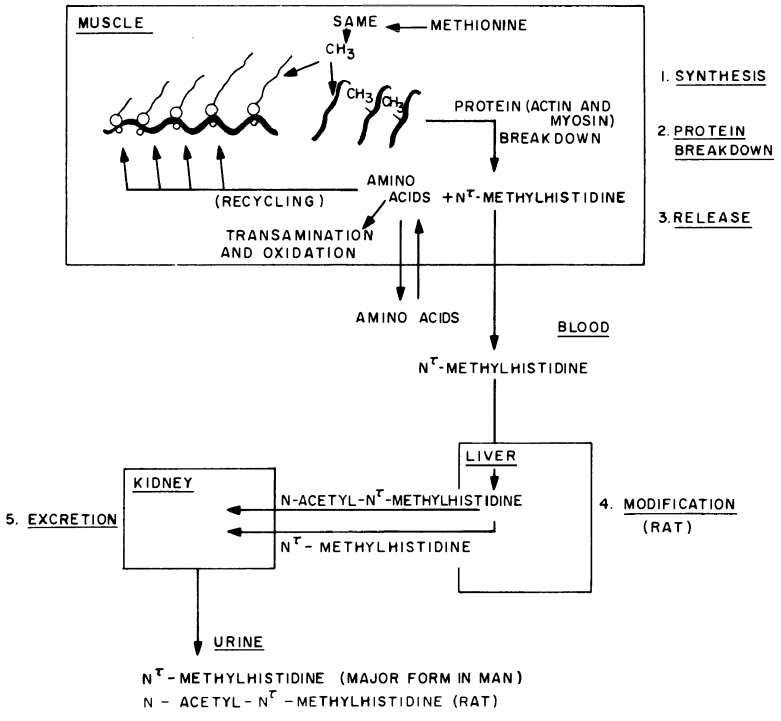

Fig. 3. Schematic outline of the origin and fate of N^{τ}-methylhistidine in the rat and human, used as an index of muscle protein breakdown in intact subjects. (See YOUNG and MUNRO 1978, for review)

sources is not yet known (e.g., MUNRO and YOUNG 1981) we have assumed that in adult man the skeletal muscles are likely to be the principal donor of the N^{τ}-methylhistidine in urine. An additional reason for exploring the status of muscle protein metabolism in vivo is because LUNDHOLM and SCHERSTEN (1975) have concluded from studies of teased muscle fibers in vitro that rates of muscle protein synthesis and breakdown are enhanced in old age.

Accordingly, the urinary excretion of N^{τ}-methylhistidine in groups of healthy young adult and elderly subjects, all consuming flesh-free diets that are free of a source of this amino acid, has been determined (UAUY et al. 1978 b, c) and some recent data are summarized in Table 6. Values for creatinine excretion are also shown in this table for purposes of estimating the size of the muscle mass. The urinary output of the amino acid is lower for elderly men than for young men. However, this appears to be due to the reduced muscle mass because N^{τ}-methylhistidine output per unit of creatinine output does not differ between the two age groups (Table 6).

Estimates of the amount of muscle protein breakdown, based on these findings are about 69 g daily in young men, or 0.9 g protein kg^{-1} day^{-1}, and 36 g daily, or 0.5 g kg^{-1} day^{-1}, in elderly males. Furthermore, in relation to the rate of whole body protein breakdown it can be seen from Table 6 that muscle accounts for approximately 30% of whole body protein turnover in young men as compared to

Table 6. Urinary N^{τ}-methylhistidine excretion and derived estimates of muscle breakdown as related to adult age. (GERSOVITZ et al., unpublished data)

	Young males[a]	Elderly males[b]
N^{τ}-methylhistidine		
μmol per day	287 ±33	151 ±9
μmol per kg BCM	7.6±0.3	5.6±0.2
μmol per g Cr	137 ±6	118 ±6
Muscle protein breakdown		
g per day	69 ±8	36 ±2
g per kg BCM	1.8±0.06	1.4±0.04
g per g Cr	33 ±1.4	28 ±1.6
% whole body	30 +2	20 +1

BCM, body cell mass determined from whole body ^{40}K
[a] Mean ± SEM for five young males
[b] Mean ± SEM for six elderly males

50% in elderly men. These new data, therefore, extend our previous findings (e.g., UAUY et al. 1978b,c) and indicate that during progression of the adult years there is a decline in the quantitative contribution made by skeletal muscles to whole body protein metabolism.

These observations in human subjects can be supplemented by studies on the effects of aging on protein metabolism in the individual organs of experimental animals (see YOUNG et al. 1976c, for review). In keeping with the decline in skeletal muscle mass and RNA concentration as age progresses, there is a reduction in the in vitro protein synthetic activity of muscle ribosomes (BREUER and FLORINI 1965; SRIVASTAVA 1969; GOLDSPINK 1972; BRITTON and SHERMAN 1975) and a decrease in the proportion of polyribosomes in muscle ribosomes, when examined on sucrose density gradients (BREUER and FLORINI 1965; SRIVASTAVA 1969). Furthermore, MUNRO and GRAY (1969) have concluded from an evaluation of the amount of total RNA in skeletal muscle, relative to RNA in the total body, that skeletal muscle protein metabolism is proportionately more important in the larger mammalian species as compared with the smaller species. A similar calculation was made by YOUNG (1970) for the rat at different ages and he concluded that the proportion of total body RNA found in the skeletal musculature, compared with that in the liver, decreased with advancing age. Thus, it can be predicted that muscle protein metabolism would be of diminished importance in the older organism, compared with that of the young adult. Our findings reviewed above, for human subjects, support this premise.

The significance of the shift in the redistribution in whole body protein metabolism in human subjects during progressive aging is not yet understood. We have speculated that it might lead to changes in the efficiency with which the dietary protein intake meets the requirement for protein (YOUNG et al. 1981). In addition, the muscles contribute to the adaptations in whole body energy and amino acid metabolism during restricted dietary energy and protein intakes (see YOUNG 1970; CAHILL 1970). Therefore, a reduced contribution by muscle to whole body protein me-

tabolism might diminish the capacity of the elderly individual to respond successfully to an unfavorable dietary situation or to other stressful conditions that depend upon mobilization of amino acids from the peripheral tissues for maintaining protein synthesis in vital organs. These questions deserve investigation.

It should be emphasized, however, that these various conclusions about changes and the amount of distribution of whole body protein synthesis and breakdown during passage of the adult years must be considered tentative. The data are based on cross-sectional studies in small groups of subjects and the methods used to quantify rates of whole body and muscle protein turnover have significant limitations, as mentioned earlier. New and improved, noninvasive methods for quantifying dynamic aspects of whole body protein and amino acid metabolism in vivo are necessary in order to validate and expand this unfolding picture of the status of protein metabolism during aging in healthy human subjects.

D. Metabolism of Specific Proteins

In contrast to a more extensive, although somewhat confusing, data base on the turnover of specific proteins in aged experimental animals (see YOUNG et al. 1976c), there are only few data available in human subjects on the dynamic aspects of metabolism of specific proteins. We have discussed above protein metabolism in skeletal muscles and here brief attention will be given to the effects of increasing age on the metabolism of albumin. Findings in aged rats suggest that they synthesize albumin at a faster rate than do young rats (OVE et al. 1972; OBENRADER et al. 1975) and that liver microsomes isolated from old rats synthesize albumin at a rate 50% higher than for young rats (CHEN et al. 1973). It might also be significant, in relation to findings reviewed below for albumin metabolism in human subjects, that albumin synthesis in old animals may already be maximally stimulated because blood loss did not result in an increase in albumin production whereas it did in younger rats (OVE et al. 1972). While these and other studies (VAN BEZOOIJEN et al. 1976, 1977) favor an enhanced rate of albumin synthesis in senescent rats, other studies suggest that general protein synthesis in the liver may be either unchanged (MOLDAVE et al. 1979) or reduced at this stage (MAINWARING 1969).

Albumin is a protein of particular interest in the biochemical evaluation of protein nutritional status in humans. We have developed a stable isotope procedure for the estimation of albumin synthesis, in relation to human aging, that involves labeling with ^{15}N-glycine administered orally every 3 h as a donor of ^{15}N for liver-free arginine. This method follows the nitrogen enrichment of the guanidine group of albumin-bound arginine and monitors ^{15}N-urea in the urine at isotopic steady state, as an index of the enrichment of the liver-free arginine pool. Thus, the progressive labeling of the arginine in serum albumin could be related to the level of ^{15}N enrichment of urinary urea to provide a measure of the albumin synthesis rate. The various assumptions applied in the application of this model have been discussed in detail by us (GERSOVITZ et al. 1980b). Thus, for young adults receiving an adequate protein, the albumin synthesis rate was 186 mg kg^{-1}day^{-1} (Table 7), a value that falls within the range obtained by the more widely used ^{14}C-carbonate method and in good agreement with the fractional catabolic rate as measured with

Table 7. Parameters of whole body albumin metabolism in young adult men studied with ^{15}N-glycine as precursor of the guanidine N or albumin-based arginine, and receiving diets adequate or low in protein. (Summarized from GERSOVITZ et al. 1980b)

Parameter	Diet		p
	Adequate[a]	Low protein[a]	
Serum albumin (g dl^{-1})	4.5 ± 0.12	4.58 ± 0.05	NS
Intravascular albumin (g kg body wt^{-1})	1.86 ± 0.04	2.22 ± 0.08	<0.01
Albumin synthesis % per day	3.97 ± 0.58	2.98 ± 0.31	<0.05
mg per kg per day	186 ± 30	140 ± 15	<0.025
% whole body protein Synthesis	6.16 + 1.22	4.57 + 0.64	<0.05

[a] Mean ± SEM for five young males

Table 8. Parameters of whole body albumin metabolism in elderly men, studied with ^{15}N-glycine as precursor of the guanidine N or albumin-bound arginine, and receiving diets adequate or low in protein. (Summarized from GERSOVITZ et al. 1980b)

Parameter	Diet		p
	Adequate[a]	Low protein[a]	
Serum albumin (g dl^{-1})	4.22 ± 0.07	4.12 ± 0.13	NS
Intravascular albumin (g kg body wt^{-1})	1.79 ± 0.15	1.90 ± 0.11	NS
Albumin synthesis			
% per day	3.35 ± 0.46	3.09 ± 0.49	NS
mg per kg per day	149 ± 22	147 ± 36	NS
% whole body synthesis	4.84 + 0.68	5.56 + 1.51	NS

[a] Mean ± SEM for six elderly males

radioiodinated albumin, approximately 200 mg kg^{-1}day^{-4} (ROTHSCHILD et al. 1977). This new stable isotope method is also sensitive in detecting a reduction in the rate of albumin synthesis (accompanied by a reduction in the proportion of albumin to whole body protein synthesis), when young adults receive a low protein diet (Table 7). Again, this observation is consistent with previous findings in the rat (SCHREIBER and URBAN 1978) and child (JAMES and HAY 1968).

Using this approach in elderly subjects, our results, summarized in Table 8, reveal a lower concentration of albumin in the plasma of subjects in this age group compared with young adults but the fractional synthesis of the albumin pool is only slightly and insignificantly less in the elderly. However, this value was not affected by differences in dietary protein level, in contrast to the impact of protein intake in the young men. This implies that only the younger subjects are able to respond to increased protein intake. In this context, it has been pointed out by MUNRO et al. (1975) that albumin synthesis in rats shows no consistent responses to increased consumption of protein when the animals already are receiving an adequate intake of protein, but became responsive when serum albumin concentration was first lowered by depletion.

From these findings, we have concluded that there is an upper rate of albumin synthesis, limited by a set point, beyond which a more generous amino acid supply cannot stimulate it further (GERSOVITZ et al. 1980 b). Based on this conclusion, it would appear that the synthesis of serum albumin in elderly subjects is maintained at a lower dietary protein level than in younger subjects because of a lower set point. This would explain why elderly subjects fail to show an increment in serum albumin synthesis in response to increasing dietary protein intake, whereas albumin synthesis in young subjects is responsive to this dietary change. These observations need to be extended in view of the fact that serum albumin levels are measured to evaluate nutritional status and the effectiveness or need for specific nutritional therapy in aged hospitalized patients.

E. Status of Amino Acid Metabolism

The relationship between adult age and the metabolism of specific amino acids might be examined by measurement of plasma amino acid concentrations and by investigation of the dynamic aspects of the metabolism of amino acids. However, few investigations of these kinds have been undertaken in elderly subjects. Furthermore, the available data do not provide a consistent picture. Thus, WEHR and LEWIS (1966) concluded that 12 of 18 free amino acids in plasma samples taken from fasting elderly subjects were elevated and ARMSTRONG and STAVE (1973) reported increased plasma levels of alanine, citrulline, cystine, and tyrosine together with a decrease in serine concentrations in older adults. MÖLLER et al. (1979) found higher total essential amino acid concentrations in elderly subjects compared with a younger group, 20–36 years old, and for tyrosine, histidine, valine, and lysine, the differences were significant. Although these differences were not great, they were generally paralleled by comparable differences in the concentration ratio of free amino acids in muscle relative to plasma. In contrast, others have reported reduced levels for most amino acids (ACKERMAN and KHEIM 1964). However, because amino acid levels in blood plasma are sensitive to various factors, including diet, (e.g., YOUNG and SCRIMSHAW 1972; MUNRO 1970), the conditions under which blood samples are taken for measurement must be standardized to evaluate critically data for plasma amino acid levels between different age groups.

For these reasons, we have examined the comparative response of changes in plasma amino acids to alterations in the intake of individual essential amino acids in young adult and elderly subjects.

When young men receive an amino acid diet providing graded reductions in leucine, the concentration of this amino acid declines as the intake is decreased (ÖZALP et al. 1972; HAMBRAEUS et al. 1976) (Fig. 4). In contrast, plasma valine levels rise when leucine intake is reduced (Fig. 5), possibly due to an effect of leucine on the uptake and metabolism of valine in muscle (HAMBRAEUS et al. 1976). Precisely, this pattern of change in plasma leucine and valine concentrations to diminished leucine is also observed in healthy elderly subjects (Figs. 4 and 5). Furthermore, in other studies, we have found that the pattern and magnitude of reduction in plasma tryptophan or valine to reduced tryptophan or valine intakes, re-

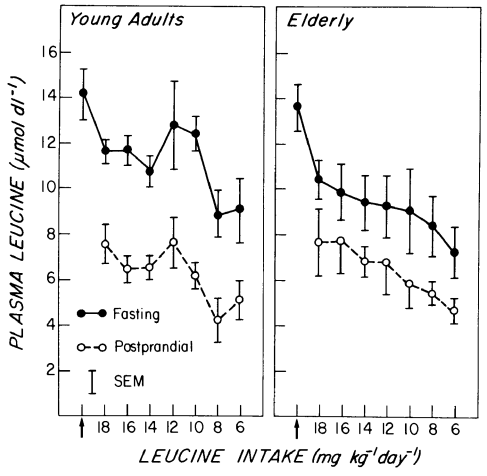

Fig. 4. Changes in plasma, drawn after an overnight fast and in the postprandial state, of leucine concentrations in young adult and elderly men given amino acid diets providing graded levels of leucine. Intake of all other amino acids remained constant. (PERERA and YOUNG, unpublished data)

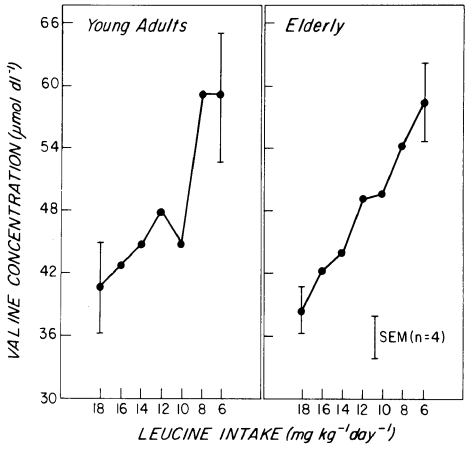

Fig. 5. Change in postprandial concentration of plasma valine with altered intakes of leucine in young adult and elderly men. (PERERA and YOUNG, unpublished data)

spectively, is similar in young adults and elderly subjects (YOUNG et al. 1971, 1972; TONTISIRIN et al. 1973).

From these studies it would appear that the regulation of plasma amino acid levels is similar in young adults and elderly subjects. Once again, however, the limited extent of the published data does not permit a definitive conclusion and there is an obvious need to further explore the response of plasma amino acids to a variety of nutritional and hormonal conditions in young and older subjects. Because exogenous glucose influences the disposition of plasma amino acids (MUNRO 1970), possibly due to the action of insulin, it would be worthwhile to know whether there are changes in plasma amino acids in response to insulin or glucose administration in young adults and elderly subjects. This is pertinent because of the reduced sensitivity of peripheral tissues to insulin during advancing old age (DE FRONZO 1979).

Earlier in this review, the dynamic status of whole body leucine metabolism, studied with the aid of 1-^{13}C-leucine, was compared in young adults and elderly

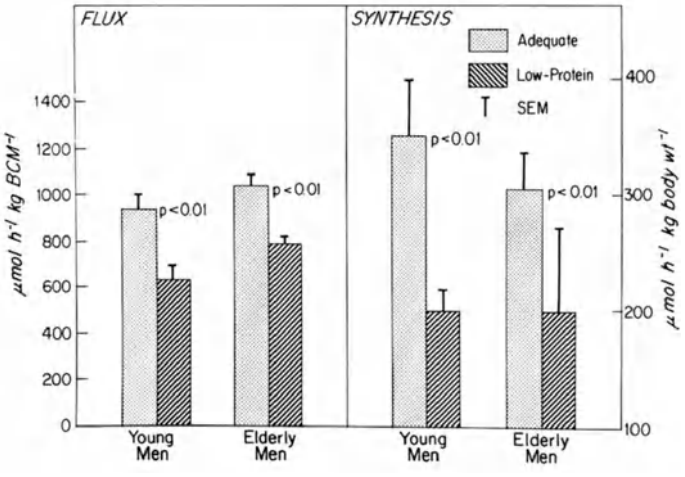

Fig. 6. Changes in glycine flux and in de novo glycine synthesis in young adult and elderly men following transfer from an adequate protein to a low-protein diet. (Drawn from GERSOVITZ et al. 1980a)

subjects, and there was little difference appearing between these groups when leucine dynamics were measured in postabsorptive subjects. In addition, using a procedure of continuous administration of ^{15}N-labeled glycine, we have estimated in young adult and elderly men the amount of glycine entering the free glycine pool from the diet, from endogenous synthesis or via release from body proteins due to their breakdown (GERSOVITZ et al. 1980a). The magnitude of the glycine flux, per kilogram body weight, was found to be similar in young and old subjects; when expressed per kilogram body cell mass (BCM), elderly subjects tended to reveal a higher flux rate (Fig. 6). Furthermore, the glycine flux was found to be much reduced in response to a decrease in dietary protein intake in both young adults and elderly subjects. Thus, our findings reveal that total synthesis of glycine by the body is extensive and is related closely to dietary protein intake. However, adult age does not appear to affect these aspects of whole body glycine metabolism. Finally, in view of the extensive transfer of N within the glycine pool, studies with other nonessential or dispensable amino acids, such as alanine, aspartic, and glutamic acids, would be a valuable contribution to an understanding of the quantitative interrelationships among the nonessential amino acids and their importance in the maintenance of body nitrogen homeostasis during progression of the adult years.

F. Protein and Amino Acid Requirements

Studies of body protein and amino acid metabolism, such as those discussed above, provide a basis for developing methods for assessment of the nutritional requirements in human subjects. Much of the published data concerned with this latter topic has been reviewed by IRWIN and HEGSTED (1971a, b). In addition, several

other reviews have concentrated on the elderly as the population group of interest (e.g. WATKIN 1957–1958, 1980; YOUNG et al. 1976a, b, c). Thus, a brief summary will be given here of the major issues and problems that confront a quantitative definition of the protein and amino acid requirements in older humans.

I. Requirements for Essential Amino Acids

In Table 9, a listing is given of the essential (or indispensable) amino acids in human nutrition. Compared with studies of amino acid requirements in infants and young adults, there have been few definitive studies of the essential amino acid requirements in the elderly. A summary of the available data is given in Table 10,

Table 9. Classification of amino acids, as indispensable or dispensable dietary constituents, according to their role in the maintenance of nitrogen equilibrium in adults

Essential (Indispensable)	Nonessential (Dispensable)
Valine	Glycine
Leucine	Alanine
Isoleucine	Serine
Threonine	Cystine
Methionine	Tyrosine
Phenylalanine	Aspartic acid
Lysine	Glutamic acid
Tryptophan	Proline
Histidine	Arginine
	Citrulline

Table 10. Some published estimates of the requirements for individual essential amino acids in young adult and elderly subjects

Amino acid	Age (years)	Estimated requirement (mg kg^{-1} day^{-1})	Author
Young adult			
S-amino acid		13	FAO/WHO (1973)
Lysine		12	FAO/WHO (1973)
Tryptophan		3	YOUNG et al. (1971)
Threonine		7	TONTISIRIN et al. (1974)
Elderly			
S-amino acid (methionine)[a]	64	46	TUTTLE et al. (1965b)
Lysine[a]	59	30	TUTTLE et al. (1965b)
Tryptophan	73	2	TONTISIRIN et al. (1973)
Threonine	72	7	TONTISIRIN et al. (1974)

[a] The high values for methionine and lysine requirements suggested by TUTTLE et al. have not been confirmed and may overestimate actual requirements

and it is evident that the findings are contradictory. This may be due to wide individual variation among subjects studied and to experimental errors and confounding factors involved in the nitrogen balance technique that has been used to determine the requirement for specific amino acids (e.g. TUTTLE et al. 1965a). Also, it is uncertain whether a higher requirement for methionine reported by TUTTLE et al. (1965b) for elderly subjects is due to an increased need for this amino acid or whether, and if true, it is related to a reduced efficiency of conversion of methionine to cystine in older individuals.

An alternative approach to the N balance technique that we have explored for estimating amino acid requirements in adults, including the elderly, is based on measurement of the concentration of free amino acids in blood plasma. Using this technique, we have estimated a tryptophan requirement in healthy, elderly subjects to be approximately 2 mg kg body wt^{-1} day^{-1} (Table 10). This is slightly lower than the values of 3 and 4 mg kg^{-1}, as determined for young men and children, respectively, by the same plasma amino acid procedure. Similarly, the threonine requirement was estimated to be about 7 mg $kg^{-1}day^{-1}$ in elderly women and similar to that for young men (TONTISIRIN et al. 1974). However, in view of the differences in body composition between young adult and elderly individuals, our findings imply that the threonine requirement *per unit of total body protein* increases with age, because lean body mass is less in proportion to total body weight in the older subject, as compared with young adults. This conclusion also applies to the valine requirement, based again on an interpretation of the plasma valine response curve.

It is evident that information about requirements for individual essential amino acids in the aging human is still fragmentary and the available data are contradictory. This is an unsatisfactory state of affairs, particularly because estimations of the requirements for essential amino acids form the basis on which to design the "protein" component of both normal and therapeutic diets for use in the elderly and to assess the significance of dietary protein quality for this age group.

II. Requirement for Total Nitrogen (Protein)

The minimum physiological needs for total protein in adult humans have been determined using one of two N balance methods (YOUNG and SCRIMSHAW 1978); (a) the factorial approach and (b) the N balance response curve method to directly determine the intake required to just maintain body N balance. In the former approach, the losses of "obligatory" N via urine and feces are measured and summated together with additional corrections for N losses via the integument and other minor routes (FAO/WHO 1973). The aim of this method is to determine the total nitrogen loss occurring from the body when the subject receives, for a brief period, a protein-free but otherwise adequate diet. The minimum dietary protein requirement is then computed to be that amount of high quality protein necessary to just balance these endogenous N losses.

In Table 11, values for obligatory N losses are summarized for young adults and elderly subjects and these data provide a basis for predicting the minimum dietary need for high quality protein in adult subjects, using the factoral calculation, to maintain body protein nutriture. Thus, our data on endogenous N losses in el-

Table 11. Some comparative estimations of obligatory nitrogen losses in young adult and elderly subjects[a]

Group	Obligatory urinary N		Fecal N (mg kg^{-1} day^{-1})	Sum of urine and fecal (mg N kg^{-1} day^{-1})	Total losses[b]	Author
	mg N per kg per day	mg per g creatine				
Young adult						
Women	25.2	1.5	8.4	33.1	38.1	BRICKER and SMITH (1951)
Men	37	1.6	8.8	45.6	50.6	SCRIMSHAW et al. (1972)
Men	38	1.7	14	52	57	CALLOWAY and MARGEN (1971)
Elderly						
Women	24.4	2.1	9.8	34.2	39.2	SCRIMSHAW et al. (1976)
Men	34.5	2.2	12.2	46.7	51.7	UAUY et al. (1978a)
Men	27.3	1.6	9.5	36.8	41.8	ZANNI et al. (1979)

[a] A more extensive compilation of the available data has been presented by BODWELL et al. (1979)

[b] Assuming an additional N loss of 5 mg N kg^{-1} day^{-1} via skin and other miscellaneous routes (e.g., see FAO/WHO 1973)

derly people suggest that 0.42 g protein (N × 6.25) $kg^{-1}day^{-1}$ would be a *safe practical allowance* for healthy elderly women and 0.52 g for elderly men. These values compare with the 1973 FAO/WHO values of 0.57 g and 0.52 g protein kg^{-1} day^{-1} for healthy adult men and women, respectively. However, as discussed below, these predictions probably underestimate the intake level that would actually be adequate for the older age group.

The minimum physiological needs for dietary protein may also be determined from the N balance response to graded protein intakes. Thus, in Table 12, a summary of some of the N balance studies and conclusions drawn from them are presented. Some investigators concluded that the needs for protein were higher in the elderly than in young adults whereas others considered that there were no substantial differences between the requirements for protein in young and old adults. However, a number of the studies referred to in this table, as well as others reviewed by WATKIN (1957–1958) and IRWIN and HEGSTED (1971 a), were not based on precise N balance determinations, and, furthermore, conclusions were made in reference to the then prevailing views on the estimated protein needs of younger adults. Also, the level(s) of protein intake tested in some of the studies did not necessarily evaluate the minimum intake which could maintain N equilibrium.

Several recent investigations in the elderly have made an attempt to standardize correlates of nitrogen of nitrogen balance in order to arrive at a reliable estimate of the protein requirement for this age group. Thus, we have measured nitrogen

Table 12. Some N balance studies, on estimations of protein needs in the elderly

Estimate and conclusion	Remarks	Author
N equilibrium in seven of eight women at 0.7 and 1.0 g protein/kg^{-1}. Dietary standards adequate	Healthy women, 52–74 years	ROBERTS et al. (1948)
Good nutritional state maintained at 54 ± 5 g protein	N balance assessed from diet records 20 women, 68–88 years	ALBANESE et al. (1957)
Protein needs not different from younger adults	Review of studies with older men and women in a mental hospital	HORWITT (1953)
No evidence of qualitative or quantitative changes with age	Balance studies in healthy old men	WATKIN (1957–58)
Elderly require 0.7 g protein kg^{-1} day^{-1}	Four men, 69–76 years, poorly nourished subjects	KOUNTZ et al. (1951)
Protein requirement for elderly women may be 20%–30% less than for young women	Nine women, 66–94 years, maintained health at self-chosen intakes	ALBANESE et al. (1952)

balances in response to graded levels of egg protein intake by elderly men and women (UAUY et al. 1978 b). However, this N-balance study was based on short dietary periods and the relevance of our findings and those of CHENG et al. (1978) based on a similar experimental design can be questioned. Therefore, the conduct of nitrogen balance studies of longer duration seemed desirable in order to assess whether there is a short-term adaptation to a given level of dietary protein intake that may complicate interpretation of results obtained in relatively brief diet periods. Accordingly, we have conducted a study to evaluate the current recommended daily protein allowance, as proposed by the Dietary Allowances Committee of the U.S. Food and Nutrition Board (NAS/NRC 1980), for older men and women by exploring the response of body protein metabolism to this level of dietary level during a 30-day metabolic study period. An additional purpose of this investigation concerned the age ranges of the present United States dietary protein allowances for older adults which are presently proposed for those aged 51 years and older without specific allowances for groups within this broad category.

A summary of results for N balance obtained in this recent study is given in Table 13. These results indicate that 0.8 g egg protein $kg^{-1}day^{-1}$ is not sufficient to support an adequate body N balance in many elderly females, even after a 30-day adaptation period.

These findings differ from two other recent studies in elderly human subjects. However, in the first of these (CHENG et al. 1978), elderly subjects, as well as a control group of young adults, were given an energy intake of 40 kcal $kg^{-1}day^{-1}$. This was probably in excess of the actual energy requirements of the older subjects, maintained under confinement, and this would have enhanced N retention beyond that which would have been achieved with an energy intake that more closely met requirements (e.g. GARZA et al. 1976; CALLOWAY 1975; INOUE et al. 1973). In the second study (ZANNI et al. 1979) N equilibrium in elderly males was achieved at

Table 13. Nitrogen balances in elderly men and women given 0.8 g egg protein kg^{-1} day^{-1} for 30 days [Summarized from GERSOVITZ et al. (Am J Clin Nutr. 35:6–14)]

	Elderly men	Elderly women
Number	7	8
Age (years)	72–82	74–99
Weight (kg)	51–89	48–69
Energy intake[a] (kcal kg^{-1})	32±3	29±5
Nitrogen balance[b] (mg N kg^{-1} day^{-1})		
Days 6–10	−7.4±3[a]	−0.8±1.9
16–20	1.5±3.8	−8 ±1.7
26–30	0.4±3.4 (3)[c]	−2.3±2.8 (4)[c]

[a] Mean±SD
[b] Mean±SEM
[c] Number in parenthesis indicates number of subjects showing persistent negative balance during last 15 of 30 days

an intake of 0.8 g protein kg body weight, but the subjects had received a protein-free diet for 17 days immediately prior to the test period. It is well recognized that such an initial period of dietary protein deprivation will influence N balance response when protein is subsequently reincorporated into the diet. Thus the body N retention in elderly subjects, as observed by ZANNI et al. (1979) was probably more favorable than would have occurred in initially well-nourished subjects. For these various reasons it is likely that the protein requirements in elderly subjects was underestimated in these two additional studies. Thus, we cannot conclude that the current NAS/NRC (1980) dietary allowance of 0.8 g protein kg day^{-1} of mixed quality protein is sufficient to cover the protein needs of a majority of the elderly population.

In view of the growing proportion of elderly in populations of technically advanced nations, it would be prudent to improve upon the limited data and state of the knowledge concerning protein and amino acid needs for this age group.

G. Effects of Infection and Other Stressful Stimuli on Protein Metabolism and Requirements

It is important to emphasize that the results of our studies and estimations for protein allowances in the elderly discussed above apply to "healthy" individuals. However, altered gastrointestinal function and the changes in metabolism that accompany aging, together with existence of infections and other chronic diseases, all may have a profound influence in the nutritional status and protein requirement of the elderly population. Because elderly people are more commonly affected by these factors, it is important to recognize their adverse effects on protein metabolism and nutrition. Furthermore, WATKIN 1957–1958) has stated: "Socioeconomic factors and presence of disease have far more practical influence than age per se in determining the status of protein nutrition in the aged."

Table 14. Characteristics of the catabolic responses to infection

A. Most prominent metabolic response to a generalized febrile infection of any case
B. Caused by increased metabolic requirements of body tissues in the presence of a generally inadequate dietary intake
C. Modulated by complex hormonal influences
D. Consistent features include:
Onset time following that of fever
Muscle wasting and weight loss
Negative balances of nitrogen and other nitracellular elements
Persistence into convalescence
E. Minimized by effective control of illness
F. Magnified during severe, uncontrolled, complicated, or recurrent illness
G. Followed by wasting and malnutrition if infection becomes chronic

Table 15. Protein needs in specific diseases (MUNRO and YOUNG 1981)

I. Normal adult:
(a) For N equilibrium: 0.55 g kg^{-1}, raised to 0.8 g kg^{-1} by protein quality correction (90%)
(b) Customary intake: 1–2 g kg^{-1}
II. Metabolic response to severe burn, injury and trauma:
(a) Acute phase: 2–4 g kg^{-1} plus energy
(b) Convalescence: 2+ g kg^{-1}
III. Malabsorption and gastrointestinal diseases:
(a) Malabsorption syndrome: 1 g kg^{-1}
(b) Ulcerative colitis: 1–1.4 g kg^{-1} [a]
(c) Ileococostomy: 1–1.4 g kg^{-1} [a]
IV. Liver disease:
(a) Acute hepatic encephalopathy: very low [b]
(b) Recovered encephalopathy: 1–1.5 g kg^{-1}
(c) Chronic encephalopathy: 0.5 g kg^{-1} [b]
V. Renal disease:
(a) Uremia: 0.5 g kg^{-1} (ketoanalogs) [b]
(b) Nephrosis: 1–1.4 g kg^{-1} [a]
VI. Malignant disease:
Increased protein and energy

[a] In each condition, losses of protein can double minimal requirement
[b] Intake restricted on clinical grounds

The qualitative effects of acute infection on dietary protein utilization and requirements have been well described (BEISEL 1977) for some infections, and a listing of the characteristics of the metabolic responses to infection is given in Table 14. Although the available data are of limited value for quantifying the effects of infection on nutrient needs in the elderly, any infection or other stressful stimulus of physical and psychological origin results in the development of a negative nitrogen balance through the cumulative effect of several different mechanisms (Table 14). Thus, in Table 15 an approximation is given of the changes in protein needs in some major disease states and, as shown here, the dietary protein

requirement may be increased twofold. This topic deserves much more exploration, particularly in reference to a more adequate definition of the nutritional and dietary needs of the elderly population.

H. Summary

In this review various aspects of body protein and amino acid metabolism during aging in human subjects have been explored. The picture that emerges is one of a slow loss of total body protein with aging, due largely to a diminution in the size of the skeletal mass. These changes are accompanied by a shift in the overall pattern of whole body protein synthesis and breakdown, with muscle mass estimated to account for about 30% of whole body protein turnover in the young adult, as compared with a lower value of about 20% or less in the elderly subject. Studies on albumin metabolism suggest that the regulation of albumin synthesis is altered with advancing old age in the human. Investigations on the dynamic aspects of metabolism of specific amino acids are limited but those currently available do not reveal any major differences between young adult and older individuals.

The determination of requirements for individual essential amino acids and for total protein has also been discussed, and it is evident that the data are limited and often contradictory. However, elderly individuals are more likely to be affected by various biological, environmental, and social factors that would tend to increase protein needs above those for younger adults. Thus, in practice, the protein needs in the elderly are probably higher than for the young. The reduction in energy intake, together with its possible consequences for reduced dietary protein utilization, will also tend to increase the protein need of elderly subjects, relative to that for active young adults. Until more data become available, it is recommended for food planning purposes, that an appropriate protein allowance would be 12%–14% of the total energy intake.

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Vitamins and the Aging Process

V. R. YOUNG

A. Introduction

For cells and organs to survive, the organism must obtain various carbon compounds, either preformed or as precursors, from its environment. These compounds are obtained from foods and, together with various minerals, water, and oxygen, comprise the approximately 50 essential nutrients in human nutrition. Vitamins represent a category of nutrients and they are of interest in reference to the aging human, particularly in view of evidence that elderly subjects or population groups may be deficient in one or more specific vitamins (e.g. EXTON-SMITH and SCOTT 1968; EXTON-SMITH 1980; BRIN and BAUERNFEIND 1978; ALBANESE 1980) and the possibility that some vitamins may be intimately associated with the cellular mechanisms responsible for aging. In addition, an understanding of the role of vitamins in health and disease by the public has not always been adequate and this might lead to inappropriate dietary habits, especially in the elderly.

This chapter will review some general aspects of vitamin nutriture, with particular reference to the aging human. It begins with a general discussion of vitamins as essential nutrients and then some factors that affect the metabolism and utilization of them. This will be followed by a brief discussion of the methods used for evaluation of vitamin requirements in human subjects and then some examples of current estimations of these requirements for the elderly. We will not be concerned with the possible relationships between vitamin intake and the mechanisms of aging since this constitutes a separate topic, mainly limited to studies in nonhuman experimental models, and the findings are not readily translated into practical concerns for human nutrition.

B. Definition

The vitamins are organic compounds required for growth and maintenance of normal cell and organ function (Table 1). Because they cannot be made by the body in sufficient quantities, they are needed in small amounts in the diet. However, for some vitamins, such as biotin, the intestinal microflora might also synthesize amounts that are significant in relation to meeting the physiological requirement of the host.

The basic reason these compounds are essential constituents of an adequate diet is because cells lack the enzymatic machinery necessary to achieve their rates of synthesis in accordance with the body's need. Two examples may be given to

Table 1. Definition of a vitamin

(a)	An organic compound required in small amounts for complete health and and wellbeing
(b)	Not utilized primarily to supply energy or as a source of structural tissue components
(c)	Function is to promote physiological processes vital to continued existence
(d)	Cannot be synthesized by the organism and must be supplied de novo
(e)	Deficiency causes a well-defined disease that is prevented or cured by the appropriate vitamin

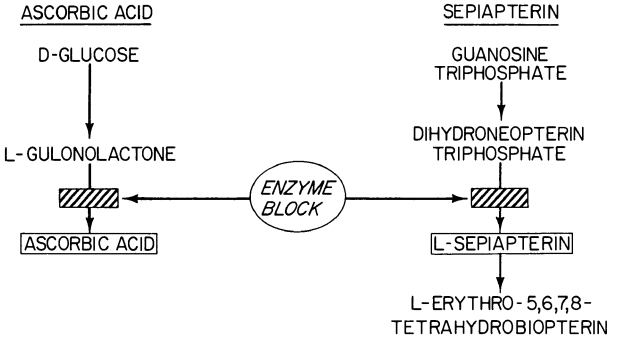

Fig. 1. Simplified metabolic pathways outlining the basis for the requirements for ascorbic acid in man and for sepiapterin in an unusual case

emphasize the impact of an enzyme deletion and, in consequence, the essentiality of vitamins in the human diet. First, in addition to nonhuman primates, guinea pigs, fishes, and flying mammals, humans are dependent on dietary sources of ascorbic acid. This has been traced to a loss of the enzyme L-gulonolactone oxidase, which catalyzes the last step in the conversion of glucose to ascorbic acid (Fig. 1). Thus, the development of symptoms of scurvy with a continued inadequate ascorbic acid intake might be considered to be the consequence of a "hereditary metabolic disease." However, this inborn error in synthesis of ascorbic acid is a dominant genetic trait for *all* members of the human population (NISHIKIMI and UDENFRIEND 1977). The second and more unusual case, also illustrated in Fig. 1, is based on a recent report of a patient with atypical phenylketonuria. Of significance here is that the coenzyme for phenylalanine hydroxylase, tyrosine-3-hydroxylase and tryptophan-5-hydroxylase is L-erythro 5,6,7,8-tetrahydrobiopterin (THB). This latter compound is normally formed through a series of metabolic steps from guanosine triphosphate (GTP) (BROWN 1971). However, NIEDERWIESER et al. (1979) discovered that a 6-month-old female infant presenting with mental retardation and elevated serum phenylalanine lacked the capacity to convert dihydroneopterin to sepiapterin (Fig. 1). Oral administration of sepiapterin reduced serum phenylalanine and improved the clinical condition, indicating a dietary requirement by this infant for this compound. The latter could be converted to the cofactor, THB, and, thus, the metabolism of phenylalanine was restored to a more normal state. Hence, as a consequence of this enzymatic inadequacy, sepiapterin becomes a vitamin for this specific patient. This recent clinical study underscores the metabolic basis for the requirements for vitamins and indicates that they are determined by the genetic machinery of cells.

Table 2. Generic descriptors and trivial names for vitamins and related compounds in human nutrition (IUNS committee on nomenclature). (Sumarized from IUNS 1970)

Vitamin term	Generic use (Compounds with qualitatively the biological activity of):
Fat-soluble vitamins and related compounds	
Vitamin A	β-ionone derivatives with retinol activity
Provitamin A carotenoids	Carotenoids with β-carotene activity
Vitamin D	Steroids with cholecalciferol activity
Vitamin E	Tocol and tocotrienol derivatives with activity of α-tocopherol
Vitamin K	2-methyl-1,4 naphthoquinone and derivatives with phylloquinone activity
Water-soluble vitamins and related compounds	
Folacin	Folic acid and compounds with folic acid activity (e.g., THFA)
Niacin	Pyridine 3-carboxylic acid and derivatives with nicotinamide activity
Riboflavin (B_2)	
Thiamine (B_1)	
Vitamin B_6	2-methylpyridine and derivatives with pyridoxine activity
Vitamin B_{12}	Corrinoids exhibiting cyanocobalamin activity
Vitamin C	Compounds with ascorbic acid activity
Pantothenic acid	
Biotin	
Choline	

Fourteen vitamins have now been identified in human nutrition. The trivial names and generic descriptors for these vitamins, and their related compounds are listed in Table 2 (IUNS 1970). These are the only compounds currently recognized as being vitamins for humans.

C. Functions of Vitamins

The vitamins participate in a wide variety of biochemical and physiological processes. This topic has been the subject of numerous reviews but a summary of the major functions of the vitamins might be given here. Thus, as outlined in Table 3, the B-complex vitamins serve as precursors of coenzymes in many enzyme systems (SHIVE and LANSFORD 1980). Each coenzyme participates in the catalysis of a specific enzyme reaction and these are associated with the metabolism of carbohydrates, lipids, proteins, and/or nucleic acids. For this reason the utilization of energy substrates, formation of cellular constituents, such as proteins and deposition of energy reserves (carbohydrate, triacylglycerols), and the integrity of the repair and defense mechanisms involve participation of vitamins. In addition, a single metabolic pathway, such as that associated with the oxidation of an amino acid, may require simultaneously many of the vitamins, in their active coenzyme forms.

Table 3. Summary of major functions of vitamins

Function	Vitamin
1. Precursor of coenzyme	Biotin Nicotinic acid Pantothenic acid Vitamin B_6
2. Transmission of genetic information (i.e., transcription, posttranslation)	Vitamin A Vitamin K Vitamin D
3. Antioxidant and electron transport	Vitamin E Vitamin C
4. "Specialized" properties	
Photosensitive reactions	Vitamin A
Neural transmission	Thiamin?
Macromolecular structure	B_6?

A second function met by some vitamins is related to the expression of genetic information. Vitamins might affect this process via (1) the synthesis of mRNA and/or its transport to the cytoplasm *(transcription);* (2), the formation of proteins at the *translation* stage of protein synthesis, including involvement of ribosomes, protein factors, and amino-acyl-tRNA; (3) the addition of a prosthetic group to a newly made protein *(posttranslation modification);* or (4) by affecting a cell surface constituent which might regulate cell function, division, or differentiation, an example being the differentiation of epithelial cells by vitamin A (WOLF 1980). Vitamin D, via its conversion to 1,25 dihydrocholesterol vitamin D_3, induces the transcription of a specific mRNA(s) that codes for synthesis of a protein(s) responsible for intestinal calcium transport (DE LUCA 1980); vitamin K participates in the posttranslational modification of prothrombin precursors, involving carboxylation of glutamate residues, with formation of active prothrombin (OLSON 1980).

Vitamins E and C carry out an antioxidant or electron transport function (JOHNSON 1979). Antioxidants reduce substances that help maintain a low redox potential in tissues. In reference to vitamin E, cellular lipids are protected from free-radical attack and this vitamin interferes with the chain reactions by which these reactive molecular species are multiplied. In relation to normal physiology, the main electron transfer role of vitamin C is in the reduction of metals so that the associated enzyme system can act in the transport of molecular oxygen, as in the hydroxylation of proline during collagen synthesis and in the formation of the catecholamine, noradrenaline (JOHNSON 1979).

Finally, a number of vitamins exhibit specialized functions that cannot be grouped into one of the three major categories above (Table 3). An example of this is vitamin A, which is associated with the formation of rhodopsin, the light sensitive pigment of the retina (WOLF 1980). Furthermore, a role for thiamine triphosphate in nerve excitation has been proposed (BARCHI 1975) and also it is possible that pyridoxal phosphate might serve to modulate the binding of receptor-steroid complexes to cell nucleii (CIDLOWSKI and THANASSI 1979).

From this overview of the various functions of vitamins, it is clear that these nutrients play a vital role in cellular metabolism and the maintenance of physiological processes. For these reasons, vitamin deficiencies or excesses can lead to changes in the status of the immune, detoxification, protective, repair, and differentiation systems of body cells and organs. Such changes underline the clinical manifestations of inappropriate dietary intakes of vitamins and EXTON-SMITH (1980) has discussed and described many of the signs and symptoms of vitamin inadequacies in the elderly person. Therefore, the clinical features of the various vitamin deficiency diseases will not be repeated in this chapter.

D. Some Aspects of Utilization of the Vitamins

In addition to the dietary content of vitamins, the supply of these nutrients to the cells and organs of the host depends upon the co-operative action of various physiological processes, including digestion, absorption, inter- and intracellular transport, activation and/or conversion to active forms, and finally their degradation and elimination via excretory pathways (Fig. 2). These processes are regulated by complex mechanisms, involving both the nervous and endocrine systems. Furthermore, these major phases of vitamin utilization are integrated at the whole body level in order to minimize their toxic accumulation when ingested in excess of physiological needs or to help conserve body stores when the intake is deficient. Furthermore, the conversion of some of the vitamins to their active form is specifically organ dependent. Vitamin D provides an example of this, as shown in Fig. 3 (DE LUCA 1980). Hence, an adequate vitamin D status depends upon the coordinated activities of two organs, the liver and kidney, and is affected by several hormones (CHRISTAKOS and NORMAN 1978) and the concentration of phosphate ions in kidney cells (TANAKA and DE LUCA 1973). Whether changes in specific cells or organs

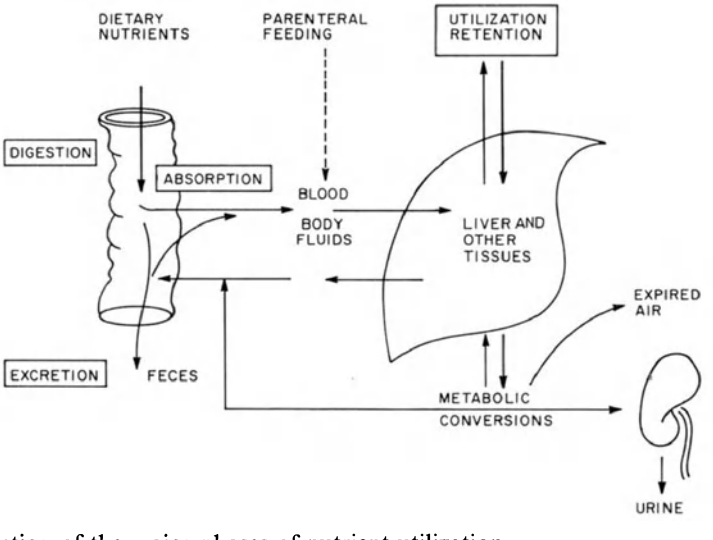

Fig. 2. Schematic depiction of the major phases of nutrient utilization

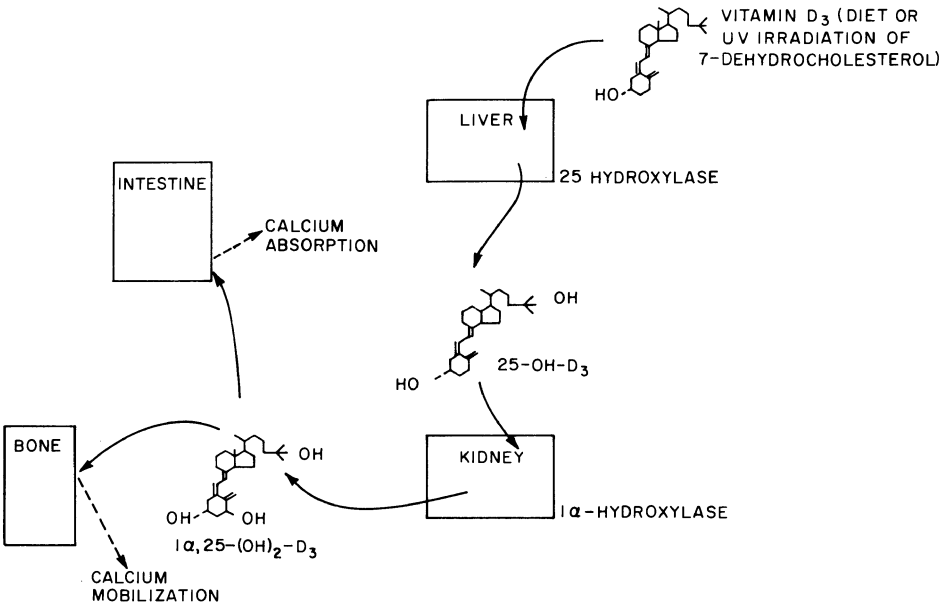

Fig. 3. A schema indicating the role of the liver and kidney in the metabolism of vitamin D and conversion to its active form (1,25-dihydroxycholecalciferol)

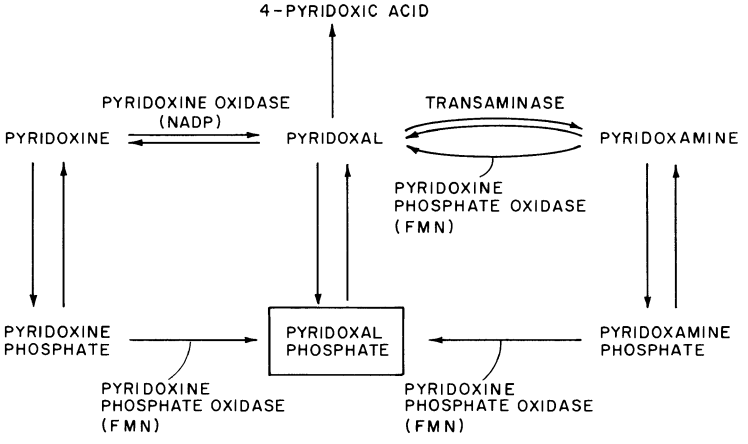

Fig. 4. Outline of conversion of B_6 active form to pyridoxal phosphate, showing participation of other vitamins in the conversion. SAUBERLICH (1968)

during senescence alters the metabolism of, and possibly the quantitative need for, vitamins or their dietary precursors is important to explore. The specific case of vitamin D will be discussed below.

The conversion of a specific vitamin to its active form and/or its utilization by cells may also depend upon the adequacy and level of intake of other vitamins and nutrients. For example, as shown in Fig. 4, the conversion of the various B_6 vitamins to the coenzyme form, pyridoxal phosphate, involves the participation of

Table 4. Factors that may affect nutrient utilization and requirements. (Adapted from BROWN 1972)

Delivery to cells and organs
Chemical forms in the diet
Diet constituents and composition
Absorption – digestion
Cellular and intracellular transport
Conversion to metabolically active form
Loss of nutrients
Renal clearance
Intestinal secretion and elimination
Oxidation and metabolism
Chemical or drug inactivation
Alterations in cellular and organ function
Size and activity of organs
Binding of enzymes

flavin-dependent enzymes (SAUBERLICH 1968). Hence, the riboflavin status of cells might affect the availability of pyridoxal phosphate for maintenance of cellular reactions. Indeed, these metabolic interrelationships between riboflavin and pyridoxine might explain why administration of either of these vitamins might reverse the clinical symptoms of angular stomatitis and glossitis in malnourished subjects (LAKSHNI and BAMJI 1976). Similarly, the interconversion of folate coenzymes involves an enzyme reaction in which methylcobalamin (B_{12}) is a cofactor (HERBERT 1976). A final example that should be mentioned is that the metabolism of vitamin B_6 is affected by the level of dietary protein intake (LINKSWILER 1978). It is obvious, then, that the utilization of a specific vitamin can be influenced by the intake and metabolism of other nutrients. These interactions make a precise assessment of the influence of adult age per se on vitamin utilization, and requirements, a complex undertaking.

In summary, various factors will determine the vitamin status of the individual and some of these factors are listed in Table 4 (BROWN 1972). The importance of these various factors may change with age and the health status of the adult. For example, the interaction between the coenzyme form of a vitamin is dependent upon the surface and spatial configuration of its apoenzyme (e.g., SCRIVER 1973). It would be of interest to know whether age-dependent molecular changes in apoenzymes (ROTHSTEIN 1975, 1977) might lead to changes in the normal steric relationship between the coenzyme form of a vitamin and its apoenzyme. This topic has received little investigation but molecular changes in enzymes are a basis for a number of vitamin-dependent disease states (SCRIVER 1973).

The absorption of many vitamins from the gastrointestinal tract occurs via active and regulated processes (ROSE 1981) and their subsequent movement throughout the circulation may also involve participation of transport proteins (e.g. JACOB et al. 1980; WOLF 1980). Unfortunately, the influence of aging per se on vitamin absorption has received little attention. For example, BHANTHUMNAVIN et al. (1974) studied folic acid absorption by everted gut sacs from rats and ob-

served no change in the rate of disappearance of labeled pteroylmonoglutamate from these sacs with advancing old age. Their observations agree with the findings of HURDLE et al. (1966) in human subjects. However, dietary folate exists in polyglutamate forms (KRUMDIECK 1976; COVEY 1980) and it appears that this form enters the intestinal cell prior to its deconjugation. It would be important then to explore, in some detail, the absorption and fate of the various dietary forms of folacin in the aging adult, particularly in view of the conclusion that folate deficiency is widespread in some populations of elderly people (e.g. BAILEY et al. 1979). Also, it is not known whether the absorption and subsequent utilization of niacin or riboflavin when ingested in their coenzyme forms (NAD and NADH; FAD and FMN, respectively) as compared to their free forms, are affected by the age of the subject. Finally, the requirement for vitamin A can be met through ingestion of its precursor β-carotene. The bioavailability of this provitamin is less than that of retinol (NRC/NAS 1980), and it would be worthwhile to determine whether the conversion of β-carotene to retinol is affected by advancing old age.

E. Vitamin Status of the Elderly

Having discussed briefly the functions and metabolism of vitamins, it is appropriate to turn now to considerations of vitamin status and requirements in older people.

A large number of surveys have been conducted to assess the nutritional status of institutionalized and noninstitutionalized populations of elderly subjects. Because many of these studies have been reviewed (EXTON-SMITH 1980; FLEMMING 1981; BRIN and BAUERNFEIND 1978) little purpose is served in presenting an extensive account of various findings. However, few surveys have been sufficiently comprehensive to provide a definitive assessment of the extent to which the health and function of the subjects has been actually affected by a change in their vitamin status. Although many of the studies suggest that there is an increased risk of vitamin deficiencies in the elderly groups examined, overt manifestations of vitamin deficiency disease are generally uncommon. Thus, low levels of leucocyte ascorbic acid (LAA) have been reported by several observers, indicating reduced body stores of the vitamin (e.g., ANDREWS et al. 1969; BURR et al. 1974).

It is unclear in many cases whether the diminished blood levels, as shown in Table 5, for example, are due to an inadequate intake of foods that contain ascorbic acid or to the processing and cooking of foods. However, in the study of BURR

Table 5. Plasma and leucocyte ascorbic acid levels in different age groups of male subjects (Summarized from BURR et al. 1974)

Group (age)	Plasma ascorbic acid (mg dl^{-1})	Leucocyte ascorbic acid ($g/10^6$ cells)
65–69	0.30	19.9
70–74	0.27	17.7
75–79	0.25	16.8
80–84	0.21	17.0
85+	0.25	15.1

Table 6. Effect of thiamine and riboflavin supplementation on the biochemical assessment of vitamin nutriture in older women. (Summarized from HARRILL and CERVONE 1977)

	Age group (years)			
	76–85		86–90	
	NS	S	NS	S
Thiamin				
Intake (mg day^{-1})	0.70	6.24	0.64	5.69
Urinary thiamin (% low values)	20	0	69	0
Riboflavin				
Intake (mg day^{-1})	1.2	5.8	1.30	4.14
Urinary riboflavin (% low values)	20	0	38	0

NS, not supplemented; S, supplemented

et al. (1974) the consumption of fresh fruits appeared to be the major but not the only factor in determining LAA levels.

Considerable interest has focused on the folate status of older people, and HERBERT (1967) has suggested that folate deficiency is a common nutritional problem. A number of surveys (READ et al. 1965; BATATA et al. 1967; BAILEY et al. 1979) indicate that biochemical evidence of a folate inadequacy is widespread in elderly subjects. Similarly, for other B vitamins, including thiamine (BRIN et al. 1965; HARRILL and CERVONE 1977), riboflavin (HARRILL and CERVONE 1977; Dibble et al. 1967), and B_{12} (EXTON-SMITH 1980), studies suggest that significant numbers of elderly people may not be in an adequate state of nutrition. In the study by HARRILL and CERVONE (1977), individuals who received vitamin supplements were at lower risk, as suggested by their findings summarized in Table 6.

As reviewed by BRIN and BAUERNFEIND (1978), an inadequate vitamin status might be expressed as one or more nonspecific complaints such as malaise, irritability or somnolescence, loss of appetite and weight, and impaired psychological functioning. An analysis of these nonspecific symptoms are not included in surveys and they vary among individuals, which increases the difficulty of assessing the clinical and public health of much of the available data on the vitamin status in the elderly populations that have been studied.

EXTON-SMITH (1980) has pointed out that vitamin D deficiency leading to osteomalacia in old people is often multifactorial in origin; a low dietary intake of vitamin D, limited exposure to sunlight, inadequate absorption or impaired conversion of 25-hydroxycholecalciferol to the active 1,25-dihydroxycholecalciferol due to a decline in renal function in old age, or a combination of these can contribute to development of vitamin D deficiency in elderly people.

F. Methods for Estimating the Vitamin Requirements in Adults

The assessment of vitamin status requires, in part, a knowledge of the quantitative requirements for vitamins. An estimation of these is based on the same principles as are applied in the determination of requirements for other classes of essential

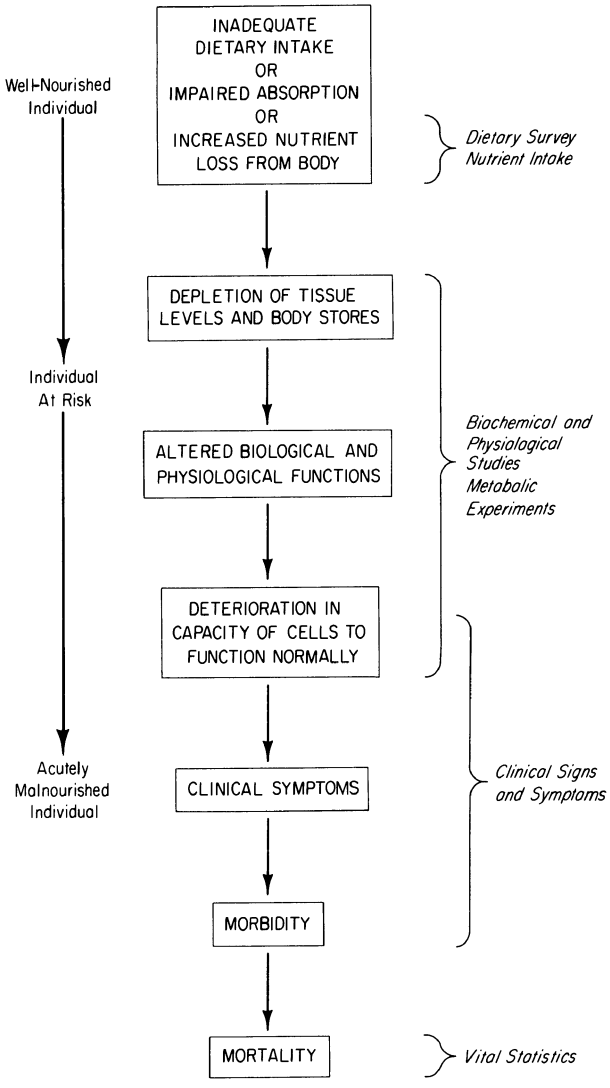

Fig. 5. Major stages in the development of nutritional deficiency disease. Nutritional deficiency begins with an inadequate availability of a nutrient to body cells and organs. This inadequacy may be due to various factors including low dietary intakes or relatively high rates of loss from the body. Subsequently biochemical deterioration occurs with the appearance of clinical symptoms. Knowledge of these various phases aids the design of different approaches that may be used to assess human nutrient requirements. BEATON and PATWARDHAN (1976)

nutrients. Briefly, the general approach that is taken in human studies is based upon the sequence of events thought to occur with the progressive development of a nutritional deficiency. This sequence is schematically depicted in Fig. 5 and indicates that an approach might be to determine by a survey of diets the vitamin intakes in populations who are adequately nourished. The estimate of intake may then be compared with nutrient intake data obtained from individuals in populations where a vitamin deficiency exists. This method will give an estimate of the approximate range of vitamin intake that is associated with health maintenance. However, this approach does not offer an exact method for estimating minimum requirements for a vitamin and it is difficult to determine precisely the level of vitamin intake by populations of free-living subjects.

Table 7. Stages in development of vitamin deficiency. (BRIN 1964)

Stage	Features
Preliminary	Diminution of tissue stores of vitamin (from inadequate dietary intake, malabsorption, abnormal metabolism). Decrease in urinary excretion of vitamin
Biochemical	Reduction in enzyme activity due to coenzyme insufficiency. Negligible urinary excretion of vitamins
Physiological	Loss of appetite and weight, insomnia or somnolence, irritability, evidence of impaired psychological function
Clinical	Exacerbated nonspecific symptoms plus appearance of specific deficiency syndrome
Anatomical	Clear specific symptoms with pathological changes in tissue that may be fatal unless patient is treated

Table 8. Estimates of the minimum thiamin requirement in adult man as determined in various studies and with different criteria

Criteria	Mean requirement[a]	Author
Clinical deficiency	0.18	ELSOM et al. (1942)
Urinary B_1 clearance	0.35	MELNICK (1942)
Comprehensive	0.23	KEYS et al. (1943)
CMI[b], comprehensive	0.18	HORWITT and KREISLER (1949)
ETK[c], Urinary excretion	0.3	SAUBERLICH et al. (1979)

[a] Mg per 1,000 kcal diet
[b] Carbohydrate metaboloism index
[c] Erythrocyte transketolase activity

If, however, the dietary content of a vitamin is low and if this diet continues, then biochemical and pathological changes will develop eventually. The various stages in the development of a vitamin deficiency, as described earlier by BRIN (1964), are summarized in Table 7. Thus, these changes may be identified as altered activities of blood enzymes or by lower levels of excretion of the vitamins, or their catabolites, in urine (for review see SAUBERLICH et al. 1974). Because some of these changes can be readily measured, they provide a basis for the design of metabolic studies conducted to determine minimum vitamin requirements in human subjects. In these metabolic studies volunteers receive experimental diets in which the level of the nutrient under study is altered during a specific diet period. In this way, it is possible to determine the minimum intake level of the nutrient that is necessary to meet a given criterion, such as the maintenance of a normal blood level, rate of excretion in urine, or in some cases the amount just sufficient to prevent appearance of symptoms of deficiency. For example, Table 8 presents results obtained in various experiments concerned with estimation of the thiamine requirement in adult subjects. Various criteria for assessing the thiamine requirement were used in the different experiments and, as shown here, there is general agreement for the requirement estimation obtained. However, the choice of different criteria may re-

sult in wide differences in a requirement value and this has been discussed by MOORE (1957) with respect to assessment of vitamin A requirements in experimental animals.

Although the metabolic study approach is a more precise method than the dietary method mentioned above, these experiments with humans are often laborious, time-consuming, and expensive. Furthermore, they may involve use of monotonous experimental diets and impose restrictions on volunteers, making it difficult for them to undertake for extended periods. For this reason such studies are frequently of short duration and usually involve small population groups. Thus, the data obtained may not be easily extrapolated for general application to large free-living populations. Nevertheless, this method has been extensively used in the determination of the vitamin requirements of humans.

For some of the vitamins, it has not been possible to utilize these methods and in that case, it may be necessary to rely on an extrapolation of data obtained in animal experiments or on epidemiological studies. In any event, it must be emphasized that few studies have been carried out directly in elderly subjects (e.g. HORWITT 1953) and the present estimates are derived almost entirely from the more extensive studies conducted in younger, healthy adults.

This brief survey of approaches used to estimate the vitamin needs in adult subjects can be supplemented with more detailed discussions for individual vitamins that have been presented in a number of reports (e.g. NRC/NAS 1980; FAO/WHO 1967, 1970; DHSS 1969; DGE 1975). The purpose of determining the mean requirement for a given vitamin in the population group of concern is to provide a basis for developing a recommended dietary allowance (RDA) and the steps involved in this are shown in Table 9. It follows that, in addition to estimates of the mean requirement for a vitamin in a given age group, the extent to which requirements vary among apparently similar individuals within that population must be known. Based on this knowledge an RDA can be set so that it covers the needs of nearly all healthy subjects within the population (e.g. BEATON and PATWARDHAN 1976). Therefore, the actual requirement for most members of the population will be less than the RDA because this should meet the needs of those few individuals with the highest requirement.

By way of an example, Table 10 presents the recent allowances for vitamins for adults of differing age, as recommended by the U.S. Food and Nutrition Board (NRC/NAS 1980). The reader may wish to consult the report by this expert group for further details concerning the philosophy applied in setting and arriving at the allowances, and of the way in which they are to be used in the evaluation of dietary survey data and the development of adequate diets. However, it is important to emphasize that the dietary allowances are for healthy people and they are not intended to represent therapeutic intakes for treatment of disease conditions. Thus, they represent intakes that should prevent the development of nutritional deficiency disease and maintain nutritional status in most healthy individuals. A diet based on a wide selection of foods will assure vitamin intakes that equal or exceed these allowances but vitamin supplements supplying levels equivalent to about the recommended daily allowances may be considered an "insurance" against the possible development of deficiencies arising from a poorly selected diet (e.g. JUKES 1979). Vitamin intakes that are considerably in excess of these allowances cannot be recommended as a broad public health policy.

Table 9. Steps used to estimate allowances for nutrients, including vitamins

Step	Description
1	Determination of mean requirement and variability within population
2	Increasing average requirement by amount sufficient to cover needs of nearly all individuals
3	Increasing allowance to accont for inefficient utilization of nutrients consumed
4	Using judgment in interpreting and extrapolating allowances when data are limited

Table 10. U.S. food and nutrition board (NRC/NAS 1980) recommended dietary allowances and esimated safe and adequate daily dietary intakes for vitamins[a]

	Females		Males	
	23–50 years	51 + years	23–50 years	51 + years
Recommended Dietary Albwance				
Vitamin A (μg RE)[b]	800	800	1,000	1,000
Vitamin D (μg)[c]	5	5	5	5
Vitamin E (mg α-TE)[d]	8	8	10	10
Vitamin C (mg)	60	60	60	60
Thiamin (mg)	1.0	1.0	1.4	1.2
Riboflavin (mg)	1.2	1.2	1.6	1.4
Niacin (mg NE)[e]	13	13	18	16
Vitamin B_6 (mg)	2.0	2.0	2.2	2.2
Folacin (μg)[f]	400	400	400	400
Vitamin B_{12} (μg)	3.0	3.0	3.0	3.0
Safe and Adequate Intake[g]				
Vitamin K (μg)	70–140		70–140	
Biotin (μg)	100–200		100–200	
Pantothenic acid (mg)	4– 7		4– 7	

[a] The allowances are intended to provide for individual variations among most normal persons as they live in the United States under usual environmental stress. Diets should be based on a variety of common foods in order to provide other nutrients for which human requirements have been less well defined

[b] Retinol equivalents. 1 retinol equivalent = 1 μg retinol or 6 μg carotene. See text for calculation of vitamin A activity of diets as retinol equivalents

[c] As cholecalciferol. 10 μg cholecalciferol = 400 IU of vitamin D

[d] α-tocopherol equivalents. 1 mg α-tocopherol = 1 α-TE. See text for variation in allowances and calculation of vitamin E activity of the diet as α-tocopherol equivalents

[e] 1 NE (niacin equivalent) is equal to 1 mg niacin or 60 mg dietary tryptophan

[f] The folacin allowances refer to dietary sources as determined by *Lactobacillus casei* assay after treatment with enzymes (conjugases) to make polyglutamyl forms of the vitamin available to the test organism

[g] Because there is less information on which to base allowances, these figures are provided in the form of ranges of recommend intakes

It is important to point out that the accuracy and precision of the various methods for estimating human requirements are usually not known. Rarely are replicate studies conducted within the same individual to determine the reproducibility of the estimated requirement for a given nutrient within an individual during more extended periods of time.

Furthermore, there is still insufficient knowledge for some vitamins so that recommended allowances cannot be made. In this case, it is only possible to suggest a range of intake that is thought to be sufficient to meet the requirements of a given population group. This safe and adequate range of intake is shown in Table 9 for a number of vitamins, in addition to those for which an RDA has been proposed.

G. Factors Affecting Vitamin Requirements in Elderly People

In considering the vitamin requirements of older people, it is particularly important to emphasize that these requirements are affected by various factors, in addition to age, and they are listed in Table 11. They have been divided according to host, and environmental and age (dietary) factors.

A fundamental component of variation in requirements is that introduced by genetic differences. The inborn errors of metabolism are extreme examples of the nutritional implications of genetic variation in humans. However, in terms of practical human nutrition, it is generally thought that the effects of various environmental, physiological, psychological, and pathological influences are of greater importance in determining the variability in vitamin needs among groups of individuals. For example, the growing infant and child require higher nutrient intakes, per unit of body weight, than the young adult. These needs are relatively high during early growth and development, and they fall by adulthood. However, other than for energy, where the daily requirement declines due to lowered physical activity (SHOCK 1972), it is uncertain whether the requirement for one or more specific vitamin changes in the healthy individual during passage of the adult years. More significantly, a characteristic of aging is increased disease incidence and mor-

Table 11. Agent, host, and environmental factors that influence nutrient requirements and nutritional status in the elderly

Agent (dietary) factors
1. Chemical form of nutrient
2. Energy intake
3. Food processing and preparation (may increase or decrease dietary needs)
4. Effect of other dietary constituents
Host factors
1. Progressive old age
2. Sex
3. Genetic makeup
4. Pathological states
(a) Drugs
(b) Infection
(c) Physical trauma
(d) Chronic disease, cancer
5. Psychological states
Environmental factors
1. Physical (unsuitable housing, inadequate heating)
2. Biological (poor sanitary conditions)
3. Socioeconomic (poverty, dietary habits and food choices, physical activity)

bidity and these are conditions that have major practical implications for the vitamin needs and nutritional status of the elderly and how older people might differ from younger adults with respect to vitamin requirements for health. Stressful stimuli, such as a general or localized infection, physical trauma, or stimuli of psychological origin have profound effects on nutrient metabolism (e.g., BEISEL 1977). Thus, early in the infectious episode there is an increased rate of synthesis of immunoglobulins and of other proteins characteristic of the early metabolic and immune responses to an infectious agent. This is followed by a net catabolic response that results in increased losses of body nitrogen and some vitamins and minerals and in decreases in blood levels of these nutrients. Furthermore, gastrointestinal absorption of nutrients may be compromised, food intake may decline (e.g., BEISEL et al. 1967), and the net result of these various responses is a depletion of body stores. This results in an increased need for nutrients during the recovery phase to promote rapid recovery and to compensate for the earlier losses. However, while the requirement for many essential nutrients is undoubtedly higher than under conditions of full health, there are inadequate quantitative data to help determine how much nutrient intakes should be increased to meet the additional nutritional demands created by these unfavorable conditions that are frequently experienced by elderly populations.

In addition, many drugs may have profound effects on vitamin requirements by decreasing their absorption or by altering their utilization and metabolism (ROE 1976; HATHCOCK and COON 1978; MUELLER 1980). The effects of drugs on nutrient requirements will depend upon the dose, period of administration, and the presence of other drugs that may have synergistic effects, further affecting nutrient needs. Finally, reduced appetite is a frequent consequence of disease and/or drug therapy and this will exaggerate the effects of the disease process and drug treatment on the individual's nutritional status, particularly if the diet has been marginally adequate to begin with.

For many of these factors their quantitative effects on vitamin requirements are not known and they are likely to have a varying impact on different individuals. However, a knowledge of their quantitative effects is critical for developing rational and safe dietary allowances for older adults.

Table 12. Some important factors that may lead to inadequate nutrition in the elderly

Apathy
Isolation, psychological stresses
Physical disability immobility at home, poor vision, arthritis
Disease, infection, cancer, cardiovascular abnormalities, diabetes
Malabsorptive and gastrointestinal disorders and discomfort (pancreatic insufficiency, bacterial stasis, etc.)
Economic difficulties
Mental deterioration
Inadequate knowledge of dietetic principles, food fads, poor dietary habits
Alcoholism
Drug reactions
Altered requirements?
Unsuitable housing

In the above context, these various factors have important implications for the nutritional status of the elderly and some conditions that are particularly relevant for this age group are listed in Table 12. Physical and mental disabilities affect the mode of living and this may lead to changes in dietary pattern and a deterioration of nutritional status. Underlying medical problems, emotional disturbance, loneliness, and poverty are all factors that diminish appetite and the ability to maintain a diet adequate in vitamins. Thus, risk of deficiencies will increase under these circumstances and these are frequent causes for inadequate vitamin nutrition in elderly people. Furthermore, because energy requirements and intake are reduced even in healthy groups (SHOCK 1972), this means that adequate intakes of vitamins may require a change in the dietary choices toward food of increased nutrient density. This is further compounded by changes in taste and the deterioration in the health of the oral tissues with increased old age.

H. Summary and Conclusions

Vitamins play multiple roles in the operation of biochemical and physiological processes and, thus, are required throughout life for maintenance of health. In this chapter their functions and requirements have been briefly reviewed, with specific reference to the aging adult. The available data on the vitamin requirements of older, as compared with younger adults is extremely limited, but numerous nutritional surveys have shown that elderly persons are at increased risk of vitamin deficiencies. Various factors in addition to age per se influence the utilization of vitamins and determine the status of vitamin nutriture of the individual. These factors include diseases, drug therapy, and various social, economic, and psychological factors. The extent to which optimum function and well-being might be compromised by inadequate vitamin intakes in large numbers of the elderly is uncertain. However, the relative ease by which these inadequacies could be corrected through changes in diet and/or supplementation suggests that it would be prudent to expand greatly upon current knowledge concerning vitamin metabolism and requirements in elderly subjects under various conditions of health and in disease.

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Human Aging and Obesity*

A. STUNKARD

A. Introduction

This chapter describes our current understanding of the relationship between human obesity and aging. Despite the widespread belief that there are strong links between obesity and aging, there have been surprisingly few studies of this relationship. Studies of experimental animals, on the other hand, although they have seldom dealt with obesity as such, have provided strong evidence that a critical intervening variable – nutrition – links obesity and aging. These studies have shown that radical restriction of food intake early in life can increase the life span of rodents by a factor of 2 and even 3 (MCCAY 1953). Even restriction of food intake in the mature animal can increase the life span, although not to the same degree (ROSS 1972). Furthermore, restriction of food intake increases the life expectancy of two quite different forms of experimentally obese animals – the genetically obese *(ob/ob)* mouse (LANE and DICKIE 1958) and the dietary obese rat (SCLAFANI 1980). The fact that death, when it comes, is due to a variety of causes (ROSS and BRAS 1974), suggests that it is a result of some aspect of the aging process itself and not due to some specific vulnerability, such as to neoplasia or vascular disease.

Compared to the careful experimental study of the influence of nutrition on aging in animals, information about the influence of nutrition and obesity on aging in humans is sparse indeed. The present chapter reflects this state of the art. It consists of a selective look at four aspects of research in humans. First, it considers the relationship between age and obesity. Second, it describes a study of the effects of changes in weight status from childhood to adult life upon blood pressure. Third, it considers in somewhat greater detail the relationship between obesity, mortality, and coronary heart disease, including newer challenges to the old orthodoxy that any degree of overweight has deleterious health consequences. Fourth, it deals with some aspects of treatment for obesity.

B. The Relationship of Age and Obesity

Age is strongly related to obesity in humans, both among the young and the old. Among the young the salient finding is that obesity tends to persist. In a study in

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Hagerstown, Maryland, 86% of a group of overweight boys became overweight men, as compared to only 42% of boys of normal weight (ABRAHAM and NORDSIECK 1960). Even more striking differences in adult weight status were found among girls: 80% of overweight girls became overweight women, compared to only 18% of average weight girls. A later study showed that the few overweight children who reduced successfully had done so by the end of adolescence. The odds against an overweight child becoming a normal weight adult, which were 4:1 at age 12, rose to 28:1 for those who had not reduced during adolescence (STUNKARD and BURT 1967). A more recent study, which used a longer time interval (35 years) and, unfortunately, a different (more rigid) criterion for obesity, found the difference in adult weight status continuing to increase: 63% of obese boys became obese men, compared to only 10% of normal weight boys (ABRAHAM et al. 1971).

The reason for this remarkable persistence of obesity among the young has been ascribed to the fact that adipose tissue of a large percentage of them is hyperplastic. The adipose tissue of obese persons may contain as many as five times more fat cells than the adipose tissue of persons of normal weight. Although a thorough consideration of this point is beyond the scope of this chapter, this reason for the persistence of obesity seems well established and the interested reader is referred to SJÖSTRÖM'S (1980) discussion of this issue.

Whereas increasing age is associated with the persistence of obesity among the young, it is associated with an increasing prevalence of obesity among adult humans. A careful study of a well-selected sample of 1,660 adults in New York City showed a threefold increase in the prevalence of obesity between the ages of 20 and 50 (MOORE et al. 1962). At age 50 the prevalence of obesity fell sharply, presumably due to the high mortality of obese persons as a result of cardiovascular diseases in the older age groups.

C. Effects upon Blood Pressure of Change in Weight Status from Childhood to Adult Life

An important feature in the study of change in weight status with aging by ABRAHAM et al. (1971) was the examination of the relationship between such changes and the prevalence of hypertension. Three basic weight change patterns were examined:

1. Stable: obese as children, obese as adults
2. Decrease: obese as children, normal weight as adults
3. Increase: thin as children, obese as adults

Table 1 shows the prevalence of hypertension by change in weight status from childhood to adulthood. It reveals that subjects whose weight status did not change during this interval showed the expected prevalence of hypertension of about 20%. It is particularly worthy of note that obese adults who had been obese as children showed no greater prevalence of hypertension. By contrast, those obese adults who had been thin as children showed a strikingly high prevalence of hypertension. Finally, the most favorable outcome was among those few children who had been either stout or obese and who had become thin adults. None of the 12 had elevated blood pressures.

Table 1. Prevalence of hypertension by change in weight status from childhood to adulthood. (ABRAHAM et al. 1971)

	Weight		Percent hypertensive	Number
	Childhood	Adulthood		
Stable	Thin	Thin	21	112
	Normal	Normal	24	119
	Stout	Stout	23	52
	Obese	Obese	20	35
Decrease	Normal	Thin	16	94
	Stout and obese	Normal	24	37
	Stout and obese	Thin	0	12
Increase	Thin	Normal	31	64
	Thin	Stout	47	38
	Thin	Obese	75	8
	Normal	Stout	22	108
	Normal	Obese	36	6

D. The Relationship Between Obesity, Mortality, and Coronary Heart Disease

It has been an article of faith for many years that obesity shortens the life span of humans and that at least part of this effect is exerted through the influence of obesity as a coronary risk factor. Very recently serious questions have been raised about this relationship and it has become the subject of vigorous controversy. This controversy is far from settled and in this chapter we will present arguments on both sides of the question, with some suggestions as to where the truth may lie.

The major age-associated affliction of humans is cardiovascular disease, with particular reference to coronary heart disease. Coronary heart disease alone accounts for half of all deaths in the United States as well as in a number of other affluent countries. As we have noted, it has long been believed that obesity contributes to coronary heart disease. The origins of this belief go back many years, to the pioneering work of the American life insurance companies, which has been reported in publications beginning in the early years of this century (Society of Actuaries 1913), and extending until relatively recently (Society of Actuaries 1960). These studies showed a linear relationship between the extent of overweight and mortality, particularly among young men (ARMSTRONG et al. 1951; DUBLIN 1953; MARKS 1960). These authors reported an increase in mortality as great as 80% among obese persons in the age group of 20–29 and estimated that as little as 20% overweight led to a 40% increase in coronary heart disease.

Although the life insurance data have been criticized from several points of view, including particularly the unrepresentativeness of their samples, some studies of more representative samples appear to support their conclusions. The early reports of the Framingham study, for example, noted that overweight contributed to increased overall mortality and to an increased incidence of coronary heart disease. KANNEL and GORDON (1974) predicted that a 20% reduction in weight of obese persons would lead to a 40% reduction in coronary heart disease and concluded

that "in affluent societies survival is more likely in those as lean as possible." Similarly, COMSTOCK et al. (1966) reported a relationship between obesity and mortality in an epidemiological investigation of 25,000 persons. Even studies that did not find an overall relationship between obesity and coronary heart disease noted it in some groups. CHAPMAN et al. (1971), for example, reported that overweight predicted myocardial infarction among men in the age group 30–39, although not among older men, and ROBERTSON et al. (1977) found that relative weight was a risk factor for coronary disease among Japanese men living in Hawaii, although not among those living in Japan. Furthermore, in other studies overweight was associated with some manifestations of coronary heart disease, but not with others. Thus, in the aforementioned study by CHAPMAN et al. (1971), overweight was associated with an increased incidence of angina pectoris but not of myocardial infarction among men over the age of 40, a finding quite similar to that reported by KEYS (1970) in the Seven Countries Study. Finally, a very recent report on morbidly obese men – those more than 100% overweight – has confirmed the long-standing impression that their mortality rates are markedly elevated (DRENICK et al. 1980). These rates were almost 12 times that of nonobese men in the age group 25–34, although excess mortality dropped with advancing age, being about six times normal in the age group 35–44 and three times normal in the group aged 45–54.

This, then, was the accepted belief until the very recent past – in spite of misgivings about the representativeness of the life insurance company data, obesity shortened life expectancy in a linear manner so that the more severe the obesity the shorter the life expectancy. This belief has now been seriously challenged. A major source of this challenge was the publication in 1980 of the massive 10-year epidemiological study of 12,763 middle-aged men in 16 cohorts from all parts of the world (KEYS et al. 1980). The size and diversity of this data base permitted the assessment of coronary risk factors in a manner that had never been possible in studies carried out in a single country. The results showed that the genesis of coronary heart disease is far more complex than we had thought and that the role of obesity is far more ambiguous. For example, as shown in Fig. 1, KEYS et al. (1980) found that the differences among cohorts in overall death rate bore no relation to differences in relative weight. Indeed, and in striking contrast to current orthodoxy, in some cohorts the death rate from all causes was inversely related to relative weight and in most cohorts the probability of death from all causes appeared to be *the least* for men somewhat over the average in relative weight. Although isolated groups in the study population showed a weak relationship between overweight and coronary heart disease, KEYS concluded that "the popular insurance company claim about mortality is grossly wrong; relative body weight is associated with risk only at the two ends of the distribution of relative weight ... unless it is extreme, overweight is not a risk factor for serious coronary heart disease."

The challenge to the traditional views on obesity and coronary heart disease had actually begun much earlier with criticism of the bias in the samples utilized by the life insurance companies. KEYS (1955) pointed out that among life insurance holders only 2% were obese, compared to a 7% prevalence of comparable degrees of obesity in the general population. The implications of this bias become clear when it was shown that mortality rates for women life insurance holders became lower as the restrictions against women receiving life insurance were relaxed.

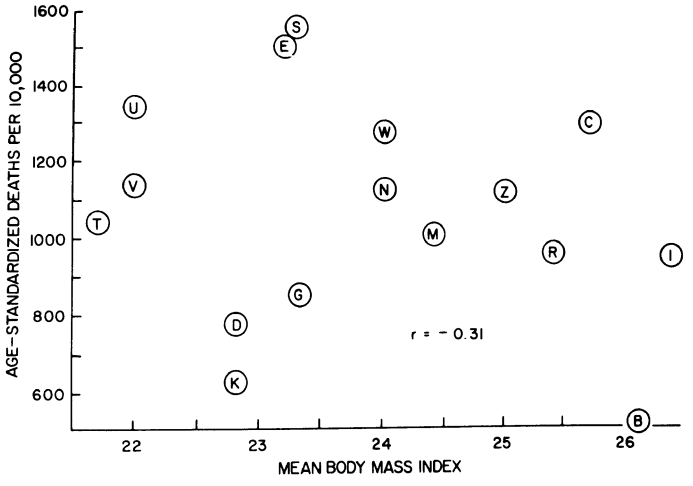

Fig. 1. Age-standardized 10-year all-causes death rates of the cohorts versus their mean body mass index at entry. *B*, Belgrade; *C*, Crevalcore; *D*, Dalmatia; *E*, East Finland; *G*, Corfu; *I*, Italian railroad; *K*, Crete; *M*, Montegiorgio; *N*, Zutphen; *R*, U.S. railroad; *S*, Slavonia; *T*, Tanushimaru; *U*, Ushibuka; *V*, Velika Kisna; *W*, West Finland; *Z*, Zrenjania. All men free of cardiovascular disease at entry. (KEYS et al. 1980)

Another challenge to traditional views on the relationship of body weight to coronary disease has been raised by the reinterpretation of the findings of earlier reports. The most aggressive, and effective, of these reinterpretations was carried out by ANDRES (1980a, b), who contends that no less than 16 studies have failed to support the traditional views. In his reinterpretation of the data of the Framingham Study, for example, he contradicts the position noted above that overweight is dangerous and leanness protective and maintains that the highest mortality rates were among the leanest people. Furthermore he points out, as had SHURTLEFF (1974) before him, that the lowest mortality rates were among men who were 25%–39% overweight. Both ANDRES and SHURTLEFF point out that there was no relationship between relative weight and coronary heart disease among women, and among men the relationship was statistically significant only for the so-called soft diagnoses such as angina pectoris. For the more reliable diagnoses of coronary heart disease, such as myocardial infarction and death, there was no relation with relative weight, even among men.

The final challenge to traditional views was posed by a number of new studies that found no relationship between moderate degrees of overweight and either overall mortality or coronary heart disease. Some findings, in fact, paralleled the reinterpreted mortality data of the Framingham Study – higher mortality rates among lean people and the lowest rates among the mildly overweight. Three well-designed large-scale studies reported no relationship between relative body weight and mortality or coronary heart disease (BORHANI et al. 1963; CARLSON and BÖTTIGER 1972; LARSSON et al. 1981). In two others, a quadratic model revealed such relationships, of a type similar to that found by KEYS et al. (1980) and by SHURTLEFF (1974). Both the Alameda County Study (BELLOC 1973) and the Chicago Peoples

Gas Company Study (DYER et al. 1975) found the highest mortality rates at the upper and lower ends of the distribution of relative weight. DYER et al. (1975) found the lowest mortality rates among men whose weights were 25%–35% above the ideal according to the Metropolitan Life Insurance Company tables, while BELLOC found the lowest rates at somewhat lower weights, but still significantly above "ideal" weight.

How are we to understand this new challenge to orthodox views of the health hazards of obesity? Must we abandon all of the old cautions and concerns? Probably not.

Clearly obesity is not the serious health hazard that it had seemed a generation ago. But it is still too early to write off the possible dangers arising from obesity. Even among the data most supportive of the health benefits of mild obesity there are discordant findings. It still seems quite possible that obesity is a danger to certain subgroups of the population, particularly in combination with other risk factors. But there are other sources of concern over the possible dangers of obesity; there is the problem of the ill effects of obesity on other disorders.

Even ANDRES, a leader in the attack on orthodox beliefs is puzzled. He notes that "... there is clearly something strange going on here. There is no question that obesity is associated with a number of serious illnesses, including diabetes and hypertension, diseases which are common and which do shorten life span" (ANDRES 1980a). The relationship between obesity and hypertension is instructive. The review by CHIANG et al. (1969) has described no less than 31 studies from all parts of the world which showed a positive correlation between overweight and hypertension and, what is more, 19 studies that showed that weight reduction lowered blood pressure. Clearly the relation between the two disorders is more than correlational. Even more impressive reductions in the blood pressure of obese hypertensives have been reported since that review. REISIN et al. (1978), for example, reported that a mean weight loss of 10.5 kg reduced diastolic blood pressure from 105.9 to 85.9 mm Hg among a group of obese hypertensives not on antihypertensive medication and a reduction from 112.9 to 89.7 mm Hg among (poorly controlled) hypertensives receiving antihypertensive medication. STUNKARD et al. (1980) reported that comparable reductions in body weight resulted in comparable reductions in the blood pressure of obese hypertensives.

Two excellent reviews have similarly documented the relationship of obesity to diabetes with its attendant hyperlipidemia (BIERMAN et al. 1968; ABRAMS et al. 1969).

At the present time there is simply no way of reconciling the influence of obesity on hypertension and diabetes, with their deleterious consequences, and the evidence that mild obesity has no ill effects. An intriguing suggestion by ANDRES (1980a) is that there may be some mysterious benefits of mild to moderate obesity that counteract its clearly deleterious influence on hypertension and diabetes. This is a good point at which to lay down the burden of understanding the confused picture of the health consequences of obesity. It is clear that obesity is bad for some people – hypertensives, diabetics, some hyperlipidemics, some arthritics, some others. For them weight reduction is clearly of benefit. We will conclude our survey with a brief consideration of measures that have proved useful in helping them to lose weight. For there has been recent progress in the treatment of obesity.

E. The Treatment of Obesity

Quite recently the state of the art of weight reduction could be summarized in the proposition that "most obese persons will not stay in treatment for obesity. Of those who stay in treatment, most will not lose much weight, and of those who do lose weight, most will regain it" (STUNKARD 1975). During the past decade, however, new approaches to psychotherapy, which appear more effective than traditional measures in modifying disturbed behavior, have been applied to the treatment of obesity. Obese patients have responded to behavior modification and specific well-defined programs for the treatment of obesity have been developed. Although the weight losses in these programs tend to be modest, a large number of studies have shown behavior therapy to be more effective than a variety of alternate treatments for mild and moderate obesity (STUNKARD 1975). The most recent of these studies will be described briefly, for it is important on two counts. First, the therapy used in this study can be specified in great detail and has been carried out in precisely the same manner in clinical practice with large numbers of patients. Second, it demonstrates that in the treatment of obesity behavior therapy is superior to both traditional office practice and to a highly effective pharmacotherapy program.

The study compared behavior therapy, pharmacotherapy, and their combination in 120 obese (63% overweight) women during 6 months of treatment and at 1-year follow-up (STUNKARD et al. 1980). One control group consisted of patients who were placed on a waiting list and received no treatment. The other control group consisted of patients who received traditional individual office management of obesity with medication, reducing diets, and instructions for exercise as well as advice and encouragement. Patients in the three major treatment groups met weekly, in four groups of 10 patients each, for 1½ hours.

Behavior therapy was presented in a highly structured program that utilized Ferguson's manual and included the standard behavioral techniques of self-monitoring, stimulus control, slowing of eating, self-reinforcement, cognitive restructuring, contingency contracting, and exercise management. Pharmacotherapy utilized the appetite suppressant fenfluramine in doses up to 120 mg/day and group discussions designed to control for the group support of the behavioral program. The combined treatment included both behavior therapy as provided in the first regimen and fenfluramine as provided in the pharmacotherapy condition.

Figure 2 shows that all treatment groups lost significantly more weight than the waiting list control group, which gained 1.3 ± 1.3 kg. Weight losses of the pharmacotherapy patients (14.5 ± 1.1 kg) and the combined treatment patients (15.1 ± 1.2 kg) were significantly greater than those of the behavior therapy patients (10.9 ± 1.0 kg).

Patients in the doctor's office medication group lost only 6.0 ± 1.7 kg, compared with 14.1 ± 1.1 kg lost by pharmacotherapy patients. The major difference between the conditions was that medication was administered in an individual format in the former and in a group format in the latter.

A striking reversal of the treatment results was found 1 year after the end of treatment – a finding whose significance is enhanced by the fact that this follow-up included every living patient who finished treatment (one patient had died). Behav-

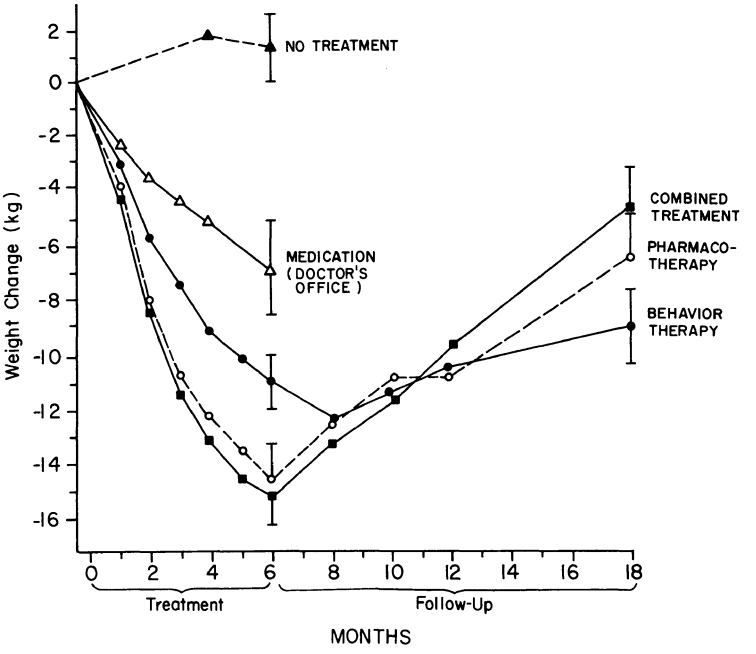

Fig. 2. Weight changes during 6 months of treatment and 12 months of follow-up. The three major treatment groups lost large amounts of weight during treatment: behavior therapy *(solid circles)* 10.9 kg, pharmacotherapy *(open circles)* 14.5 kg, and combined treatment *(solid squares)* 15.3 kg. Behavior therapy groups continued to lose weight for 2 months and then slowly regained it, in contrast to rapid regain of weight by pharmacotherapy and combined treatment groups. Among the control groups, the no-treatment (waiting list) control group gained weight, while the doctor's office medication group lost 6.0 kg. Patients in these two groups received additional treatment at 6 months and so were not available for follow-up. Vertical lines represent one standard error of the mean. (STUNKARD et al. 1980)

ior therapy patients regained far less weight than pharmacotherapy and combined treatment patients (1.9 ± 1.0 kg vs 8.2 ± 1.2 kg and 10.7 ± 1.2 kg). The result was a net weight loss from the beginning of treatment to 1-year follow-up of 9.0 ± 1.3 kg for behavior therapy patients compared with only 6.3 ± 1.5 kg for pharmacotherapy patients and 4.6 ± 1.6 kg for combined treatment patients. Although they weighed significantly more than the other two groups at the end of treatment, 1 year later behavior therapy patients weighed less.

The majority of these patients were hypertensive and, as we have noted above, there were large mean reductions in blood pressure, with the majority of patients reaching normotensive levels with weight reduction.

This study not only showed that behavior therapy could produce weight reduction sufficient to lower the blood pressure of most hypertensive obese patients to normal. Three results also showed that behavior therapy was probably superior to traditional pharmacotherapeutic measures for the treatment of obesity. *First*, although fenfluramine and group therapy produced greater weight losses during treatment, they were followed by more rapid regaining of weight after treatment. As a result, 1 year after treatment behavior therapy patients showed a greater net

weight loss than those who had received medication. *Second*, cost factors also favored behavior therapy, which did not require the services of costly medical personnel. *Third*, the surprising effects of combined treatment provided additional support for behavior therapy. The long-term effects of behavior therapy were actually poorer among patients who had received fenfluramine than among those who had not.

The developments in behavior therapy exemplified by this study give grounds for cautious optimism that such treatment can have a significant impact upon obesity-related illnesses. Further development of this relatively new and inexpensive treatment could make it available to large numbers of persons who might benefit from it.

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Drug Treatment

Drug Treatment in the Aged

D. PLATT

A. Introduction

The physiological changes of ageing do not progress uniformly in all parts of the body; on the contrary, they advance at different speeds in different organs. Though there are certain changes which are genuinely "age-induced," these are nearly always overlaid by superimposed diseases. The multiple pathology typical of old age carries with it the danger of polypharmacy on the part of the physician. The physiological and pathological changes of ageing have a bearing on pharmacotherapy in all its stages (Fig. 1).

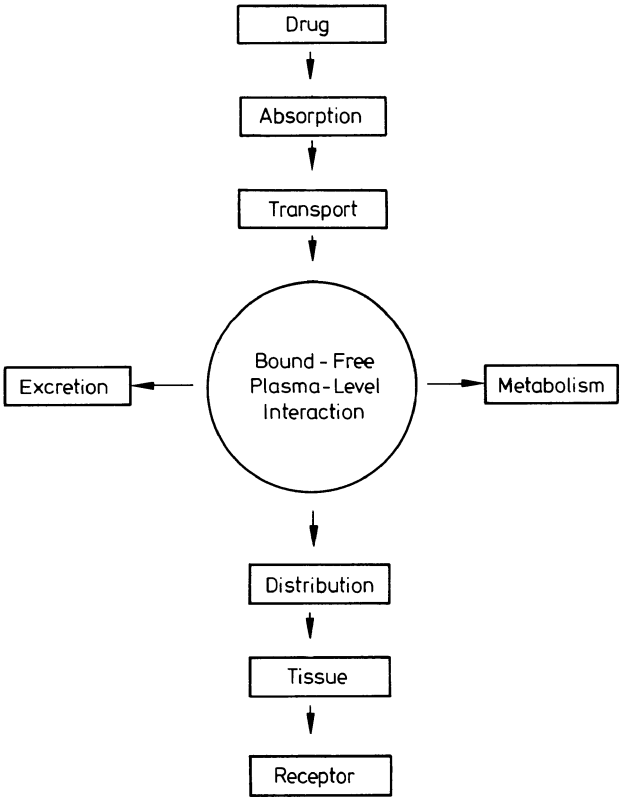

Fig. 1. Possible effect of ageing on pharmacology in all its stages

B. Pharmacokinetics

Drugs can be administered by various routes: oral, intramuscular, intravenous, or subcutaneous. In advanced age most drugs are given by mouth. This means that age-related changes in the gastrointestinal tract may affect absorption and interfere with treatment.

I. Absorption

Advancing age is accompanied by a decline in the secretion of acid by the stomach – both basal and maximal histamine-induced secretion (BARON 1963). Besides the pH change, atrophic gastritis, which becomes more and more frequent as age advances, can modify the solubility of various drugs. ANDREWS et al. (1967) demonstrated that the severe forms of atrophic gastritis were associated with loss of chief and parietal cells and with decreased secretion of hydrochloric acid and intrinsic factor. Apart from these changes in gastric acidity, the peristaltic activity of the stomach plays an important role in drug absorption. If the stomach empties quickly, the absorption of drugs in the upper jejunum will be more rapid and more nearly complete. Examples of this include warfarin (KEKK et al. 1971), aspirin (SIURALA et al. 1969), and barbiturates (KOJUMA et al. 1971). Intestinal metaplasia in the gastric mucosa or drugs which delay gastric emptying can compromise the results of drug therapy. Parkinson's disease is a common condition in advanced age. In this disease the concentration of dopamine in the corpus striatum and caudate nucleus decreases. Its precursor, L-dopa, is employed therapeutically. The work of RIVERA-CALMIN et al. (1970) has shown that L-dopa is rapidly metabolized in the stomach and that those patients in whom gastric emptying is delayed have lower serum levels of L-dopa. BIANCHINE et al. (1971) reported the treatment of a patient with Parkinson's disease in whom gastric emptying took roughly three times as long as normal. Although there was no evidence of any interference with absorption in the duodenum, this patient had blood levels of L-dopa approximately one-third of those found in comparable patients. Because of the delayed gastric emptying, the patient was unresponsive to L-dopa therapy. This example shows how factors acting remote from the target organ can lead to complete failure of therapy.

Age-related changes in the small intestine are evidently not very pronounced. CORNES (1965) noted a decrease in Peyer's patches in the small intestine with advancing age, together with a decrease in the follicles in individual patches. According to FRY et al. (1960) and LESHER et al. (1961), the half-life of the mucosal cells of the small intestine increases with age. The absorption of drugs in the small intestine is affected by several factors, such as intestinal motility and blood flow, the activity of the digestive processes, bacterial colonization, the functional activity and numbers of the cells concerned in drug absorption, and the rate of gastric emptying. The transport of a drug from the intestine into the blood may be passive or active, though in most instances of oral drug therapy passive absorption plays the larger role. Active absorption of a drug is the responsibility of a carrier system located in the cell membrane. Evidence of age-related changes in drug absorption has been found in investigations of the transport of xylose (GUTH 1968), iron (DIETZE et al. 1971), and glucose and galactose (BENDER 1965; HOLLOWAY 1974; LAMY and

KITLER 1971). GARATTINI et al. (1973) and KLOTZ et al. (1975) and OCHS (1981) studied the influence of ageing on diazepam blood levels. In elderly subjects they found that after oral administration the rise in concentration was slower and the half-life of the drug was longer.

Intestinal blood flow decreases with advancing age, if only because of the diminution in cardiac stroke volume. In addition, there is a decrease in splanchnic blood flow with advancing age (BENDER 1965). Both these age-related changes affect the absorption of drugs.

II. Distribution

After a drug has entered the blood stream it becomes bound to circulating plasma proteins. A dynamic equilibrium exists between the bound fraction and the unbound fraction of the drug, and it is the latter which is responsible for the effect on the receptors. Drugs are bound to plasma albumins, and with advancing age the rate of synthesis of these proteins decreases (PLATT 1977). Besides albumin, other plasma proteins, and even erythrocytes operate as transport systems.

1. Plasma Proteins

The degree of protein binding varies widely from one drug to another. In the case of some drugs such as phenylbutazone the proportion bound to protein may be as high as 98%, while for other drugs, such as barbiturates, the proportion bound to plasma proteins is quite low. The decrease in albumin concentration in old age explains why the protein binding of some drugs is reduced. In view of the age-related changes involving the histones in DNA and in the scleroproteins collagen and elastin, it is conceivable that structural changes in transport proteins might affect the protein binding of drugs. However, the investigations so far carried out (BENDER et al. 1975; HAYES et al. 1975 a, b; HAYES and LANGMAN 1974; WALLACE et al. 1976) do not support this conjecture. For example, BENDER et al. (1975), studying phenytoin, penicillin G, and phenobarbital acid, were unable to demonstrate any age-related change in plasma protein binding, although the plasma albumin concentrations in subjects under 50 years of age (4.0 g/100 ml) were significantly higher than those in older subjects (3.4 g/100 ml). In their investigations with warfarin, HAYES et al. (1975 a, b) confirmed these findings and showed that there was no change in protein binding with advancing age. The similar investigations of WALLACE et al. (1976), who studied the protein binding of phenylbutazone, sulfadiazine, and salicylates, showed no significant decrease in protein binding in advanced age except in the case of phenylbutazone. However, salicylic acid and sulfadiazine did not display such clear dependence on binding to albumin as did phenylbutazone. It is conceivable that these differences in the degree of protein binding may be explained in terms of the affinity of the drugs for albumin. KLOTZ et al. 1975) studied the binding of diazepam and its metabolite desmethyl-diazepam to proteins and found no change with advancing age. However, they give no information regarding albumin concentration determinations. In parallel with the decrease in plasma albumin concentration in old age, warfarin (HAYES et al. 1975 a) and carbenoxolone (HAYES and LANGMAN 1974) displayed decreased protein bind-

ing with advancing age. MATHER et al. (1975) investigated the binding of meperidin to proteins and found an age-dependent decrease.

As old people often have two or more illnesses concurrently, they are often given several different drugs aimed at each of their illnesses. The ingestion of several different medicines at once brings with it the danger that side effects will be more frequent and will arise earlier than would otherwise be expected, to say nothing of interactions between the drugs. The simultaneous decrease in the transport protein albumin means that drugs, in particular those which bind strongly to protein, will compete for the transport protein and in advanced age there is some danger that the unbound component of certain drugs may increase. The researches of LINDUP (1975) and WALLACE et al. (1976) provide examples. They showed that in the presence of other drugs there is a significant decrease in the binding of salicylates, phenylbutazone, and sulfadiazine to plasma proteins. To what extent the structural changes in the albumin molecule in old age contribute to alterations in protein binding is a question which cannot yet be given a clear answer.

2. Erythrocytes

Drugs are transported not only on plasma proteins but also on erythrocytes. As yet, there have been few investigations into the influence of age on the binding of drugs to erythrocytes(CHAN et al. 1975; NATION et al. 1976; PLATT and VÖMEL, unpublished results). Studies carried out with pethidine, chloromethiazol, and piracetam show that binding to erythrocytes decreases or remains constant as the age of the donor increases. Investigations by EHRNEBO et al. (1974) with pentazocine and by KLOTZ et al. (1975) with diazepam showed no age-dependent differences in binding to erythrocytes, i.e., between the bound and unbound fractions.

3. Tissue Composition

Besides the binding of drugs to proteins, there are certain age-dependent changes in the transit pathway to the target organ which also affect the action of the drug on the cell. These include changes in the concentrations of proteoglycans and the scleroproteins collagen and elastin and changes in water and electrolyte balance. All these changes differ in degree from one organ to another. Qualitative and quantitative changes in chondroitin sulfate proteins, heparin sulfate proteins, and keratan sulfate proteins lead to shifts in the concentration of intramolecular water. These changes are most pronounced in structures which are rich in proteoglycans, such as cartilage, vessel walls, and intervertebral disks. However, the transit pathway between the vessel wall and the receptor on the cell of the target organ is also relevant to drug transport. More than half the weight of the human body is made up of water, and organs and tissues differ in their water content. As all the metabolic processes of the body require an aqueous milieu in which to take place, precise regulation of water balance is absolutely essential. The water requirements of the body are influenced by various factors including heat production, renal concentrating power, and water loss by transpiration through the skin. Water is also needed for the functioning of the mucosae, the kidneys, the intestines, and the lungs. The extensive intracellular and extracellular changes which occur during

ageing are reflected in the water balance of the body. Shifts in water balance inevitably affect the transport of drugs to the target organ. According to SNIVELY and SEENEY (1958), the solid matter of the body amounts to 23% in infants, 40% in adults, and 45% in the aged. Extracellular fluid makes up 29% in infants, 15% in adults, and 12% in the aged, but the changes in intracellular fluid are much smaller; it falls only slightly from 48% in infants to 45% in adults and 43% in old people. At variance with the findings of SNIVELY and SEENEY are the results of SCHWAB et al. (1963), who found that total body water (expressed in terms of body weight) decreased after the age of 50, this decrease being due to a reduction in intracellular fluid. These shifts have some influence on the distribution of drugs in old people. Another important factor is the change in body fat content which accompanies advancing age. Fat soluble drugs are more readily distributed than drugs of low fat solubility, as has been shown by studies of diazepam (KLOTZ et al. 1975) and chlordiazepoxide (SHADER et al. 1977). In contrast to these, propicillin undergoes an age-dependent decrease in its distribution volume (SIMON et al. 1972).

When it has arrived at the target organ, the action of the drug may be influenced by qualitative and quantitative changes in the receptors. Research in this field has been very meager (CONWAY et al. 1971; LONDON et al. 1970; SCHOCKEN and ROTH 1977), but the investigations of VESTAL et al. (1979) indicate that the sensitivity of β-adrenoreceptors for isoproterenol and propranolol decreases as age advances.

III. Metabolism

The liver lies at the center of drug metabolism. In advanced age the liver weight decreases and deposits of lipofuscin, the so-called wear-and-tear pigment, become more conspicuous (PLATT 1977). There is an increase in scleroproteins and the number of degenerating cells rises. Other features of old age include increased numbers of polyploid cells, chromosomal aberrations, and mitochondrial changes (PLATT 1976).

A drug cannot be excreted through the kidneys unless it is water soluble or can be converted into a soluble form. There are only a few drugs which possess groups suitable for conjugation with sulfuric acid or glucuronic acid. Most drugs must first of all be hydroxylated. The enzymatic system of the endoplasmic reticulum activates molecular oxygen for the oxidation of fat soluble compounds. This reaction takes place on cytochrome P_{450}, which is present in the endoplasmic reticulum. The enzymes required to make drugs water soluble are attached to the lipid constituents of cell membranes. For example, the oxidation of aliphatic and aromatic groups (barbiturates, phenodiazines, phenytoin, antihistamines, antipyrine, digitoxin) is catalyzed by cytochrome P_{450}. The hydrolysis of esters and acid amides (lidocaine, procaine, atropine) is carried out by esterases, while binding to glucuronic acid is catalyzed by transferases. Age changes at microsomal level may impair the activities of microsomal enzymes and may hence exert a significant effect on the steady-state level of drugs in the plasma. Most biochemical research on age changes in microsomes has been carried out in animals. This work has shown that there is a decrease in phospholipid levels with advancing age. This is a matter of some importance because, of all the various lipids, it is the phospholipids which

play the major role in the functioning of most membrane systems. KRATZ (1978) measured the activity of microsomal enzymes in human liver tissue. From this work it is apparent that there are no changes in coumarin-7-hydroxylase or 7-ethoxycoumarin-hydroxylase in subjects between the ages of 20 and 70 years, provided they have healthy livers. IRVINE et al. (1974) showed that the metabolism of amylobarbituric acid in elderly people was approximately 50% slower than in younger controls. This finding confirms the clinical impression that older people are unduly susceptible to barbiturates and frequently react with confusional or depressive states.

Most of the evidences suggesting that drug metabolism in the liver is impaired in old age is based on indirect methods. Measurements of the plasma half-lives or clearances of certain drugs have shown age-dependent differences (Table 1). For example, the half-life of aminopyrine in subjects over 75 years of age is roughly twice as long as in controls under 30 (JICK et al. 1968). O'MALLEY et al. (1977) investigated age changes in the half-lives of antipyrine and phenylbutazone. They found that the plasma half-life of antipyrine rose by 45%, while that of phenylbutazone fell by 29%. KLOTZ et al. (1975) found that the half-live of diazepam in

Table 1. Drugs with delayed elimination caused by an age-dependent decrease of liver metabolism

Reference	Drug	Age-dependent decrease of hepatic metabolism: Pharmacokinetic consequences	Clinical importants side effects
	Analgetics and antiphlogistics		
JORI et al. (1972)	Aminopyrine	Prolonged half-life from 3.3 to 8.1 h	Cumulation, typical side effects caused by antiphlogistic agents (gastro-intestinal symptoms change in the blood picture)
VESELL (1981)	Antipyrine	Prolonged half-life from 12 to 17.4 h	Cumulation, typical side effects caused by antiphlogistic agents (gastro-intestinal symptoms change in the blood picture)
O'MALLEY et al. (1971) TRIGGS et al. (1975)	Phenylbutazone	Prolonged half-life from 81.2 to 104.6 h (shortened half-lifes were also reported by some authors)	Cumulation, typical side effects caused by antiphlogistic agents (gastro-intestinal (symptoms change in the blood picture)
TRIGGS et al. (1975) BRIANT et al. (1975)	Paracetamol	Prolonged half-life from 1.79 to 2.27 h	
GREENBLATT and SHADER (1981)	Acetaminophen	Prolonged half-life (age-dependent decrease of glucaronide conjugation) reduced clearance	

Table 1 (continued)

Reference	Drug	Age-Dependent decrease of hepatic metabolism: pharmacokinetic consequences	Clinical important side effects
	Barbiturates		
VESELL (1981)	Amylobarbitone	Decrease of unrinary metabolite from 14.2 to 4.3%	Cumulation, toxic effects (state of confusion, depression, cave wrong diagnosis of cerebrovascular circulatory failure!)
EADIE et al. (1977)	Phenobarbital	Prolonged half-life from 71 to 107 h	Cumulation, toxic effects (state of confusion, depression, cave wrong diagnosis of cerebrovascular circulatory failure!)
	Psychopharmacologic agents and tranquilizer		
NIES et al. (1977)	Amitryptyline	Higher steady-state plasma levels	Decrease in blood pressure, ischuria, state of confusion, tachycardia
NIES et al. (1977)	Imipramine	Higher steady-state plasma levels of drug and metabolite Prolonged washout ($t_{1/2}\beta$) of metabolite	Decrease in blood pressure, ischuria, state of confusion, tachycardia
ROBERTS et al. (1978)	Chlordiazepoxid	Prolonged half-life ($t_{1/2}\beta$), larger V_d, reduced clearance	Dizziness, diplopia, urinary incontinence, headache
GREENBLATT et al. (1980)	Diazepam	Prolonged half-life from 20 to 90 h (!)	Excessive tranquilisation, repiratory depression rate of confusion, drowsiness
GREENBLATT et al. (1979)	Lorazepam	Reduced V_d (by 11%) reduced clearance (by 22%)	Exzessive transquilisation, respiratory depression rate of confusion, drowsiness
IISALO et al. (1977)	Nitrazepam	Prolonged $t_{1/2}\beta$, larger V_d	Excessive tranquilisation, respiratory depression rate of confusion, drowsiness
	Cardiac remedies		
CASTLEDEN et al. (1975)	Propranolol	Plasma level approximately 4× in elderly compared to young Decreased metabolism (first-pass-effect)	Bradycardia, life-threatening disordered action of the heart
VESELL (1981)	Quinidine	Reduced clearance (40%)	Bradycardia, life-threatening disordered action of the heart

Table 1 (continued)

Reference	Drug	Age-Dependent decrease of hepatic metabolism: pharmacokinetic consequences	Clinical important side effects
	Antiepileptic drugs		
VESELL (1981)	Phenytoin	Serum level (equal maintenance dose) increased 2× from 20 to 80 years old	Toxic effects, allergid, toxic gastroenteritis, hyperkinesia, nausea, state of confusion
	Anticoagulants		
HEWICH et al. (1975)	Warfarin	Prolonged half-life from 37 to 44 h	Gastroenteritis, allergid, alopecia, intermittant thrombocytopenic purpura, interference with other drugs
	Liver function test substances		
	Bromsulphtaleine	Reduced storage capacity of the liver in elderly patients	
VESELL (1981)	Indocyanine Green	Reduced metabolic clearance in the elderly (decrease of liver blood flow)	
	Anticoagulants		
HEWICH et al. (1975)	Warfarin	Prolonged half-life from 37 to 44 h	Gastroenteritis, allergid, alopecia, intermittant thrombocytopenic purpura, interference with other drugs
	Liver function test substances		
	Bromsulphtaleine	Reduced storage capacity of the liver in elderly patients	
VESELL (1981)	Indocyanine Green	Reduced metabolic clearance in the elderly (decrease of liver blood flow)	

elderly people was 90 h, as compared with 20 h in younger controls. Turning to drugs which are conjugated in the liver, it may be of interest to cite certain work on paracetamol and sulfametizol (TRIGGS et al. 1975) and on indomethacin (TRAEGER et al. 1973). In older subjects the plasma half-life of paracetamol was significantly prolonged. Some elderly subjects produced low urinary concentrations of conjugated substrate, a finding which suggests the possibility of diminished hepatic conjugating power. Whereas the mean plasma half-life for indomethacin was roughly the same in young and old alike, elderly subjects had a smaller proportion of the free drug, an observation which prompted the authors to surmise that biliary

excretion may be increased in old people. There was no significant difference in the acetylation of sulfametizol between young and elderly subjects.

Old age brings with it a multitude of ills. The tendency to give "a pill for every ill" carries serious risks of drug interactions and side effects. Digitalis is very widely used in elderly patients and can produce side effects even in low concentrations. Among the factors which increase this hazard are depressed potassium levels in the blood or the myocardium, an effect commonly produced by diuretics. The action of digitalis on the receptor in the myocardial cell membrane (K^+ Mg^{++}-ATPase) is affected by the local concentration of potassium, and any decrease in potassium concentration enhances the digitalis effect. Simultaneous treatment with several drugs can lead to interference with drug metabolism in the liver. Phenobarbitone or diphenylhydantoin can "induce" increased activity on the part of microsomal enzymes and can thus modify the metabolism of many other drugs which are metabolized in the vicinity of the endoplasmic reticulum, as for example dicoumarols and phenothiazines. The therapeutic effect of an antidiabetic agent such as tolbutamide can be modified by simultaneous administration of chloramphenicol or phenylbutazone, the result being hypoglycemic reactions (ROWLAND et al. 1974).

Apart from these changes in the enzyme systems responsible for the metabolic breakdown of drugs, blood flow through the liver plays an important part. For example, the elimination rate of drugs which are excreted in the bile is limited not so much by the activity of drug-metabolizing enzymes as by the perfusion rate of the liver (GILLETTE 1971). The clearance of drugs with a low intrinsic clearance rate is not materially affected by changes in liver blood flow (NIES et al. 1976). SHERLOCK et al. (1950) studied liver perfusion in relation to age and showed that blood flow diminishes by approximately 1.5% a year. According to their figures, the regional perfusion rate in the liver in a 65-year old is approximately 40%–50% of the rate found in a 25-year old.

IV. Excretion

1. Kidneys

Changes in the kidney resulting purely from ageing are difficult to evaluate because – as in most other organs – they are overlaid and obscured by changes caused by disease, and these of course become more and more frequent as age advances.

KAPIDES and ZIERDT (1967) used various methods to investigate renal function in healthy subjects, both young and old. They found no relationship between age and renal function; on the contrary, they believe that the well-known decline in renal function in advanced age is primarily due to the increased incidence of disease. The weight of the kidneys falls significantly with increasing age. Conventional microscopic studies have shown that glomeruli and nephrons diminish in numbers in advanced age. At the same time the nephrons decrease in size. As a result of this loss of parenchymal cells there is some widening of the intercellular space and an increase in the scleroproteins situated in it. With advancing age the distal convoluted tubules display increased numbers of diverticuli, which DARMADY et al. (1973) regard as possible starting points for pyelonephritic lesions in elderly people. Further evidence of an increased prevalence of pyelonephritic changes in old

age is provided by the investigations of BROCKLEHURST (1971). It is clear that renal function in old age may be seriously impaired both by purely age-dependent renal changes and by the pathological lesions which become more and more frequent as age advances. In old people renal blood flow decreases, as do the clearances of creatinine, inulin, and PAH. At the same time the concentrating power of the kidney declines (PLATT 1976). The decrease in glomerular filtration rate may be due to diminished renal blood flow or to the decline in the numbers of glomeruli and their functional capacity; both factors may be involved. This decline in renal function is of relevance to drug therapy in old people. Drugs which are mainly eliminated by the kidneys tend to reach higher concentrations than in younger people and may therefore produce side effects earlier. In order to avert these side effects it seems logical to measure the endogenous creatinine clearance and to adjust the dose for elderly patients as necessary. In this connexion mention should be made of the work of EWY et al. (1970) and BAYLIS et al. (1972) with digoxin. They found that the plasma levels of digoxin in elderly patients were significantly higher than in a corresponding younger control group. Though EWY et al. found a direct relationship between digoxin clearance and creatinine clearance, BAYLIS et al. were unable to demonstrate any such positive correlation. As already mentioned under the heading "Metabolism," drugs of high lipid solubility are converted into water soluble form by hydroxylation in the liver so that they can be excreted by the kidneys. This means that age changes in the liver, because they reduce its capacity for hydroxylating drugs, may impose limitations on renal excretion. The crucial factor in the clearance of drug metabolites is the functional capacity of the glomeruli, because these metabolites are for the most part not reabsorbed in the renal tubules. However, there are certain substances, such as penicillin, which are excreted through the renal tubules by specific transport systems. Any numerical decrease or pathological change in the cells of the renal tubules may thus have repercussions on the blood levels of such drugs. There have been several trials in which high plasma drug levels were found in elderly subjects and were ascribed to diminished renal elimination. However, these studies do not withstand critical scrutiny. Either urine recovery was not measured or the authors failed to exclude the possibility that the elevated plasma concentrations might have been due to abnormalities in distribution of the drugs.

2. Liver

Far less important than the elimination of drugs through the kidney is their excretion in the bile. There are two liver function tests which the clinician can use to assess the patient's capacity for eliminating drugs: the Bromsulphalein (BSP) test and the indocyanin green (ICG) test. THOMPSON (1977) carried out the BSP test in subjects of different ages and found that the capacity of the liver to extract BSP from the circulation declined with increasing age. KITANI (1977) studied liver function with ICG and came to similar conclusions. In both studies elderly subjects had significantly higher plasma levels of BSP or ICG. However, the fact that extractive capacity for these dyes is reduced does not necessarily mean that overall liver function is impaired. CALLOWAY and MERRILL (1965) and KOFF et al. (1973) have shown that there is no age-dependent change in liver function as regards drug clear-

ance. DE LEEUW-ISRAEL et al. (1969) reached similar conclusions. TRAEGER et al. (1973) found that the binding of indomethacin to glucuronide remains unaffected by advancing age and that biliary excretion of the drug increases in old age.

V. Side Effects

The multiplicity of drugs prescribed for elderly people not unexpectedly produces an abundant crop of side effects. These adverse effects may be either pharmacological or allergic in nature. The allergic side effects arise either as the result of sensitization by previous treatment with the same drug or from genetic predisposition. According to CARANASOS et al. (1974) the vast majority of drug side effects are attributable to pharmacological reactions. Various studies have shown that side effects occur more frequently in old people. For example, HURWITZ (1969) showed that the number of side effects in patients over 60 years of age was $2 \geqq$ times higher than in a control group of younger subjects. Side effects were more frequent in women than in men. According to PEMBERTON (1954), the incidence of side effects in elderly people during treatment with phenylbutazone rises by approximately 30% for each decade, and tolerance for gold decreases considerably in old age (DE BOSSET and BITTER 1973). The larger the number of drugs being taken concurrently, the greater is the risk of side effects. HURWITZ (1969) showed that among patients taking from one to five drugs the incidence of side effects was 3.4%, whereas among patients who were taking six or more drugs simultaneously the incidence rose to approximately 25%. It seems likely that in such circumstances the risk of side effects is increased by the overload imposed on the drug metabolizing mechanisms of the liver.

1. Glycosides

Large numbers of elderly patients take glycosides for heart failure. Increasing age brings with it a decline in potassium levels in the blood and in heart muscle cells, and these low levels predispose to side effects at an early stage. To prevent or minimize such side effects the process of saturation with glycosides should be gradual and the physician should endeavour to keep the serum potassium level in the middle or upper part of the normal range. This can be done by giving potassium supplements or prescribing drugs (spironolactone) which raise the potassium level. The relative advantages of digitoxin as against digoxin preparations in old age are still uncertain and further work is needed to resolve this point. Until we have adequate information on the protein binding of the various glycosides in elderly people it is difficult to express a firm preference for one digitalis product or another. EWY et al. (1970) carried out investigations with digoxin and found significantly higher plasma levels in elderly people.

2. Diuretics

Diuretics are nearly always prescribed in conjunction with digitalis preparations. As already emphasized in a previous section, their uncritical use, especially if combined with inadequate supervision of the patient, entails a risk that increased potas-

sium loss in the urine may rapidly provoke the side effects of digitalis therapy. Furthermore, potassium loss caused by diuretics may directly and independently of any digitalis therapy produce adverse effects on the heart. In addition it may interfere with glucose tolerance and, by causing hyperuricemia, may even provoke an attack of gout. Excessive fluid loss may lead to hypovolemia with a fall in blood pressure, while the rapid elimination of fluid from the lower limbs may cause a pre existing thrombus to break loose and may thus lead to fatal pulmonary embolism. According to CARANASOS et al. (1974), diuretics were the cause of side effects in 6% of cases.

3. Antihypertensives

Conventional teaching to the effect that blood pressure rises with age is incorrect (PLATT 1974); all that happens is that the number of patients suffering from hypertension increases. The treatment of hypertension in old age must be undertaken more cautiously than in young or middle aged patients. The blood pressure should be brought down step by step and should not be reduced below 160–170 mm Hg. The reason for this caution is the changes which exist in the vessel walls at arteriolar level. In young people a drop in blood pressure can be made good by dilatation of small vessels and blood supply to vital organs can thus be ensured. In advanced age this is no longer the case, and a drop in blood pressure inevitably impairs blood flow in the tissues situated beyond an arteriosclerotic lesion. The supply of oxygen and nutrients to the tissues becomes insufficient. There are occasional instances in which an excessively rapid or pronounced reduction in blood pressure has been followed by myocardial infarction or a cerebrovascular accident. Age-induced changes in the reactions of the baroreceptors (GRIBBON et al. 1971) and a reduction in peripheral venous tone (CAIRD et al. 1973) are further factors which may increase the risk of side effects during treatment with antihypertensives. Long-term treatment with methyl-dopa or with drugs containing reserpine (DOLLERY and HARINGTON 1962) may induce depressive states in elderly patients, and reserpine may cause lesions in the gastric mucosa, progressing even to ulceration.

4. Analgesics

Old people are often troubled by pain of musculoskeletal origin. Among the factors which underly such pain are age-related changes in connective tissue, especially in the neighborhood of joints, the changes of osteoporosis and osteomalacia, and bone metastases from malignant neoplasms. To list all the available analgesics would need far more than the space available. Mention should be made of salicylates, phenacetin, phenylbutazone, indomethacin, and paracetamol. These drugs have already been dealt with elsewhere in this contribution. BELVILLE et al. (1971) found no evidence of any age-dependent differences in the incidence of side effects from morphine and pentazocine.

5. Anticoagulants

Advancing age brings with it an increased incidence of venous thrombosis and hence of pulmonary embolism. There are several reasons for the increased

frequency of venous thrombosis in later life: changes in the vein walls in old age, slowing of the circulation with decreased stroke volume and cardiac output, increases in blood viscosity and fibrinogen concentration, and shortening of the clotting time in old age (PLATT 1974). Anticoagulant therapy is often necessary, especially in connexion with surgical operations. Age in itself is not a contraindication to anticoagulant therapy. The contraindications are the same in old age as in other phases of life. According to JICK et al. (1968) and O'MALLY et al. (1977) elderly people are more sensitive to heparin and warfarin than young people. The side effects of warfarin are gastrointestinal upsets and dermal reactions such as urticaria or hemorrhagic necrosis of the skin. Certain drugs such as antibiotics, sulfonamides, phenothiazines, and salicylates heighten the patient's sensitivity to warfarin when given concurrently with it, whereas barbiturates and corticosteroids may have the opposite effect. Among the toxic side effects are urticarial and anaphylactic reactions, transient thrombocytopenic purpura and alopecia.

6. Sedatives

It is a well-known fact that sedatives given to elderly people may produce paradoxical reactions ranging from restlessness to an acute psychosis. These reactions are thought to be due to changes in the metabolic breakdown of the drug in the liver. For this reason barbiturates should never be used in elderly people. Alterations in the half-life of sedatives are described in Sect. B.III. CASTLEDEN et al. (1977) reported heightened sensitivity to nitrazepam in old people. It has been surmised that the side effects may be due to diminished clearance (EVANS and JARVIS 1972). However, in view of the work of CASTLEDEN et al. (1977), it seems likely that the clinical picture is due to the altered reaction of the ageing brain, as the plasma concentration and the half-lives were almost identical in both age groups.

7. Antiparkinsonism Drugs

Parkinson's disease is primarily due to abnormalities in the basal ganglia, characterized morphologically by degeneration of the melatonin-containing neurons in the substantia nigra. Neurochemically, there is a pronounced fall in the concentration of dopamine in the substantia nigra, the corpus striatum, and the globus pallidus. Patients can be treated by giving a precursor of dopamine, namely, L-dopa. Elderly patients with Parkinson's disease are often unduly sensitive to antihistamines and anticholinergic drugs. These drugs can cause forgetfulness, confusion, and disturbed sleep. In patients with preexisting dementia they may worsen depressive states and aggravate paranoid symptoms. Incontinence of urine and feces is another side effect.

8. Antidepressive Drugs

The action of tricyclic antidepressants is apparently not the same as it is in young people. NIES et al. (1977) found that elderly patients treated with tricyclic antidepressants were subject to frequent side effects such as lowering of blood pressure, retention of urine, confusion, tachycardia, and signs of cardiac failure. These

workers demonstrated that, like other drugs, imipramine and amitriptyline attain higher blood levels in older patients than in young people. A comparative study of the clinical and pharmacokinetic data for doxepine has been carried out by FRIEDEL (FRIEDEL and RASKIND 1975; FRIEDEL et al. 1979).

C. General Principles of Drug Therapy

Old age brings changes in all the organs of the body and when prescribing drugs for elderly patients the physician must be even more careful in tailoring treatment to individual needs than when treating younger patients. As already pointed out in previous chapters, because of the wide range of biological variation in old age, the reaction to any given drug may differ enormously from one individual to another. It is therefore extremely unwise to draw up a uniform therapeutic schedule for the routine administration of drugs in old age. It is important to adjust the dose to suit individual requirements. Before starting treatment with any drug there are certain essential conditions which must be fulfilled: a detailed history must be taken, a diagnosis must be made, and logical and appropriate treatment must be chosen. The multiple pathology of old age often requires the use of several different drugs. It is therefore essential to know what drugs have already been prescribed, and to be familiar with their effects and side effects. In view of the physiological and pathological changes associated with ageing it seems advisable, especially if pharmacokinetic information is not available, to give less than the usual dose. In order to ensure that the patient will comply with the doctor's orders, it is esential to give clear instructions in writing, with an indication of the action of the drug and of the times at which it is to be taken. Because of the deterioration of vision in old age, packs should be labeled with the name of the medicine in large letters and should if possible be distinguished by different colors. The closures of bottles and other containers should be so devised that elerly people can open them without difficulty. Although many old people suffer from more than one disease, the physician should strive to consolidate treatment as far as possible and to reduce the number of drugs in concurrent use to a minimum.

D. Drugs to Combat Ageing

Certain products are advocated as remedies against ageing. They contain heterogeneous mixtures of hormones, agents intended to increase brain blood flow, vitamins, vasoactive drugs, and antiarteriosclerosis agents. The alleged indications for their use in old age are: prolongation of life, revitalization, psychological disharmony, dysfunction of cellular tissue, exhaustion, and disorders affecting the heart, circulation, liver, stomach, and intestines. Special claims are made that such remedies are effective against arteriosclerosis, depression associated with old age, senile dementia, arthropathies, skin diseases, senile polyneuropathy, etc.

Most of these remedies for old age contain vitamins; indeed these are their basic constituents, although there is no evidence that the incidence of vitamin deficiency

increases in old age, nor is there any evidence of low vitamin levels in patients receiving a normal diet. Among these remedies are two main groups, those containing procaine and those containing ginseng. POSTFELD et al. (1977) reviewed the results of 285 studies of the action of procaine. These papers comprised a total of more than 100,000 patients who had been treated for up to 25 years. From this compilation of results, the authors concluded that – apart from a possible antidepressant effect there was no convincing evidence that procaine or gerovital, the main constituent of which is procaine, is of any value in the treatment of any disease in old people. The number of papers dealing with the influence of ginseng on ageing phenomena in man is much smaller than the body of work on procaine and there have been no double-blind trials with appropriate scientific controls to support the claims that these drugs influence the typical phenomena of ageing. However, even in geriatric practice placebos are sometimes indispensable. Nevertheless, these "revitalizing" products are too expensive to be used merely as placebos and furthermore they are by no means free from side effects. MICHEL (1980) found that the adverse effects of ginseng included morning diarrhea in 35.3%, skin rashes in 24.8%, insomnia in 19.5%, nervousness in 18.8%, hypertension in 16.6%, and edema in 10.5%. There is no evidence that these products can slow down the normal processes of ageing or that they can prolong life expectancy. The therapeutic claims for the products at present on the market are based mainly on inferences drawn from findings in experimental animals and there is as yet no proof that they in fact produce the desired clinical effects (MICHEL 1980).

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