Early Gastric Cancer

Current Status of Diagnosis

Edited by

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With 82 Figures

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Contents

Doubtful Cases and Precancerous Lesions. (Indicative List for the Various Methods of Examination, for Surgery, for Observation and for Prophylactic Screening

Discussions by Invitation

Problems of and Recommendations for Organizing Early Stomach Cancer Diagnosis in Hospitals, Out-Patient Clinics, Doctor's Offices and in Mass Screening

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Introduction

Presidential Address

E. Grundmann

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The first two symposia of our society dealt with epidemiology of cancer and mechanisms of carcinogenesis; as suggested by Dr. Grunze and Dr. Witte, the present one is dedicated to a clinical topic. Both our chairmen have prepared this conference by selecting participants and their papers and by organizing the program of discussions. Dr. Grunze is a member of the society of long standing whose helpful co-operation is always present. Beside him, we have my old friend Dr. Witte, our guest, whom I wish to thank for his readiness to lead this conference and to make his expert knowledge available to us.

Like other malignant disorders, gastric cancer has certain pre-stages where it is still restricted to the mucous membrane. A pioneer in this field of research is Prof. Gutmann of Paris; he was the first to establish the value of early diagnosis for a successful treatment of gastric cancer, and we are honoured by his attendance at this symposium. The same is true for our Japanese colleagues who by introducing the fibrescope, have contributed so much to our understanding of stomach micro-carcinoma. We are glad to welcome Prof. Kawai, Director of the Endoscopy Department of Kyoto University and a representative of this leading gastroenterological school. The German participants of our conference are mainly followers of Prof. Henning and the "Erlangen Group". The mention of this group calls to mind various technical improvements in endoscopy, as well as fundamental cytological and histological studies.

We feel honoured by the presence of our foreign colleagues from Austria, Brazil, France, Hungary, Italy, Japan, Norway and the United Kingdom, who did not refuse the inconvenience of travelling in order to attend this meeting and to participate in our discussion.

I should like to stress the fact that progress in science can only be promoted by the interchange of experience and knowledge in the course of international meetings such as ours today. The "half-life" of scientific knowledge is shrinking rapidly, but this is not the moment for giving up. Our patients are always entitled to get the best treatment available, and that can be guaranteed only by keeping science up to date.

In my capacity as a pathologist and histologist I should like to remind the audience briefly of some facts. In Germany, stomach cancer is still the tumor incurring the highest death rate. It is closely followed by bronchus carcinoma; only a few cities show an inverted relation of these two . High mortality statistics and a discoura - ging rate of therapeutical success may give rise to a feeling of resignation. The five-year-survival rates are below 10%; the cause seems to be none other than a

lack of early diagnosis. More than 50% of all gastric cancer patients are already in a state of inoperability on the day of their first diagnosis. When they undergo surgery, i.e. radical removal of the tumor and its metastases, these patients are yet bound to die within two years' time.

Survival chances for gastric cancer patients do improve if the tumor can be detected in an early stage. You are all familiar with the progress in early diagnosis of obstetric carcinoma which was made possible by the invention and application of new methods. For the past two decades and under the direction of my predecessor, Prof. Flaskamp, our society has contributed a great deal of leadership and practical help to this campaign. For anatomical reasons, the early diagnosis of gastric cancer is definitely more difficult than that of cervix carcinoma.

This audience will have to discuss and evaluate all future aspects of the problem, notwithstanding many promising developments in radiology, endoscopy, histology and cytology that have recently shown us new paths. Epidemiology of cancer and especially of gastric carcinoma have been topics of an international symposium held by our society last year (GRUNDMANN and TULINIUS, 1972), therefore this item has been excluded from this year's program. Nevertheless, I wish to inform you of some results of the previous conference:

The frequency of gastric carcinoma varies in different parts of the world; in the USA and in Australia it is relatively low, in Japan, Chile, Poland and Germany, the incidence is relatively high. Today, as we are aware that racial components are of no importance, the disparity can be traced back to two factors:

1. The mean life expectancy of the population in general. Stomach carcinoma is a tumor which occurs at an advanced age of the patient, usually above fifty years. Therefore a lower rate of stomach carcinoma will be found in countries with shorter life expectancy. Statistics of Third World countries are influenced by this fact.
2. Environmental factors are important, but nutritional factors and eating habits in particular. In general, inhabitants of cities are in a better position than people living in rural areas, and females are better off than males (STASZEWSKI, 1972).

Fortunately, stomach cancer is on the whole continually decreasing. Death due to a malignant tumor of the stomach has declined in Germany from 54 per 100.000 males in 1956, to 41,8 in 1967. The same decline is evident in other countries, above all in the USA, but also in Japan (DOLL, MUIR and WATERHOUSE, 1970) which has the highest incidence of stomach cancer in the world.

Gynecologists have been great pioneers in the field of early cancer detection, and that is why we have asked Dr. Zinser, one of these pioneers, to give us the first lecture. We have invited him to report on approved models and methods in gynecology in order to provide aims and ideals for which we could strive in gastroenterology.

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Some Historical and Topical Remarks Made by the Chairmen

H. Grunze and S. Witte

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Early diagnosis of gastric cancer, being a major step towards gastric cancer cure, is a challenge of long duration.

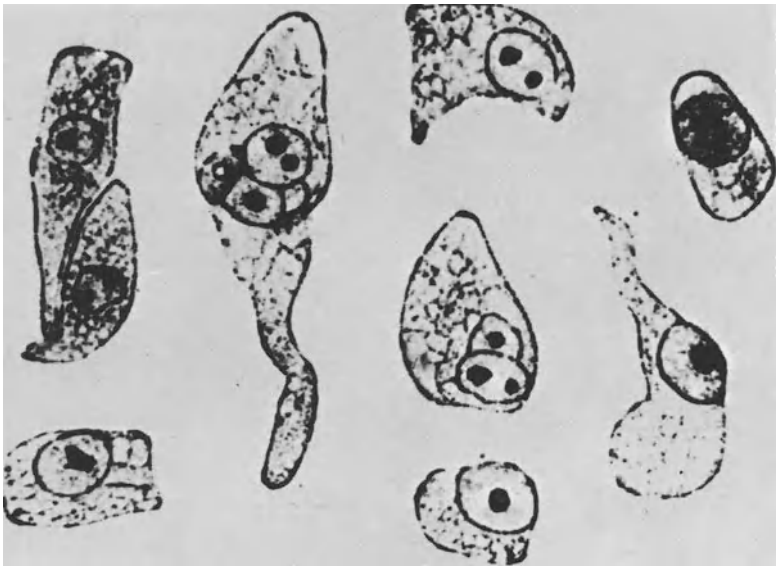

Fig. 1. G. MARINI. Typical tumor cells in a gastric washing (1909)

It was in 1909 (Fig. 1) when MARINI in Bologna decided that in the future, physicians convinced of the usefulness of cytological examinations on gastric washings as firmly as they were already convinced of the value of microscopical analysis of the urine sediment, would no longer retard the diagnosis of a gastric cancer until the tumor is palpable, i. e. in a stage when surgical intervention , if not definitely pernicious, would not be of any use whatsoever.

All efforts for promoting early gastric cancer diagnosis have been listed in a complete survey by WANKE (1971). The names of TURCK (1895), KONJETZNY (1913), PAPANICOLAOU (1947), HENNING (1947) and especially that of Dr. GUTMANN (1932) should be mentioned. It was GUTMANN who together with his Paris colleagues, inaugurated the modern synoptic approach towards early gastric cancer diagnosis, as is documented in Figs. 2 and 3. The widespread use of combined

LE CANCER DE L'ESTOMAC
AU DÉBUT

ÉTUDE CLINIQUE, RADIOLOGIQUE ET ANATOMO-PATHOLOGIQUE

PAR

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PRÉFACE DU P[R] A. GOSSET

AVEC 563 FIGURES DANS LE TEXTE

G. DOIN & C[IE]
ÉDITEURS
8, PLACE DE L'ODÉON, PARIS - VI[E]
1939

Fig. 2. Photo set-up composed of the front-page and some items of the contents of Dr. GUTMANNS monography. The modern synoptic approach of this pioneer book is obvious

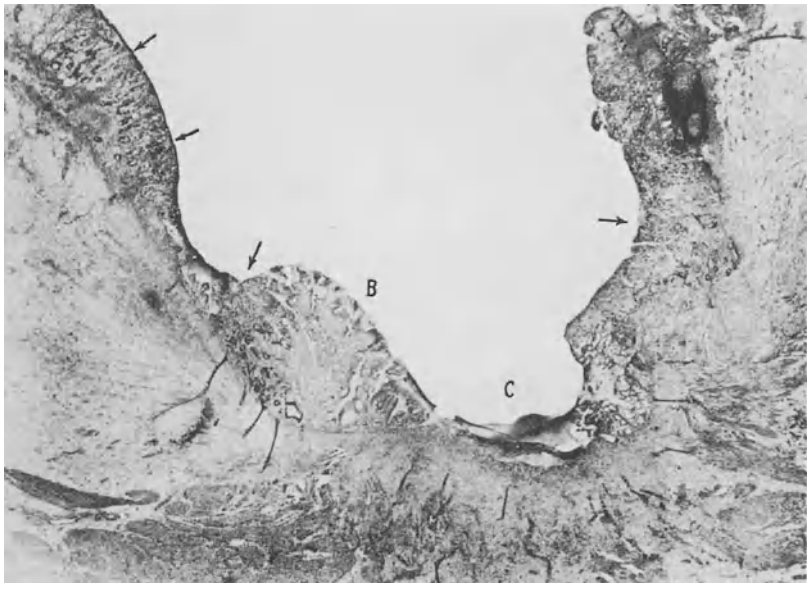

Fig. 3.= Fig. 436 of Dr. GUTMANNS Monography: Ulcer with partial cicatrisation and cancerisation. C: Granulomatous ground, B: Adenomatous knot, partly degenerated (left of the arrow). The 3 other arrows indicate epthelial areas being transformed into cancer

radiological, endoscopical and histological examinations of patients in today's diagnostic centres has its precursor in the work of this French research group. Another rapid improvement in diagnostic techniques was stimulated by the gastrofiberscope which had been originally devised by HIRSCHOWITZ (1958) and was then improved in Japan, where the leading centres of the world for detection of the so-called "early gastric cancer" have been established (Ref. see Monograph ed. by MURAKAMI, 1971).

All over the world, diagnostic results of colleagues interested in early cancer diagnosis are rather promising, as far as single and individual examinations are concerned. Since gastric cancer has a very high frequency it now appears justified to raise the question whether, besides the well-known Japanese efforts towards mass screening, the time may have come for European programs, too. With intention to analyse this problem the "Society for fighting Cancer, North-Rhine-Westphalia" (GBK) has organized this symposium, and all participants have been asked by the chairmen to answer, if possible, the following questions:

1. Which stages of gastric cancer disease have been detected so far?
2. Which technical means, efforts and ways of organisation have been employed in hospitals, outpatient clinics, in the G.P's consulting room or in mass screening? In the present stage of development, are there already any propositions for an improvement of procedures such as may result from the participants' own experience?
3. Which difficulties and problems have been met so far?

4. Were the expenditures in various fields of application justified from an economical point of view? Would anybody want to advocate a pilot study on gastric cancer mass screening in Europe, or, which other problem should have priority before such studies were taken up?

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Experiences in Early Detection of Carcinoma Colli Uteri

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As you all know, the gynaecologist has at his disposal certain optical methods for detecting cancer in the cervix uteri : colposcopy and colpomicroscopy. Besides these, there is another valuable method, the colpocytology. The advantage of the latter lies in that material for examination can be taken directly out of the areas most susceptible for tumor. The application of these methods is simple. In fact, they can be used in every routine examination, and may be repeated as often as necessary. We see, therefore, that favourable conditions are existing for extensive medical examinations. Their effectiveness and efficiency in cases of cervix cancer shall be critically appreciated.

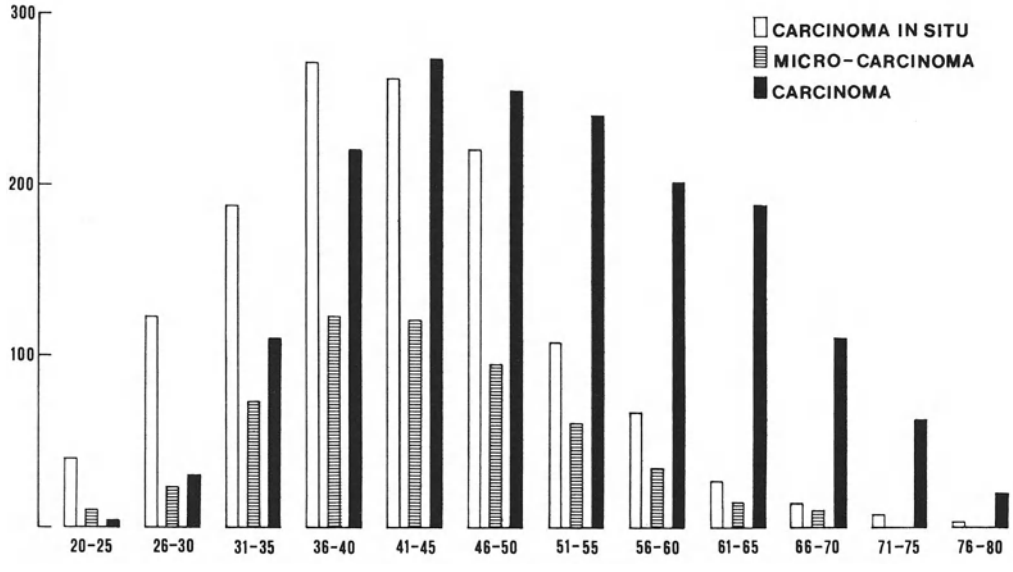

Fig. 1. Age-distribution of 3598 cases (1957 - 1964)

The colposcopic viewing of the ectocervix with magnification from 10 to 40x will give characteristic pictures which, in principle, could be attributed to irregularities in the morphological structure of the capillary vessels. This corresponds to

a variety of atypical epithelium occurring in areas of squamous and columnar epithelium with different behaviour. (Nearly 70% of all pre-cancerous diseases could be recognised optically with the help of acetic acid and SCHILLER's test). However, about 30 % of the atypical epithelia evade the colposcopic viewing because they are hidden intracervically.

After vital staining of the surface of the portio vaginalis with toluidine blue, it is possible to judge, with the help of colpomicroscopy, the structure of the nuclei in the superficial cell layer. There is, in fact, nothing but cytology in vivo to supply the necessary information about the situation in the ectocervix. Its assertive value is almost equivalent to that of colposcopy.

In gynaecology, colpocytology is one of the most important methods for cancer detection. The cytological interpretation of a cervical smear allows differentiation between benign changes of cells derived from metaplastic epithelium and other cell types originating from dysplasia.

From the constituent of cells found in a cervical smear, one can recognize the atypical epithelial proliferations related to carcinoma in situ; finally, a pointer to genuine exuberance of cancer cells can be expected. The indication for a histological examination based on cytological findings, will be laid rather early in the dysplasia stage and not wait for final diagnostic corrective.

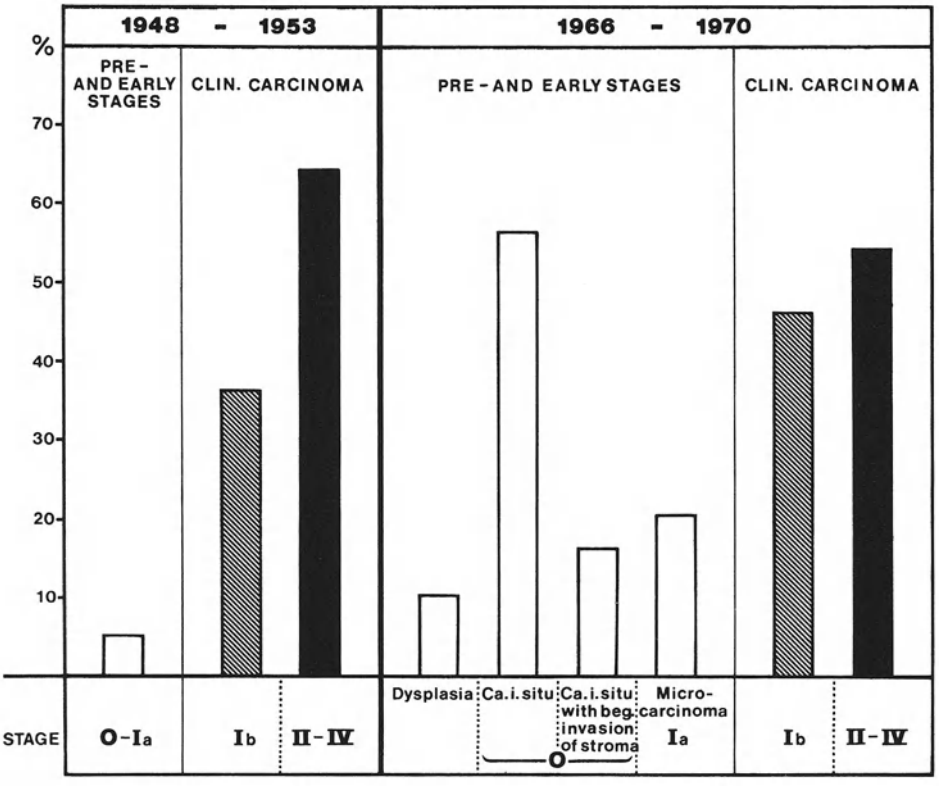

Fig. 2

The procedure for early gynaecological diagnosis does not only enable us to completely register the early cancer cases or the clinically occult malignant processes, but also helps us to identify their presumptive and obligatory precursors.

But of course, excellent working conditions are a prerequisite for the techniques of collecting samples, and making cytological assessments and histologic preparations.

Among all cancer localizations, the cervix uteri is the only region where the problems not only of early diagnosis, but also of prevention of cancer have been solved methodically. Before a severe dysplasia as the facultative, or, especially, a carcinoma in situ as the obligatory prephase will develop into cancer, a period of 10 years may have elapsed. This fact is proved for non-invasive and for invasive stages of cancer among the different age groups (Fig. 1). There is sufficient reason to believe that yearly medical examinations of women over 30 will lead to , at least, a significant reduction in the incidence of cervix cancer. About 50% of carcinoma in situ is found in women between 30 and 40 years.

On the other hand, out of the 16 000 000 women in the Fed. Rep. of Germany aged between 25 and 65 and as such liable to cancer, only a small group of some 20 or25%, (probably even only 12 to 15%) will go regularly for medical check-ups or prophylactic examinations. The efficiency of an extensive screening program can be seen from the results of a cytologic-medical check-up conducted by the Society for Cancer Control (GBK) over several years (Table).

Table

Years	Total of cases	Histologically confirm. cases	carcinoma in situ	%	carcinoma	%	Yield
1957-71	1.195.524	12.608	7.898	62	4.710	38	1%

Partial results from a cytology laboratory reveal that among 1000 000 women examined, 12.608 showed histologically atypism of epithelium. 38% of these were genuine cancer. The rest of them (62%) were cases in initial stages. There was a gain of 1 %. Out of 100 early cases, only 3 or 4 could not be registered cytologically. Success and overall expenses for such a screening operation remain altogether in a satisfying relation. The cost involved in detecting positive cases cytologically, and non-invasive cases histologically (conisation included) approximates 150 to 200 Dollars per case, while the expenses incurred for cancer-treatment, (including all medical therapies) are estimated at 7.500 Dollars.

A certain number of problems related to mass screening could easily be solved if a practicable way of counter-checking cytological diagnoses could be found. One promising method seems to be impulse-cytophotometry, but then its adequacy as a screening method has to be proved yet.

Since the introduction of extensive prophylactic measures, a remarkable change has taken place in the composition of clinical material. Fig. 2 shows the situation before the years 1948 - 1952, and after intensifying cancer detection by means of early diagnostic methods in the years of 1966 - 1970. Before, the rate of precan-

cerous and early cancer stages had totalled 5% at most, but these had been results obtained at random and by accident. Today, these two groups amount to 60% . In a detailed and very careful histological survey (1450 cases) we find the following rates of incidence:

Besides a severe form of dysplasia occurring at a rate of 10% and which, as a rule, is irreversible and liable to turn directly into cancer, there is also the carcinoma in situ amounting to 55%. Next comes the carcinoma in situ with early invasion of

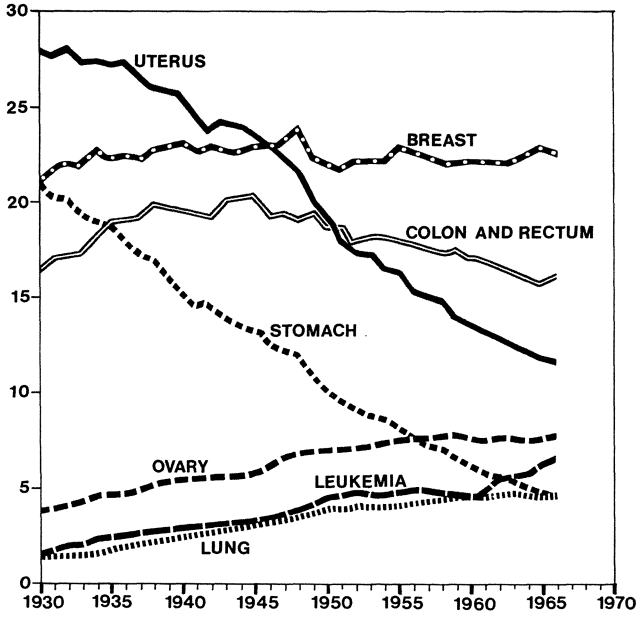

Fig. 3. Death-rate per 100 000 women

stroma (16%), and finally the microcarcinoma with a deep growth of 0,5 cm and a diameter of 1 cm which occurs at a rate of about 20%. The non-invasive atypical epithelia (including histological forms with early stromal invasion) are arranged under a special group 0. Microcarcinoma, being a separate group by itself, is listed under group Ia. This means it is completely distinguished from the cancerous stage Ib, the histologically more advanced one. Stage Ib could be recognised macroscopically, except in about 30% of cases where it is situated intracervically. This meticulous division is necessary because the extent of surgical therapy will depend on histological findings : For cases belonging to group 0, conisation or a simple hysterectomy should be tried. For the Ia cases, the more extended hysterectomy is indicated. Moreover, classification is a necessary condition for comparative monitoring of the healing rate based on a period of five years or more.

No conclusions can, as yet, be drawn from the fact that macrocarcinomas (listed under groups Ib to IV following the international convention) have shown an obvious decrease in their incidence among clinical material. We have still to find out to what extent the methods applied long before the era of early diagnosis, reflect a recurrent tendency in the frequency rate of cervix cancer.

During the past 30 years the mortality rate relative to a population of 100.000, has gone down from 28 in 1930 to 12 in 1960; and the incidence rate among the female population sank from 22 to 12 per 100 000, as we all know. (Fig. 3.)

Stage	1912-1925				1924-1936		
	Five-years survival Operation	Irradation	Five-years survival of all cases	Primary mortality	Five-years survival According to stage	All operated cases	Five-years survival of all cases
I, II, III	45%	WERTHEIM 35% SCHAUTA 38,2%	32,5%	OPERATION 16,7% IRRADATION 17,2%	WERTHEIM 15-18% SCHAUTA 7,7% IRRADATION 2,3%	I 69% II 50% III 25%	50%	36,1%
IV					IV 0%		

Stage	Annual report 1949-1953			Own cases 1966-1970					
	Percentage of cases	Five-years survival in % According to stage	All cases	Percentage of cases	Five-years survival in % According to stage	All cases	Percentage of cases	Five-years survival in % According to stage	All cases
I							20,0	98,0	19,6
Ib	24,3	72,2	17,54	39,0	72,2	28,2	31,0	72,2	22,4
II	39,4	50,9	20,05	36,5	50,9	18,6	29,0	50,9	14,8
III	29,6	28,0	7,29	21,6	28,0	6,1	17,0	28,0	4,8
IV	6,7	7,7	0,52	2,9	7,7	0,2	3,0	7,7	0,2
Five-years cure (all cases)			45,4			53,1			61,8

Fig. 4. Results of treatment of uterine cervix carcinoma. a 1912 - 1936, b 1949 - 1972

Strikingly enough we find in clinical stages a certain degree of deviation to the left in favour of group Ib which has the best therapeutical prognosis. This is shown in Fig. 4 where a compiled group within a period of 6o years has been carefully studied.

Finally, we investigated therapeutical results in that same period; here are the most important figures from the facts compared:

Operability has risen from 45% towards 65-70%. First, the five-year-healing border rose from 17 to 36%. This increase in the rate of therapeutic success is due partly to the important progress made in surgery and in radiotherapy, partly to a decline in the primary death rate, today notably reduced from 15-18% to 1%. On the other hand, because of improved initial conditions for clinical cases, the rates of surgical performance have risen in the past 20 years. This can be seen in cases with favourable prospects of treatment (groups Ib and II) within the five-year-healing period; these groups comprise 45 to 53% of cases, and 62% when the group Ia is included.

When we ask how many women could be saved from death of cancer - considering that even group 0 is potentially cancerous - we may get a survival rate of 80 to 85%.

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Surgical Treatment on Malignant Tumors of the Stomach

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CARCINOMA

General Aspects

Carcinoma of the stomach begins as a circumscribed lesion in the mucosal layer; it grows, produces metastases and will, without treatment, lead to death within 5,5 months up to maximally 30 months after diagnosis (REMINE, PRIESTLEY, BERKSON, 1964). The speed of growth is usually irregular, but may be steady in an individual case. Clinical symptoms develop in a comparable manner: they begin with a so-called silent period which is then followed by indifferent symptoms; the latter will not become more distinct until the carcinoma is spreading. Therefore, the classical clinical diagnosis based on subjective discomfort, clinical symptoms and a positive histological diagnosis comes normally too late for every second patient. The treatment of choice is a radical partial or total resection of the stomach and the adjacent organs in so far as they are affected or endangered. The patient is cured if the entire tumor has been completely removed. For patients who have survived this operation for five years or more, the mortality risk is similar to that of the normal population. This statement based on clinical and surgical experience remains fundamental even though new immunologic and kybernetic models of carcinogenesis may arise and force us to modify our concepts.

The most important objectives in diagnosis and therapeutic treatment are as follows:

1. Investigation for and detection of malignant tumors while they are still in a locally resectable dimension.
2. Systematic radical resection of the affected stomach in the same fashion as employed for other organs.
3. Careful consideration of physiological conditions when the reparation of the gastric defect is planned.

Although it is possible to outline the main requirements for a successful therapy, the results of surgical techniques are not yet satisfactory (AMGWERDT and HAMMER, 1972; SCHWAIGER and v. LESSEN, 1966). These incongruous aspects for the treatment of stomach carcinoma seem to spring from several special difficulties encountered in normal clinical routine.

Diagnosis

The importance of an early diagnosis of gastric cancer is proclaimed in almost every paper dealing with this subject; however, such repeated postulations did not lead to any visible progress in surgery until very recent years. The results of several Japanese teams (HAYASHIDA and KIDOKORO, 1970; JOJIMA, 1969; OSHIMA, 1969; OSHIMA, WITT and BURGER, 1972) show that the detection of early cancer is indeed possible. It was recorded that 90% of patients diagnosed by means of intensive fiberscope endoscopy, were still alive five years after the stomach resection (Table 1). Admittedly, a comparable rate of success is not evident in Western Europe.

Table 1. Five year survival rate of patients with early gastric cancer classified according to endoscopic and macroscopic findings (HAYASHIDA 1969)

Type of early gastric cancer	No. of cases	five year survivals	survival rate (%)
I	46	40	87%
IIa	33	29	88%
IIb	7	6	86%
IIc	109	102	93%
IIc + III	83	82	99%
III + IIc	30	29	97%
III	31	29	94%
IIa + IIc	11	9	82%
IIc + IIa	6	4	67%
Others	5	4	80%
Total	361	334	93%

Endoscopical examinations of the stomach have two different functions and aims:

1. The early diagnosis of gastric cancer. We can see a remarkable difference in frequency of early cancer between Europe and Japan (up to 30%!). Direct correlation with better survival rates is the immediate result. We may assume, therefore, that the full range of the available diagnostical techniques are not being sufficiently exploited.
2. Endoscopical examination of the cancerous stomach as a prerequisite for surgical planning and tactics. This implies necessarily an exact and detailed description of the macroscopic type of cancer and of its distal limits. The examiner must be familiar with surgical treatment and operation "strategy".

Although endoscopy seems to be the predominant technique in diagnostical progress, other well-known and approved clinical, biochemical and roentgenological findings have also proved valuable, in particular for diseases with a higher risk of cancerous degeneration. These are for example large solitary and multiple polyps, atrophic gastritis combined with hyperchromic anemia, and ulcers of the proximal lesser curvature and of the resected stomach. The same applies to the so-called uncertain or suspect findings in the upper gastrointestinal tract, e. g. an ulcer that does not heal within six weeks or more, an ulcer of the greater curvature, and certain changes in diseases which are taken for benign.

Three factors seem to be of great importance:

1. Critical re-examination of the given diagnosis;
2. the essential information obtained from the patients during exploration;
3. the critical and watchful attention of the general practitioner.

If these main points are observed, surgical procedures should have better results. Even a delay in diagnosis may be compensated when all symptoms of the stomach, including the unsignificant ones, are clarified quickly and completely.

For the fight against gastric cancer, early diagnosis as well as adequate, radical proceeding during the operation are essential. The balance of these two factors is necessary. Experience has taught us that a diagnosis that was made too late, can not be compensated by increased radicality; for the future we may presume that radical surgery will not be rendered unnecessary by perfected early diagnosis. One of the very important tasks in the near future should be the establishment of endoscopical examinations and biopsy as routine methods for the early diagnosis of gastric cancer.

Surgical Procedure (Tactics)

The most important aspects of stomach cancer surgery during the last decades have been standardization and radicality. The improvement in surgical results supports these principles. Evaluating the data from the Surgical Department of the University of Bonn (GÜTGEMANN and SCHREIBER, 1964; SCHREIBER, 1966) we find that the rates of five-year-survival after distal partial gastrectomy rose from 1,9% (until 1925, 568 cases) towards 5,1% (until 1947, 474 cases) on to 9,6% (from 1947 to now, 312 cases). Proximal partial gastrectomy and total gastrectomy rose up to 10,1% (445 cases). The real mark of surgical efficiency which means relative resectability, went up from 7,1% (156 cases) to 16,1% (149 cases) and on to 29,1% (103 cases with distal partial gastrectomy). The percentage for proximal partial gastrectomy and total gastrectomy rose from 7,4% to 20% (212 cases). Among the correctly diagnosed patients, every tenth patient survived more than five years after radical surgical treatment, and out of this group, every fifth patient who was resected showed this success. This means in detail that after distal partial gastrectomy every third patient can be cured, after total gastrectomy every fifth patient, and after proximal partial gastrectomy every fifteenth patient.

Thus, rates of surgical efficiency and success have doubled since 1948, and this seems to be a common trend (AMGWERD and HAMMER, 1972; BOECKL, 1963; HEGEMANN and SCHAUDIG, 1966; OSHIMA, 1969). This progress is based on systematically extended resection and can be derived from the constant rates of operability and resectability. It is significant that mortality rates have not risen in the period under observation: until 1925, mortality was 27,6% (156 cases); until 1947, 22,8% (149 cases); until 1962, 22,8% (189 cases); when proximal and total gastrectomy are included: 26,5% (332 cases). These latter operations carry still a high risk and have a mortality rate of 30,4% and 32,8% respectively.

The operative procedure (we call it "tactics") has several main objectives:

1. Confirmation of diagnosis: Histological examination and classification should be undertaken during the operation if any doubts still remain. Histological examinations should be performed in any case, even if the situation does not allow resection. This is the only way to prevent possible errors. Tumors, if present, should be classified and further information gained. So-called rare tumors and specific granulomas can be definitely diagnosed only by histology.

2. Clarification is necessary for : localization, spread and macroscopic type of cancer, infiltration in gastric lymphonoduli, situation of the greater and lesser omentum, transverse colon, pancreas, diaphragma and liver.

3. Search for distant metastases within the peritoneal cave. Monitoring is required for: parietal peritoneum, Douglas cavity, mesenteric hilus of the liver, lymphonoduli above pancreas and spleen.

4. Based on these data a decision should be made as to whether radical or palliative treatment is indicated.

5. It is often difficult to decide about the exigence of a resection. The final resolution should be made by a well trained and experienced surgeon. Radical resection is contraindicated for tumors broadly invading the retroperitoneum and having multiple distant metastases. But size is not the only relevant factor: a large tumor is not necessarily unresectable, and small tumors do not always have a good prognosis.

6. We are not sure of the value of cytotoxic agents for gastric cancer surgery. Some surgeons use solutions of formaline (0,5%), mechlorethamine (1-2 mg%), sodium-hypochlorite (0,35%), Thio-TEPA, Pipobroman and sublimate (2%) Mechanical blocks used for the prevention of tumor spread are probably useful.

7. All essential data regarding tumor and organ characteristics should be retained for documentation.

When a radical resection of gastric carcinoma is possible, the following rules should be respected (GÜTGEMANN, 1964) :

1. Radicular resection of all (four) gastric arteries.

2. Resection of all lymphatic organs of the stomach, even the collecting nodes, and splenectomy in cases of proximal and total gastrectomy.

3. Resection of the greater and lesser omentum.

4. Sparing of the so-called "limits or zones of security".

5. Resection en bloc.

Special attention to the "limits of security" seems to be of great importance. We collected the following anatomical information on this subject :

There is a tendency to spread within the stomach wall and the lymphatic organs towards the oral end of the lesser curvature, on to the celiac trunc and to the mediastinum; this trend can be expected in more than 80% of gastric carcinomas. Ulcerating and exophytic carcinomas usually have a lesser degree of infiltration. This is true even for highly differentiated carcinomas, whereas anaplastic tumors grow at a more rapid pace in the submucosal layer without any palpable or visible trace. Every second recurrent carcinoma will be found on the gast ric side of the anastomosis.

In consideration of these tendencies great care should be taken to ensure that a large proximal limit of security is maintained near the lesser curve. In the scirrhous type we propose resection at a distance of 10 cm, in other types at a distance from the tumor of at least 4 cm. Usually, a span of 2-3 cm between the aboral end of the tumor and the incision will be sufficient. In carcinoma of the cardia, routine should command the resection of the lesser curve down to the cardia. Exact classification of the tumor and determination of the security zone will lead to an optimal

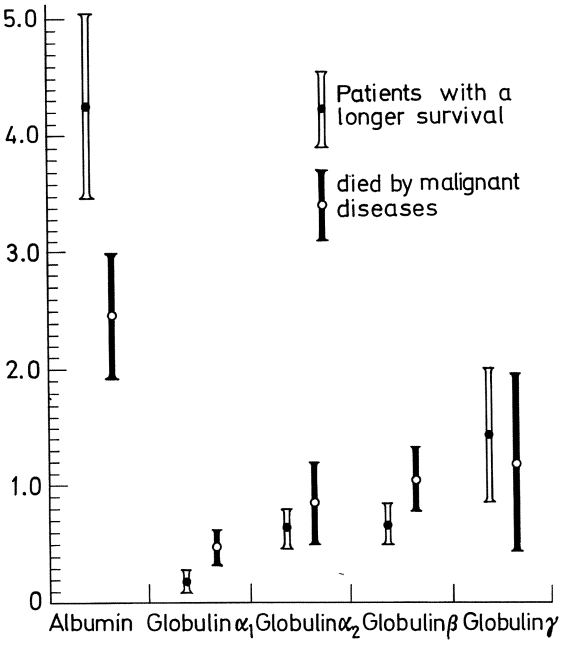
pattern of resection. The most appropriate form seems to be a partial resection of the stomach. According to the site of tumor we distinguish distal and proximal partial gastrectomy. All resections in our study were made stepwise, so that a proximal partial gastrectomy seemed to be a Billroth-I-resection, but turned over. When a carcinoma of the proximal stomach invades the terminal oesophagus, we prefer transthoracic resection or combined transthoracic-transabdominal incisions.

Total gastrectomy is indicated only in cases where partial gastrectomy seems to be not sufficiently radical. Total gestrectomy may also be indicated for anaplastic carcinoma in more than half of the stomach, and for an atypical wide lymphatic spread such as, for example, a proximal gastric carcinoma with metastases in parapyloric nodes.

Besides these general rules, particular individual factors must be taken into account. In difficult situations a decision in favour of radical resection may be modified by the presence of signs of better prognosis:

1. Carcinoma of Bormann-type II with central necrosis and wall. The visibility of such forms is better than that of other types of gastric cancer in patients surviving five years after operation (SCHREIBER, 1966).
2. Normo- or hypochloric acidity of gastric juice. The correlation between this condition and the malignancy of the tumor, mortality risk and late results has not yet been clarified. Achlorhydria and rare hyperchloric acidity are correlated with bad prognosis.
3. Normal level of albumine with an increase in the alpha$_1$-globuline fraction. A significant discordance between these proteins correlates with bad prognosis (Table 2).

Table 2. Proteins and vital prognosis



The duration of clinical symptoms is of little prognostic value. Even the histologic type of the carcinoma has no influence on the choice of a therapeutic approach. The distribution of histologic types among patients surviving the operation more than five years, does not differ from the pattern defined at the time of their operation. Of course, this may be the result of an extremely well chosen strategy in operative procedures.

Although radicality in surgical treatment is accepted and approved in general, its results are often not statistically comparable. The available data concerning resectability, mortality risk and survival rates differ widely (BERNDT and GUMMEL, 1967). Besides others, the following reasons may be responsible:

1. Patients treated at random are not comparable.
2. Indication criteria and surgical procedures (tactics) are not uniform.
3. Statistical methods of assessing significant factors are not generally accepted.

This situation ought to be improved by the use of better means of documentation. All special aspects of patients and of their tumors should be defined exactly and recorded. We propose to apply to the problem of gastric cancer a modified TNM-system, in accordance with BERNDT and GUMMEL (1967). If there was a better comparable situation from the start, the results of treatment could also be meaningfully compared. Thereby, we should be able to reduce the number of factors that are still imponderable and only suspected to be significant. A most important task for the immediate future is, therefore, to establish radical operation and subsequent careful documentation as a generally accepted proceeding.

Reparation after Resection

Progress in the surgical treatment of stomach cancer is sometimes jeopardized by unsatisfactory results after partial and, in particular, after total gastrectomy. Many papers deal with the grave impairments of essential metabolic processes; similar problems were found in patients whose remaining stomach capacity is very small. As these defects could hardly be remedied by medical treatment alone, a number of modifications were developed for gastrointestinal reparation techniques. Poor results were evident in all cases where the resected stomach was not or unsatisfactorily replaced. A good voluminal capacity is the most important factor for a satisfying stomach function. Our method was to take a long jejunal loop (25-35 cm) which is isoperistaltically interposed. Most of the previously observed problems following a resection are thus avoided : peptic oesophagitis by reflux is negligible, adequate stomach capacitiy and food-retention time can be guaranteed and the essential functions in the whole upper gastrointestinal tract are timed regularly. Parenteral substitution of Vitamin B_{12} at regular intervals is necessary. After this, the operated patients will develop a proper appetite and do not need any dietary supplements. Some of them recover completely and are able to work. Out of 36 working men, seven survived and five of them were able to return to their previous jobs (SCHREIBER, 1966).

These results in total gastrectomy were to the benefit even of proximal and distal partial gastrectomy. When the capacity of the gastric remnant is too small (one third or less) we take an isoperistaltic jejunal segment of 12-15 cm and place it between a proximal stomach and the duodenum, or between oesophagus and a distal stomach respectively. In proximal interposition we add a plastic closure to prevent regurgitation, in accordance with NISSEN, FRANKE-NEY, HOLLE and others.

SARCOMA

Regularly monitored stomach resection cases show that the incidence rate of sarcoma is about 5%. Problems of diagnosis and surgical treatment are not different from those in carcinoma cases. Three special points are important:

1. Patients often suffer considerable pain.
2. A discordance is apparent between the wide local spread of sarcoma and the subjective condition of the patients.
3. Characteristic prognostical criteria.

We have learnt that the historically conditioned poor prognosis is not valid for all types of sarcoma; some of them do not show so much destructive growth. When searching for reliable prognostic criteria, HAMPERL found out that a reduced level of albumine pool and a rise in alpha$_1$-globuline indicate a trend towards bad prognosis, whereas a normal protein distribution correlates with better prognosis (cit. in SCHREIBER, BARTSCH and SIEDECK, 1964). These correlations were found in reticulosarcomas, the most frequent type. They should influence surgical indication and tactics when followed by radiological and cytotoxic treatment.

RARE TUMORS

Indications and tactics in operative procedures are analogous for the rare malignant tumors of the stomach, e.g. lymphogranuloma, chorionepithelioma etc., and also for carcinoma in the stomach that has already been operated. Prognosis for these recurrent or new tumors is still very bad (AMGWERD and HAMMER, 1972). In so far as the stomach is attacked by systemic malignant diseases, e.g. leukemia, reticulosis, or sclerodermia, palliative surgical procedures may become necessary in addition to specific medical care.

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Pathogenesis of Stomach Cancer

Problems of Formal Genesis of Carcinoma of the Stomach

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For early diagnosis, classification and prognosis of stomach carcinomas, the problems concerning their formal genesis are of the same importance as those of frequency, different in each country of the world. We know from numerous studies (SEGI and KURIHARA, 1966; DOLL et al. 1966, and others) that the highest mortality rates for stomach carcinoma occur in Japan, Chile, Iceland and some East-European countries. Germany still has a relatively high mortality rate, whereas in the USA, Canada, Australia and other countries the risk of stomach carcinoma is relatively low. Such big difference in frequency usually concerns a younger age-group; stomach carcinoma is differing substantially less in its incidence among the respective older age-groups. This fact has some relevance also for the problems of formal genesis: LAUREN (1965), TAUCHI et al. (1960) and others have shown that, despite all heterogeneity, different types of stomach carcinoma (oviously developing differently also in terms of form) have differing age distributions. In fact, MUNOZ et al. (1968) were able to show that there are really differences in frequency of carcinoma types, and that they depend on the different total frequency.

Problems related to formal genesis of stomach carcinoma in general are much more complicated than those concerning comparable intestinal carcinomas, and many questions closely connected with early diagnosis have not been clarified either. There are essentially three reasons for this:

1. The parent tissue, i. e. the gastric mucosa, is an organ of very complex composition, consisting of cells with different proliferative activity and differentiation. It has to be checked, therefore, to what extent each of these cell types may be responsible for giving rise to the formation of a carcinoma.
2. The experimental induction of carcinomas in the gland stomach for the purpose of studying formal genesis, has so far been restricted to a few useful models: N-N-2,7-fluorenylenbisacetamide and N-methyl-N-nitro-N-nitrosoguanidine are especially suitable. Even after the examinations carried out by STEWART et al. (1969), SUGIMURA et al. (1969), BRALOW (1972), SNELL et al. (1969) and others, many questions concerning formal genesis have not yet been clarified satisfactorily by experimental examination.
3. The early alterations observed in man have already led to interesting findings (NAGAYO et al. 1965). However, comparisons that would allow significant conclusions, have to be based on a sufficient number of examination series on the subject of early gastric cancer, collected for countries with a medium or low incidence rate for gastric carcinoma in general.

In contrast to the development of carcinomas on the skin or at the portio, it is unfortunate that no observations can be made about the development of cancer in the

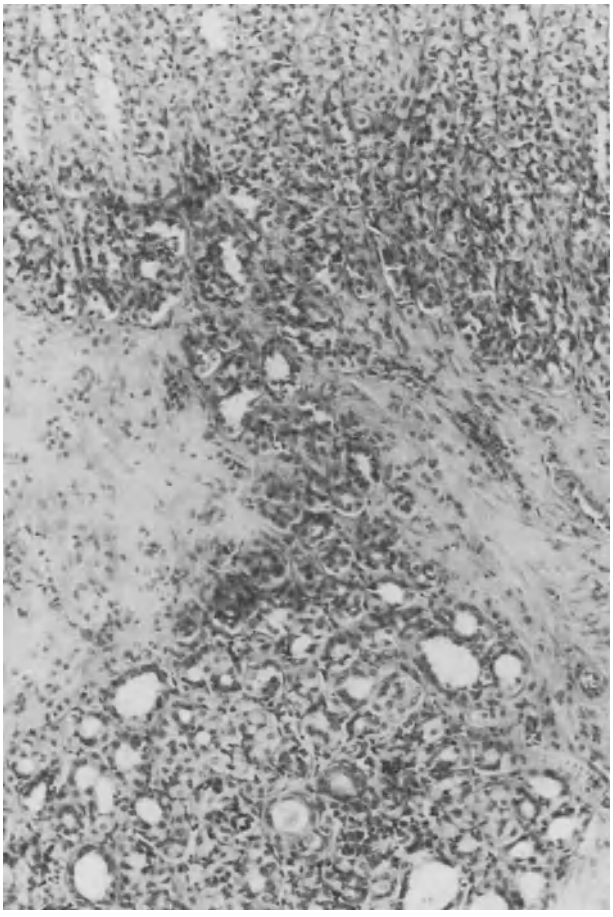

Fig. 1. Infiltrating adenocarcinoma at the base of the fundus mucosa. Rat, NNG. (SCHAUER and KUNZE)

stomach. Despite such restrictions it is already possible to make essential statements about formal genesis of stomach carcinomas by applying our general knowledge of carcinogenesis to our notions about the parent tissue, the gastric mucosa with its different proliferation and differentiational behaviour. Further conclusions can be drawn by comparing findings collected in experimental stomach carcinomas with findings in human patients.

1. Which cells in the gastric mucosa can be cancerised and thus formally become the starting point of stomach carcinoma?

In the specific glands of the mucosa at the stomach fundus, the chief and parietal cells are differentiated cells with an extremely low renewal rate, similar to that of the liver cells. It is not known whether they can be cancerised in the same way as the latter, and whether carcinomas of the stomach may develop from them. A decrease in the number of chief and parietal cells, observed in the pre-malignant phase after application of FAA, a gastric carcinogen, is probably due to a toxic effect. SCHAUER and KUNZE of our study group have induced experimentally with

NNG, an adenotubular carcinoma at the base of the fundus mucosa; possibly, it may originate from this kind of cells (Fig. 1).

We can only say for sure that up to the present day, no differentiated cells have ever been observed in stomach carcinomas either in experimental animals or in man. Such cells, analogous to those in highly differentiated hepatomas, would allow formal derivation from chief or parietal cells. However, it is much more likely that a carcinoma develops from either the mucous neck cells or the cardiac or antral glands. These glandular cells can divide without belonging to a tissue of high proliferative activity; thus, they may pass carcinogen-induced cell alterations on to daughter cells. The role played by the mucous neck cells is yet not clear. Some findings in experimental carcinogenesis by FAA and NNG seem to indicate the possibility that mucigenous adenocarcinomas may have their starting-point mostly in antral-pyloric and Brunner's glands. Highly proliferating surface epithelium is most important for determining where the starting-point of stomach carcinoma is. In normal gastric mucosa there is a proliferation zone of non-differentiated cells which provides for the physiological replacement of cells in various places: in the surface epithelium, in the fundus at the base of the foveolae, and in the antrum in the depths of the glands at their neck. Part of the daughter cells formed there will differentiate, lose divisibility and migrate to the surface in order to be shed into the lumen. Theoretically, an attack of carcinogens upon these differentiated cells is also possible. Yet, the lifetime of these cells migrating to the surface is so short that under the conditions of a normal mucosa, they could not possibly offer a formal startingpoint for stomach carcinoma.

Another condition is found in the cells of the proliferation zone; there are always daughter cells which may be able to transmit a carcinogen-induced malignant transformation to other daughter cells (EDER, 1969). This starting condition is fundamentally altered when there is no differentiation in cases of long lasting chronic gastritis - as has been demonstrated by autoradiographical examinations performed by KLEIN and LENNARTZ(1972). Then DNS-synthesising divisible cells can also be identified on the surface. In cases of intestinal metaplasia - according to intestinal mucosa - cells capable of proliferation are shifted towards the base after the typical mucous structure has disappeared. Such transformations are important since - as LAUREN and others have shown - certain groups of stomach carcinoma occur preferably at a higher age. These developed in most cases in a polypous form and resemble intestinal carcinomas so much that we may speak of an "intestinal type" of stomach carcinoma. Enzyme examinations made by WATTENBERG (1959) and by PLANTEYDT et al. (1960) are in conformity with this observation. This very type is - as MUÑOZ et al. have shown - more frequent in countries with a high rate of stomach carcinoma than in regions with a lower risk in general.

2. How do cancerised cells behave during the further formal genesis of carcinoma of the stomach?

The results of experimental carcinogenesis of stomach and intestines are essential for finding an answer to this question. When mucosa cells capable of proliferation are affected by a carcinogen and transmit this alteration to daughter cells as a consequence of their divisibility, there are two possible ways toward formal genesis - irrespective of the localisation of such cells and independent of the purely cellular alterations: These cells may, on one hand, maintain the physiological property of migration in spite of their transformation. Then the whole surface will be experimentally populated by more or less cytologically atypical cells (Fig. 2) which, along with increased proliferation activity, will lead to new polypous formations. Infiltrative growth will begin sooner or later, often with maintenance of

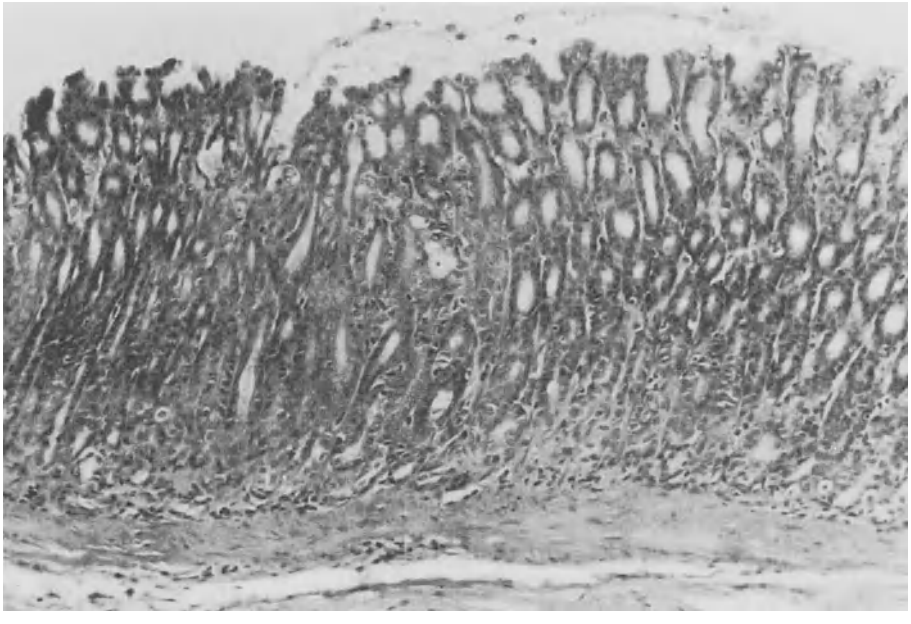

Fig. 2. The glands of the mucous membrane are populated by atypical cells. Antrum rat, NNG (SCHAUER and KUNZE)

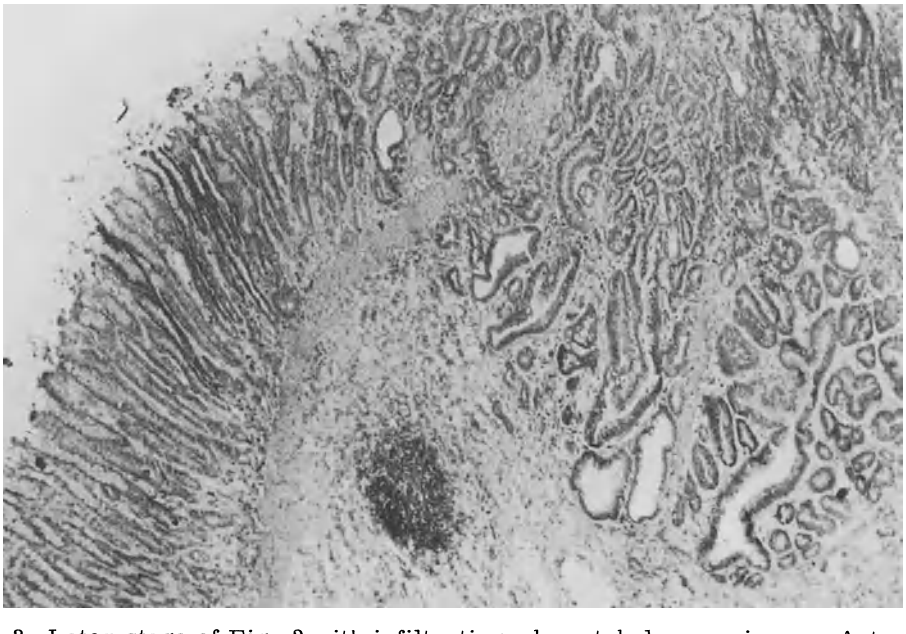

Fig. 3. Later stage of Fig. 2 with infiltrating adeno-tubular carcinoma. Antrum rat, NNG (SCHAUER and KUNZE)

the capacity for tubular structural formation (Fig. 3) Comparable findings in human patients with polypous neoformations are, in the early phases, known as borderline types or, later, as polypous carcinomas.

In the other case - with loss of the formation of contacts - separation from the epithelial complex and invasion of the stroma is effected, frequently in parallel with the property of monocellular mucilaginisation. The occurrence of both may happen in more or less pure form and thereby determine formal genesis. Observations of early alterations in experimental animals, but also in man (NAGAYO et al. 1965) revealed that both ways may be taken simultaneously or, at least, in short succession; this means that the formal genesis differs from that of a carcinoma of the intestine (WIEBECKE et al. 1973).

The interruption of physiological cell migration and the disturbance of differentiation have a serious consequence: the easy vulnerability of the surface epithelium during the activity of the stomach and the development of erosive or ulcerous defects. They are observed not only in man but also in experiments (BRALOW, 1972). Thus, it is intelligible that type I (protruded type, according to the classification of the microscopical early forms made by the Japanese Society of Gastroenterological Endoscopy) corresponds mainly to the first of the two ways of formal development. The main group of early stomach carcinoma is, however, found in group IIc.

3. Another problem in formal genesis, equally important for early diagnosis, is outlined by the observation of normal, non-atypical epithelium existing occasionally above an early carcinoma. With respect to the formal understanding of such findings, several interpretations are possible. There is, on one side, the suggestion that it may be only a mucosa spread beneath a normal epithelium, of a carcinoma far more developed at another site. A second possibility discussed would be that an eroded early carcinoma may be covered by normal surface epithelium growing from the sides and within the meaning of a regeneration. The third interpretation assumes the development of a carcinoma in the depth of the mucosa with early infiltration; at least in the beginning, there would be no chance of its occurring at the surface of the mucosa. The possibility of such a development in the intestines was demonstrated by experiments carried out within our study group (WIEBECKE et al. 1973). Observations on the experimental development of a stomach carcinoma reported by SCHAUER and KUNZE suggest that this possibility exists also for the stomach (Fig. 4).

Until now, observations of a similar nature have not been made in human patients. This is, however, not unexpected as it might be rather difficult to diagnose them as early carcinomas; in the advanced stage this form of development is no longer recognizable. It is therefore not known at present whether such a formal development is possible and if so, how often.

The present status of our knowledge about the formal genesis of the different forms of stomach carcinoma shows that some fundamental phenomena are clear. Many problems, however, still remain undetermined. Due to a more detailed analysis of the experimental carcinogens, progress has been made in the problems of the stomach and the increasing number of early alterations observed in man. A comparative analysis between countries which have a high and those which have a low rate of stomach carcinoma enables us to hope that the numerous unanswered questions will be clarified in the near future.

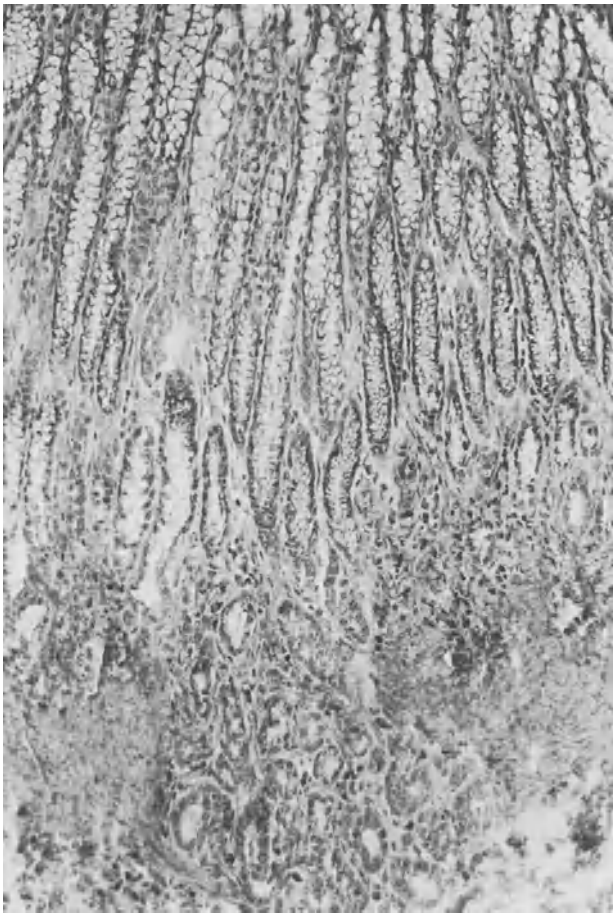

Fig. 4. Infiltrating adenocarcinoma at the base of antrum mucous membrane. The upper part of the mucous membrane shows abnormal mucus producing cells. Rat, NNG (SCHAUER and KUNZE)

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Discussions by Invitation

Malignant Degeneration of Gastric Polyps?

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Differentiation of gastric polyps based on biopsy specimens is not only problematic, but virtually impossible. The adenomatous polyp often shows a surface structure which corresponds to that of the hyperplastic polyp (SEIFERT and ELSTER, 1972). Therefore, a clear-cut diagnosis as we are used to perform in colonic polyps, is not obtainable in gastric polyps. It cannot be decided whether one is dealing with an absolutely benign process of hyperplasia or with an adenoma, i.e. a true neoplasm that might become malignant. The practical answer to this dilemma of diagnosis is the total removal of the polyp. But can this procedure, mandatory as it is for colonic polyps, also be applied to gastric polyps? Comparing the histological features of an adenomatous polyp of the stomach with a polypous adenoma of the large intestine, one is bound to observe differences that are due to the diversity of the matrix. The polypous adenoma of the colon is characterized by a dedifferentiation of the epithelium with loss of functional structure, that is, the goblet cells disappear and rod-shaped nuclei are developing (MORSON, 1970).

Adenomatous proliferation of gastric polyps, on the other hand, consists mostly of highly differentiated glands which correspond partly to the mucoid type and partly to the chief cells. If there are dedifferentiated epithelia we usually have to consider not an adenomatous polyp, but a proliferation of the neck region of the gland, or even the so-called proliferative type of intestinal metaplasia or epithelial atypia (a name coined by Japanese authors). I shall refer to this problem in another presentation. To express it in a more sophisticated way: one should think rather of a so-called epithelial atypia or an early adenopapillary cancer than of a "true" adenomatous polyp, when proliferation of glands with dedifferentiated or indifferent epithelium is observed. In other words, a comparison of the polypous adenoma of the large intestine with the adenomatous polyp of the stomach with respect to potential malignancy is at least problematic if not, to use a modern term, even irrelevant.

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Pathogenesis of Stomach Cancer

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Declining patterns of gastric cancer in countries with a high industrial development suggests that some environmental and probably dietary factors may be involved in pathogenesis. But we know today that complex metabolic inter-relationships are often responsible for the action of a carcinogen, and that host factors also play an important role. In order to obtain a better understanding of gastric-cancer - chronic gastritis inter-relations, two main guidelines may be of interest:

1. To clarify whether the incidence of atrophic gastritis (a typical "host factor" in gastric cancer) is also decreasing at the same rate as stomach cancer does in those countries, in comparison with countries whose incidence of gastric malignancies remains still high. The alarmingly high incidence of gastric cancer - in the order of 10% - in individuals with atrophic gastritis is clearly established by the three statistics already published (SIURALA 1966, HANIK 1970, WALKER 1971). Moreover, the interest of a comparative study on the incidence of atrophic gastritis is supported by some data from the following literature:

   a) Japan: A postmortem study performed in comparison with data from the USA (IMAI et al. 1971) showed increased incidence of atrophic gastritis in Japan (36 to 80%, depending on age groups) contrary to the USA (6, 7 to 37%), although criteria employed for this classification could be exposed to some criticism.

   b) Finland: In this country with a high incidence of gastric cancer, a bioptic survey of a rural population held at random, showed atrophic gastritis in its various stages, at a rate of 28% (SIURALA et al. 1968). Here too, the criteria and techniques employed may have led to some overestimation.

   c) USA: In a pilot study of 7.074 asymptomatic individuals, a maximal histamine test determined achlorhydria in 25% of them; 19 cases of cancer developed during a 10 year follow-up (HITCHCOCK 1955).

2. It could be of interest to establish an experimental animal model in which known mutagens or suspected dietary carcinogens could be tested on atrophic gastric mucosa, and in which all metabolic, morphological and biochemical parameters of a stomach mucosa shifting towards atrophy could be monitored. This is the direction in which we are now trying to aim our research programs.

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Early Gastric Cancer

Surface Carcinoma of the Stomach

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A surface or intramucosal carcinoma of the stomach may be described as a carcinoma which is either confined to the mucosa or showing minimal deeper infiltration, but is not forming a large mass. Diagnosis can only be made by histology in this type of case, which is recognized by the abnormal epithelial pattern and associated cytological abnormalities. Following the work of GUTMANN, BERTRAND and PERISTIANY (1939), several authors have described the histological features of these lesions, including more recently BAMFORTH (1955), FRIESEN, DOCKERTY, ReMINE (1962) and MASON (1965). The lesion involves the interstitial tissue of the mucosa and does not confine itself to the glands alone (Fig. 1).

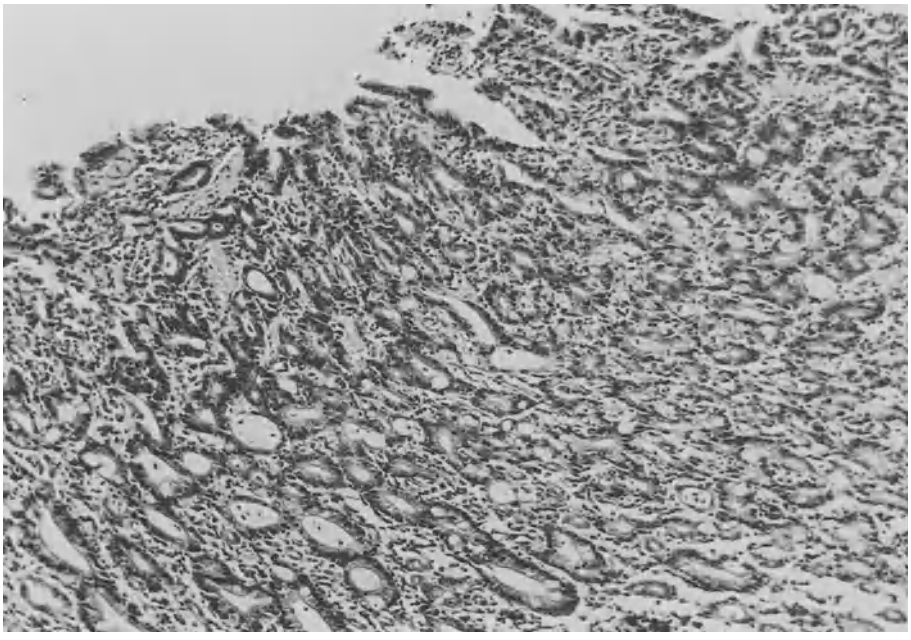


Fig. 1. Surface carcinoma in the pyloric mucosa (x 145)

When a large area is involved the mucosa can sometimes by seen by the naked eye to be much thinner than normal, but in many cases the whole thickness of the mucosa is not yet involved by tumor (Fig. 2), in which case the naked eye features may

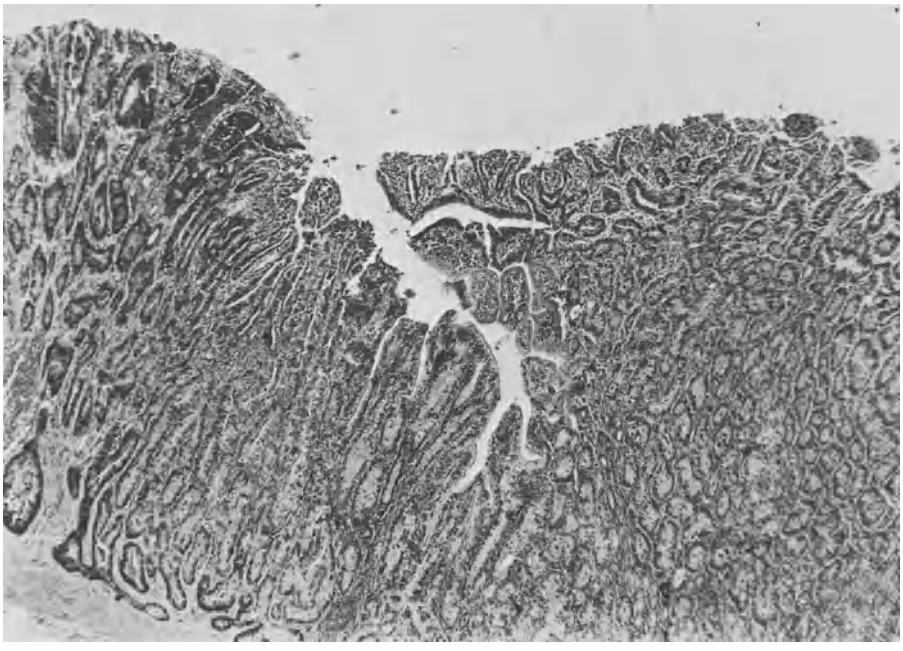
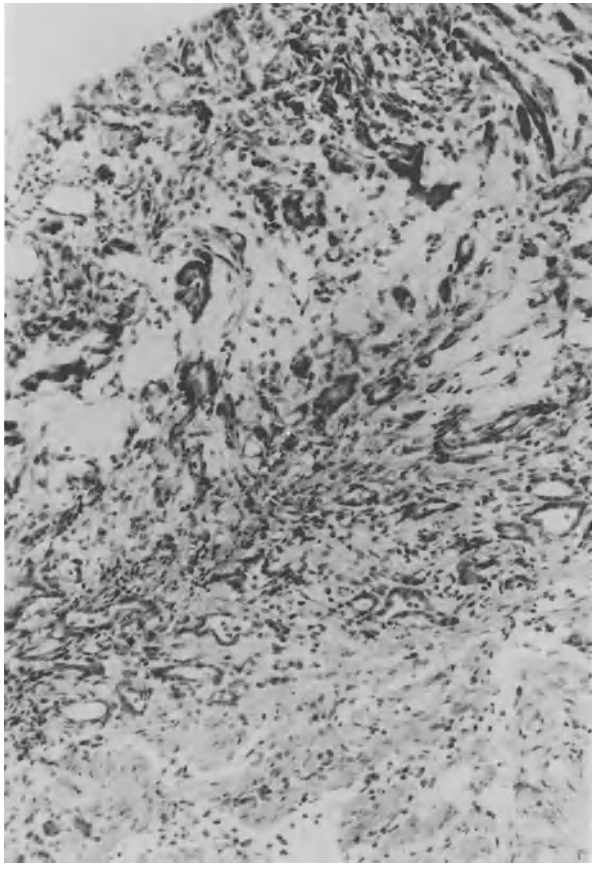


Fig. 2. Surface carcinoma showing malignant change in the upper third of mucosa only (x 40)

not be clearly apparent. The gastroscopic features have been studied intensively in Japan and the mucosal appearances which may be found, have been classified in detail by the Japanese Gastroenterological Society (KURU, 1967). The histology strongly suggests that these carcinomas are arising initially from the part of the mucosa bordering the lumen of the stomach, and that it is only later on that the deepest glands are involved. In slightly more advanced cases, infiltration through the muscularis mucosae can be seen (Fig. 3); occasionally one may see a small metastasis in a regional lymph node with only a surface lesion present in the stomach. Histologically, the tumors are adenocarcinomas: some of them show mucoid change which may be extensive (Fig. 3). A true carcinoma in situ is found on rare occasions on histological examination of the stomach and is by definition confined entirely to the glands, with no evidence of any interstitial spread (Fig. 4). These carcinomas are also seen to be commencing at the uppermost part of the epithelium and not in the more specialised deeper glands. All the lesions which have been found so far have been situated in the pyloric mucosa where they may cover a fairly extensive area. By taking numbers of sections the extent of the lesion can be determined (Fig. 5); by this means it can be shown in many cases to be arising from separate foci, some of them bordering a pre-existing benign gastric ulcer, if present, and others well away from it.

Histological examination of other areas of the stomach in these cases has shown atrophic gastritis in all of them, with or without intestinal metaplasia (Fig. 6) and occasionally also in areas where no intestinal metaplasia can be identified (Fig. 7).



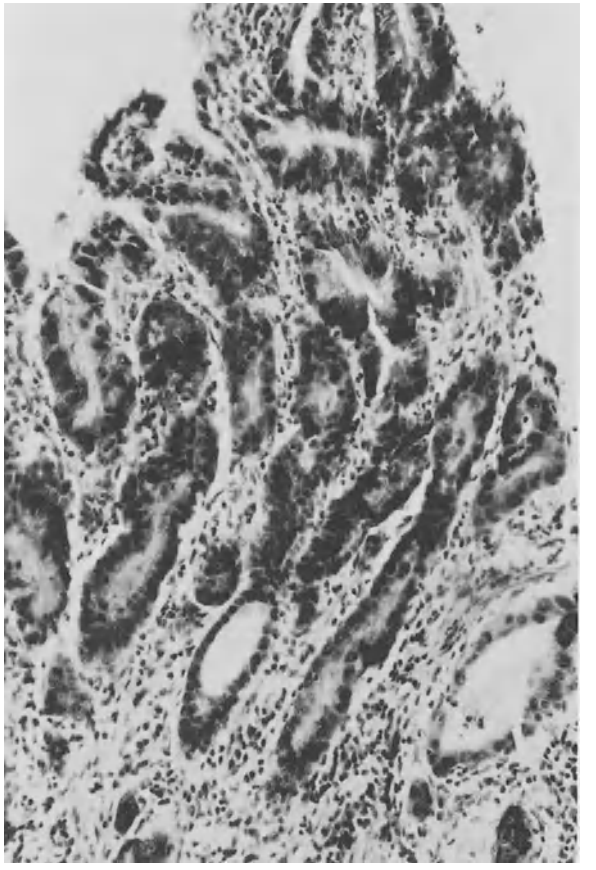


Fig. 3 (left). Early infiltration into the muscularis mucosae. The carcinoma shows mucoid change (x250)
Fig. 4 (right). Carcinoma in situ of pyloric mucosa. A gastric ulcer is present nearby (x250)

DISCUSSION

Surface carcinomas are not uncommon in partial gastrectomy specimens when the operation was performed for a lesion thought to be benign, and in the series reported by MASON (1965) 10, 3% of such specimens contained a surface carcinoma. In 6, 4% of these the carcinoma was associated with a benign gastric ulcer, and in the remaining 3, 8% it formed part of a primary malignant condition. The co-existence of a carcinoma and benign gastric ulcer is nevertheless a rare event. According to FRY (1969) only 19% of gastric ulcer patients come to surgery, so that the co-incidence of benign ulcer and gastric carcinoma probably occurs in less than 1% of cases. In view of the multifocal origin of many of these tumors it appears that the development of a carcinoma is not the result of a straightforward malignant change in a benign ulcer (i. e. ulcer-cancer), but that the pyloric mucosa as a whole is more likely to undergo malignant change if it is also liable to develop a gastric ulcer, as earlier suggested by SWYNNERTON and TANNER (1953). Since stomachs in which there is a gastric ulcer always show a severe gastritis as well, it may be that this is a much more significant factor than the ulcer itself. Further support for this view is provided by HELSINGEN and HILLSTAD (1956) who reported a much increased incidence of carcinoma in the gastric remnant after gastrectomy for gastric ulcer, but not if the operation had been performed for duodenal ulceration. However, this finding was not confirmed in a more resent study by STALSBERG and TAKSDAL (1971) who, in a necropsy series, were unable to find any difference in the incidence of gastric cancer between the two groups: further data is therefore needed on this point.

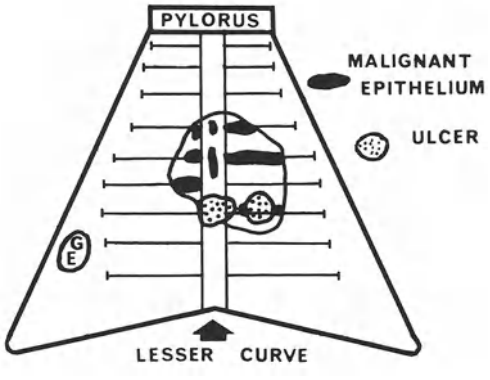


Fig. 5. Method of sectioning a stomach and mapping out a surface carcinoma.
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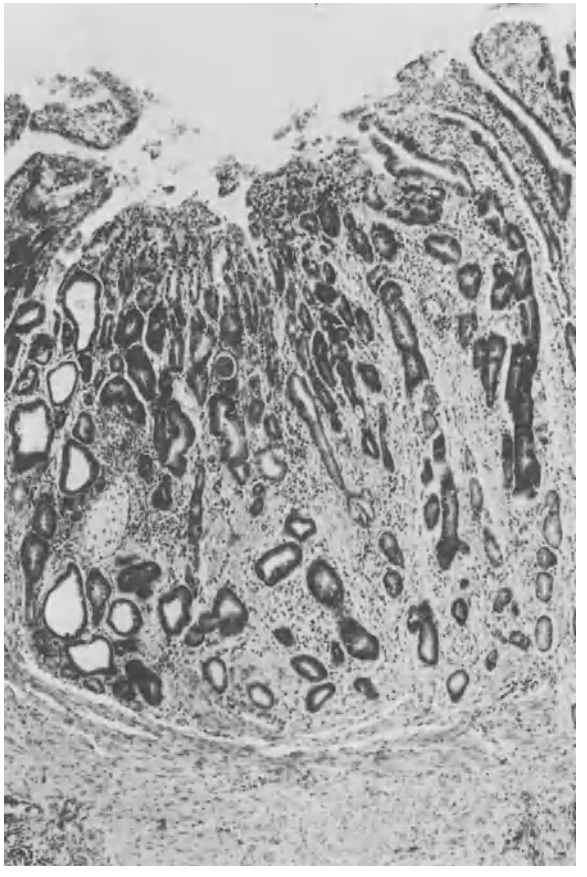
The relationship between atrophic gastritis and carcinoma is not clear: in this series atrophic gastritis has so far always been found in stomachs in which there is a surface carcinoma, usually but not always accompanied by intestinal metaplasia. Since surface cancers can be seen arising from areas both with and without any intestinal metaplasia, this suggests that intestinal metaplasia is not an invariable precursor of stomach cancer, although it appears to be so in the majority of cases. Although carcinomas are seen arising in stomachs with atrophic gastritis and intestinal metaplasia, these two are such common findings anyway that it seems



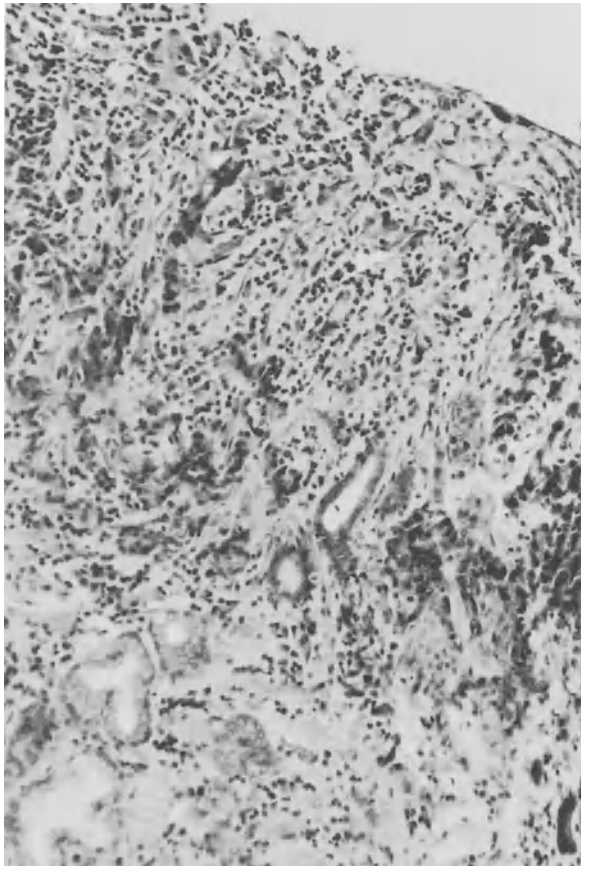


Fig. 6 (left). A surface carcinoma arising in an area of stomach where there is intestinal metaplasia (x100)
Fig. 7 (right). A surface carcinoma arising from pyloric mucosa which shows no evidence of intestinal metaplasia (x250)

unreasonable to regard them as "premalignant conditions". This term implies a high risk of carcinoma developing which does not seem to be the case, but they may be "potentially malignant conditions". The use of this term carries the implication that there is a definite possibility that a carcinoma will subsequently arise in the tissue, but not a strong probability.

An important feature of these surface carcinomas is that they have a good prognosis even when early invasion is present, as shown particularly well by KUHLENCORDT (1959) in his follow-up of such cases. It follows, therefore, that their early recognition is important. This is difficult to do, and can only be achieved by close co-operation between the clinician, the radiologist and the pathologist, all of whom must be aware of these lesions and look for them with particular care.

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The Borderline Between Benign and Malignant Lesions in the Stomach

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During the last twenty years our interest has centred around the detection and histological diagnosis of early gastric cancer. The term "early malignant lesion" varies according to the point of view of the observer. In this paper an attempt will be made to describe changes which precede such lesions as the superficial carcinoma. We have, in fact, looked for criteria which allow with a measure of certainty the histological diagnosis of carcinoma in situ or intra-epithelial malignancy.

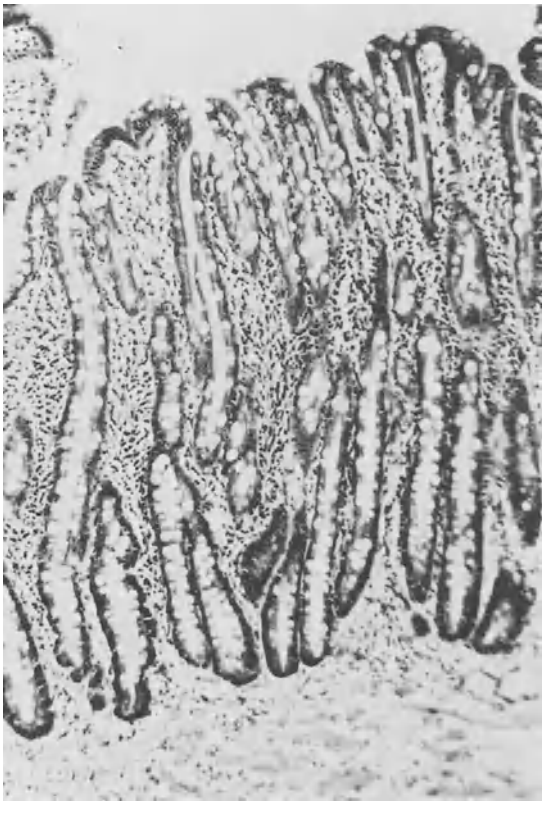

Fig. 1. Well differentiated intestinal metaplasia. Numerous goblet cells, basal nuclei, no mitotic activity . H. E. x 78

The superficial carcinoma is a well defined and well described entity which - in our opinion - already represents a truly invasive carcinoma, as the connective tissue stroma of the gastric mucosa is, in all cases, invaded by neoplastic cells. That the diagnosis and subsequent excision of such lesions results in a reasonably good prognosis for the patient is a subject in itself and not under discussion in this paper.

In recent years the Japanese authors - with their extensive experience in the study of gastric cancer - have evolved a classification of "early gastric cancer" which recognizes three main categories, all of which seem to be invasive tumors whatever their size. Theoretical considerations suggest that a still earlier stage of carcinogenesis must exist, namely intra-epithelial carcinoma. As yet, the latter has not been described, although many authors speak of borderline lesions which approximate the theoretical concept of carcinoma in situ.

It is generally accepted that a close relationship exists between chronic gastritis with intestinal metaplasia and the development of gastric cancer. Carcinoma of the stomach is never observed to occur in a normal mucosa. Intestinal metaplasia generally shows itself at first in the gastric pits, that means in the zone of

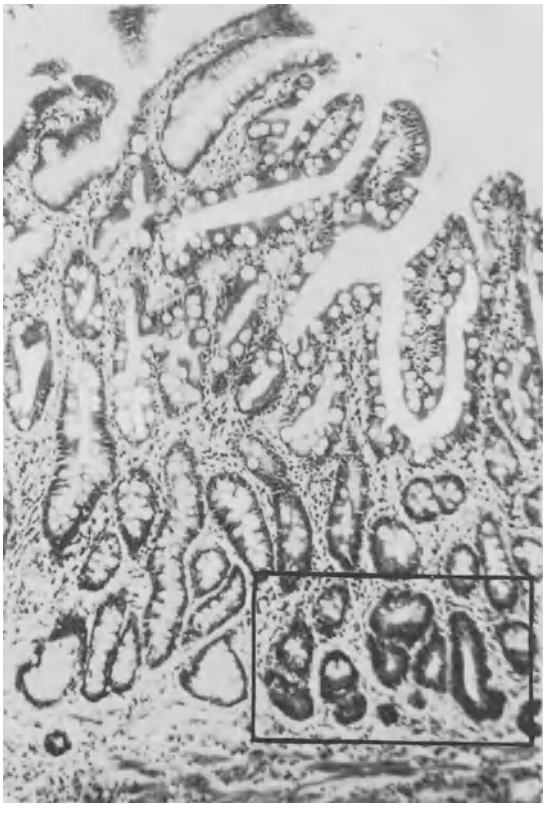

Fig. 2. Intestinal metaplasia with mildly atypical lining in the deep portions of the glands and mitotic activity. H. E. x 78

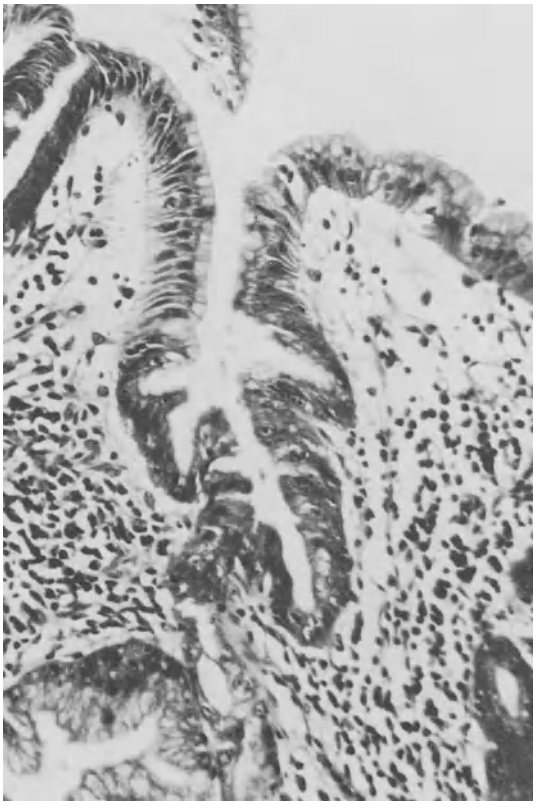

Fig. 3. Gastric pit with multi-layered atypical epthelial lining in its deeper parts. H.E. x 225

cell renewal. It displays a wide variety of histological patterns, a fact which contributes to the difficulties of diagnosis. Assuming that the intestinal metaplasia is related to the development of gastric cancer, we studied the metaplastic epithelium, paying particular attention to the shape of the glands, their course and relation to the gastric surface. Their epithelial lining was examined, taking particular notice of the presence or absence of mucus secreting cells and of the frequency of mitotic figures. Furthermore, it was recorded whether the glands had a single or multi-layered epithelial lining. In addition, we particularly noted the structure of the individual cells of the lining epithelium. Features such as the shift of the nucleo-cytoplasmic ratio, the shift of the nucleolo-nuclear ratio and the basophilia of the cytoplasm were all taken into consideration when the diagnosis was made. An attempt was also made to define areas in which the basement membrane surrounding the glands, appeared to have been penetrated by atypical cells.

As material for our study we used a series of gastrectomy specimens, excised on the basis of clinical symptomatology and radiological findings which pointed, in most cases, to the presence of peptic ulceration. Gastroscopy, gastric biopsy and cytodiagnosis played no part in the diagnosis. On our request the specimens were received fresh, unfixed, immediately after excision. The stomachs were opened along the larger curvature, pinned out and fixed in formol-saline. In this way the mucosa and its covering mucus were disturbed minimally.

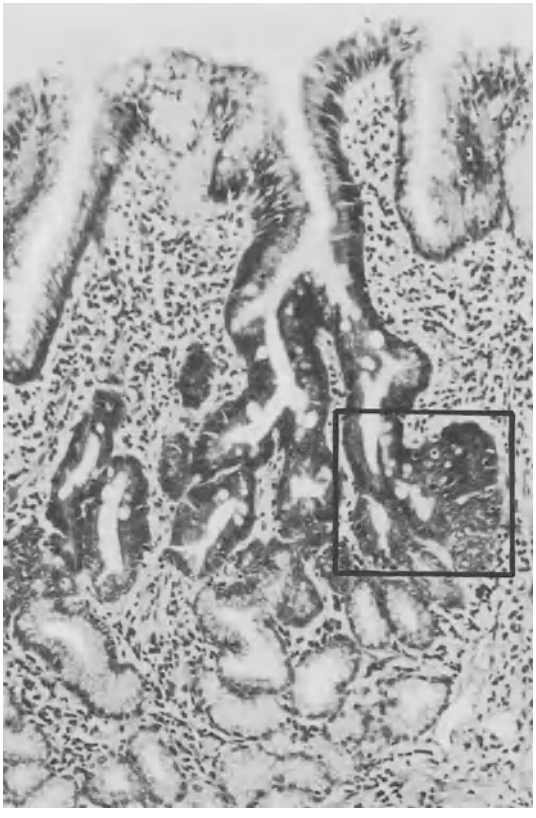

Fig. 4. Atypical branching of intestinal gland with atypical epithelial lining and growth of epithelial cells into the stroma. H.E. x 140

A previous study of superficial carcinomas had shown that these tumors are almost regularly covered by an inflammatory exudate which, after fixation, appears as a grey film within the mucus. Assuming that similar changes may be present in cases with intra-epithelial carcinoma, all areas covered with even a trace of exudate have been examined and serially sectioned. Some of the lesions found below the exudate will be described. During this investigation several unexpected superficial cancers came to light accompanied by lesions in the neighbouring gastric pits. They represent borderline lesions or, indeed, intra-epithelial carcinoma. All the cases were accompanied by a widespread chronic gastritis with intestinal metaplasia in the remaining parts of the stomach.

Uncomplicated intestinal metaplasia (Fig. 1) is characterised by the regularity of the glands which are, in general, straight without branching. Their main axis runs in right angles to the surface. The lining epithelium consists of a single layer of cells with basally situated nuclei and very numerous goblet cells. Mitotic activity is inconspicuous, the interstitial tissue shows little chronic inflammatory infiltration. Intestinal metaplasia of this type does not infer any suspicion of atypism.

Intestinalisation with lining cells which exhibit a considerable basophilia of their cytoplasm in the deep parts of the glands is often found (Fig. 2). There is an in-

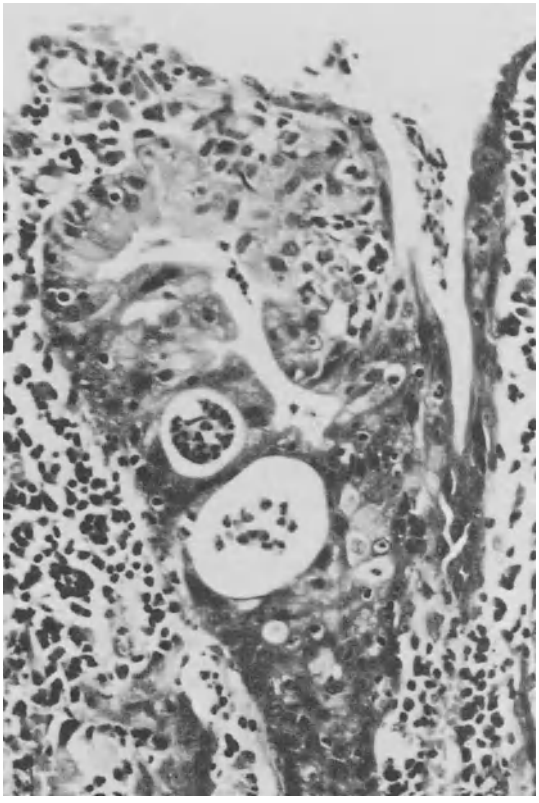

Fig. 5. Collections of inflammatory cells within atypical gland. H. E. x 285

creased mitotic activity as well as a decrease of the number of goblet cells, and a lining epithelium consisting of several layers. Specific conclusions cannot be drawn from this variant of intestinalisation which is so frequently seen that one must assume it to belong to the normal range of the picture of intestinalisation.

Fig. 3. shows a gastric pit with a striking difference of the lining epithelium in its outer and deeper portions. The outer portion is lined by a single layered epithelium with abundant mucus producing cells, while the deep portion of the pit is lined by a multi-layered epithelium with cells showing a basophilic cytoplasm. The nuclei of this epithelium vary in size and shape; some of the nuclei display prominent nuclear membranes and enlargement of individual nucleoli as well as multiplication of nucleoli. (Shift of nucleo-cytoplasmic and nucleolo-nuclear ratio). This kind of change reminds one of the alterations - often seen in the epithelium of intestinal polyps - which, in that situation, are generally interpreted as an indication of intra-epithelial carcinoma. The stroma surrounding the atypical glands showed frequently a heavy plasma cellular infiltration.

A further frequently demonstrable feature of intestinal glands is irregular branching (Fig. 4.) The gland is no longer straight but forms a complex system of branching structures in its lower pole. The branching portions are closely approximated to each other, and are only separated by a minimal amount of stroma (back to back

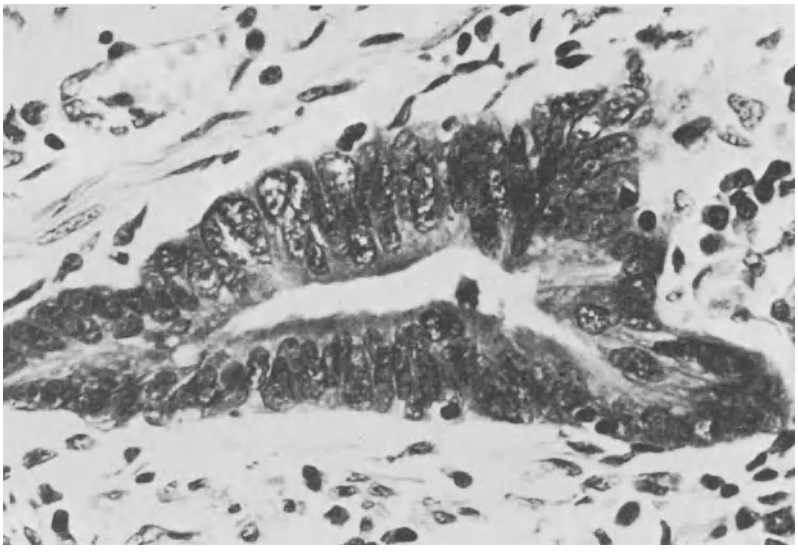

Fig. 6. Cross section of an atypical gland with striking nuclear changes - carcinoma H.E. x 560

arrangement). The lining epithelium consists of multiple layers of epithelial cells, mitotic figures are numerous, basophilia of the cytoplasm and a decrease in goblet cells etc. are seen. Additionally, an eccentric proliferation of epithelial cells which has apparently penetrated the basement membrane and invaded the adjacent stroma, can be seen (Fig. 4). As such lesions are commonly found in the neighbourhood of small superficial cancers, and as we are confident that gastric cancer is multifocal in origin, it was felt that the appearances described are, in fact, more than borderline changes: they represent cancerisation of the gastric mucosa, i.e. a form of carcinoma in situ. It must be added that in all instances, care has been taken to avoid flat cuts; serial sections of such areas have confirmed our impression that we are dealing with early cancer changes in the gastric mucosa.

A further feature never observed in non-neoplastic changes of the stomach, but possibly indicative of a malignant change, is the presence of collections of inflammatory cells within atypical glands (Fig. 5). Such intraglandular inflammatory cell collections are commonplace in large cancers of the stomach and large intestine, and are also present in superficial cancers of the gastric mucosa. It is, therefore, suggested that their presence may also be of significance in the diagnosis of intraepithelial cancer.

The histological differential diagnosis between benign and malignant lesions will be the more impossible the higher the magnification. This becomes obvious when one looks at the cross section of an intestinal gland (Fig. 6.) which, in our opinion, must be considered on cytological grounds alone to be of neoplastic origin. The gland shows still certain features of intestinal metaplasia such as the eosinophilic margins of the individual cells. However, the multi-layering of the epithelium, the structure of the nuclei, the basophilia of the cytoplasm and the absence of goblet cells, suggest a malignant change of the epithelium.

Although it is important to examine minute details of individual glands and their epithelium, it is even more necessary to study the pattern of the mucosa over a wider area. Figs. 7 and 8 are an example of this. Both microphotographs come

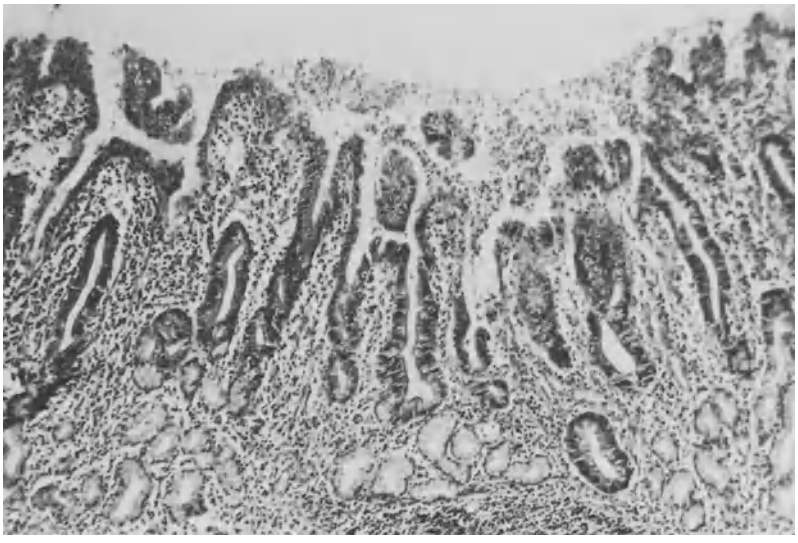

Fig. 7. A field of atrophic gastric mucosa suggestive of intra-epithelial carcinoma. H.E. x 78

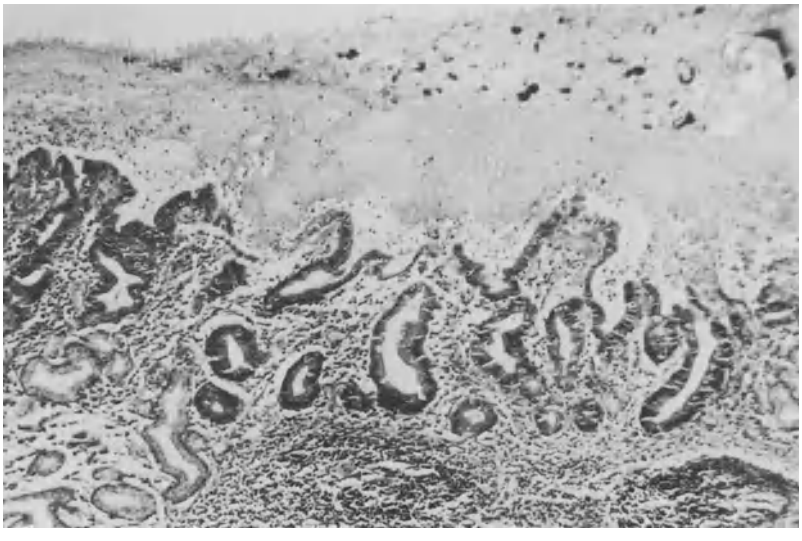

Fig. 8. A field of atrophic gastric mucosa suggestive of intra-epithelial carcinoma. H.E. x 78

from different but neighbouring areas of the stomach of a patient aged 50. The fixed specimen showed patches of inflammatory exudate near the lesser curvature in the pyloric antrum. The histological appearances, apart from the tell-tale leukocytic-fibrinous exudate in one area, show straight glands with a highly atypical epithelial lining and erosion of the surface epithelium; the other adjacent area exhibits again the exudate, erosion of the surface epithelium, and distorted and dilated glands with an atypical epithelium. We believe from our experience that the two lesions represent areas of intra-epithelial carcinoma, multifocal in origin.

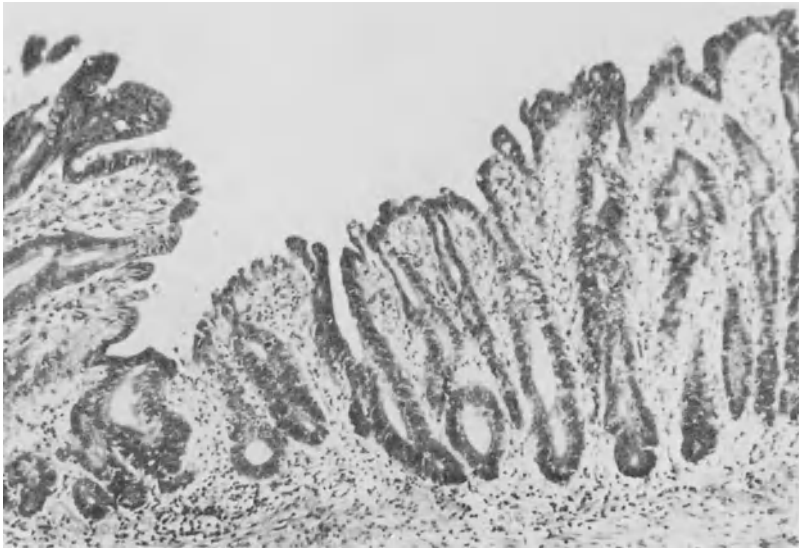

Fig. 9. A well differentiated intra-epithelial carcinoma. H.E. x 140

A section from another patient (Fig. 9) shows similar appearances to those of the preceding figures 7 and 8, but more advanced. It should also be noted that these early neoplastic alterations of the mucosa have taken place in a very thin, atrophic gastric mucosa.

We have tried to enlist different ways other than the ordinary histologic techniques to identify intra-epithelial malignancy. An attempt to analyse the many mitotic figures of atypical lesions has been totally unsuccessful. We failed to obtain satisfactory chromosomal spreads. Histochemical studies have demonstrated that in lesions of the above nature, alkaline phosphatase is present in abundance as it is in a well differentiated intestinal metaplasia. Leucine aminopeptidase was also detected in many of the lesions, an enzyme which is commonly found also in intestinalisation and in advanced gastric tumors of intestinal cell type. However, no additional information resulted from these studies which could help with the confirmation of the diagnosis of intra-epithelial neoplasia.

It is felt that the study of the minutiae of the morphological changes under discussion is still the most reliable support for diagnostic purposes. In conclusion, it appears that the following histological criteria, separate or in combination, are a good guide for the diagnosis of intra-epithelial neoplasia.

1. The transformation of a single layered, well differentiated intestinal type epithelium with numerous goblet cells into a heaped up, multilayered epithelium with increased mitotic activity, with absence of goblet cells and changes in nuclear and nucleolar structure and basophilia of the cytoplasm ("dunkle Zellen" after KONJETZNY).
2. The formation of epithelial buds which penetrate the basement membrane and grow into the surrounding stroma.
3. Atypical branching of the glands associated with an atypical epithelial lining and a back-to-back arrangement of the branched glands, i.e. without any intervening stroma.

4. The appearance of inflammatory cells within dilated glands.
5. Superficial erosion of the mucosa with outpouring of a fibrinous-leukocytic exudate which often includes also exfoliated malignant cells.
6. A disorderly pattern of the glands, combined with some or all of the features described under the previous headings.

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Incidence, Localization and Accuracy of Endoscopy and Guided Biopsy

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In the Medical School of Hanover we have until now diagnosed 18 cases of gastric carcinomas limited to mucosa and submucosa, i.e. cases of early gastric cancer as defined by the Japanese Endoscopic Society. Among the total of gastric carcinomas, the number of early cancers recognized remained constant during recent years and averaged approximately 8% (Table 1).

Table 1. Yearly incidence of gastric cancer

Year	No. of gastric cancer	No. of early cancer	%
1970	70	7	10%
1971	67	4	6%
1972 (-Sept)	97	7	7%
Total	234	18	8%

In comparison to Japanese studies this result is rather depressing (FUCHIGAMI et al. 1966; KASUGAI et al. 1966; KASUGAI and AOKI, 1972; MASUDA et al. 1970). At the moment, there is no explanation for this discrepancy. The average age of our patients with early gastric cancer was 58 years, while the mean age of those with advanced carcinoma was 62 years. Localization and frequency of the different types of early cancer in our material show a certain difference to that of Japanese authors (FUCHIGAMI et al. 1966; KASUGAI et al. 1966; KASUGAI and AOKI, 1972; MASUDA et al. 1970; NAKAMURA et al. 1967) (Fig. 1).

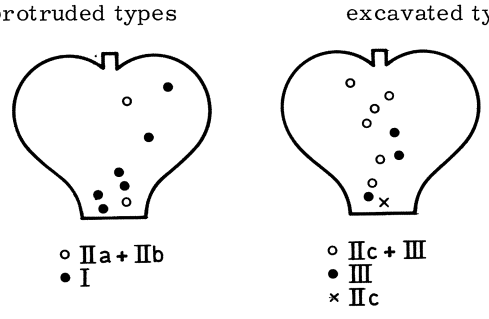

Fig. 1. Localization of early gastric cancer

In most cases the lesion was located in the antrum and showed type I. In Japan, on the other hand, the most frequent localization was the angulus, and the lesion was mostly of type IIc. While in Japan early cancer in the cardial region and in the upper part of the corpus is very rare, lesions were located in this regions in 4 of our 18 cases. With respect to the small number of cases involved, one should not put too much accent on this comparison between the Japanese results and our own. We shall have to see whether this dicrepancy will be confirmed when a larger number of cases is considered.

There is no correlation between the type and the extension of an early cancer (Fig. 2) just as there is no correlation between the extensiom of an infiltration and its depth.

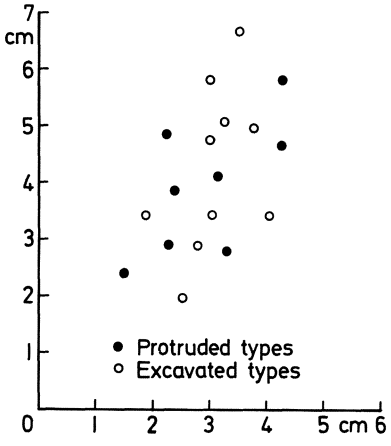

Fig. 2. Relation between type and size of early gastric cancer

This confirms the results of KASUGAI et al. (1966). Endoscopy with guided biopsy is the best diagnostical aid in recognizing early gastric cancer; this was proved by comparison between the results of gastroscopy, guided biopsy and surgical histology (Table 2).

Table 2. Endoscopic diagnosis of early gastric cancer

Endoscopical diagnosis	No.	bioptical histolog. diagnosis	histological diagnosis of resected stomach			scar	not operated
			early Ca.	adv. Ca.	ulcer		
early gastric cancer	16	pos. 12	10	-	-	-	2
		susp. 1	-	-	1	-	-
		neg. 2	1		1	-	-
		Ly. Sa. 1	early Ly. Sa.				
suspicion of early gastric cancer	13	pos. 6	3	2	-	-	1
		susp. -	-	-	-	-	-
		neg. 7	2	-	3	2	-
Total	29	29	16	2	5	2	3

On the basis of endoscopic criteria , early cancer was diagnosed definitely in 16 cases, and was suspected in 13 patients. Of the 16 cases definitely diagnosed by endoscopy, only 12 were positive in histology, in 1 case cancer was suspected, in 2 cases histology was negative, and one patient was found to have lymphosarcoma. Of these 16 cases, 14 were operated on, and the resected parts of the respective stomachs were examined histologically. Every bioptically diagnosed carcinoma was confirmed by the resected specimen showing the carcinoma limited to mucosa and submucosa. In the one case of suspected early cancer in biopsy, the examination after resection revealed a benign ulcer. Of the two bioptically negative cases, one proved to be an early cancer in the resected part of the stomach, and the other was a benign ulcer. In the case bioptically confirmed as lymphosarcoma, the tumor was limited to mucosa and submucosa. This shows that out of 14 cases (79%), 11 were accurately diagnosed by endoscopy, and that all bioptically definite cases were confirmed by the resected specimen : the accuracy of biopsy was 91,7%.

In the endoscopically suspected cases the accuracy was much smaller. This group includes lesions which could not be differentiated gastroscopically from benign alterations; cases having deeper cancerous infiltration could not be separated either. Of these 13 cases 6 were positive, one of which was not operated on. Of the 5 patients operated, 3 were found to have early cancer, and 2 advanced carcinoma. Surprisingly enough, 2 of the 7 negative cases revealed early cancer in the resected specimens. In this group only 5 of 12 suspected cases (42%) were diagnosed correctly. In 2 bioptically positive cases, the infiltration rate of the carcinoma was not recognized before operation. In the negative cases 3 benign ulcers and 2 scars were misinterpreted as early cancers. For this group the accuracy of biopsy was 71,4%. For both groups together, the assumed diagnosis of "early cancer" was confirmed in 16 out of 26 cases which means a percentage of 61. In addition to the 16 cases, twi others formerly misinterpreted endoscopically as benign ulcers, were found to be early cancer by biopsy and examination of the resected specimen.

The greatest source of endoscopical misinterpretations were ulcers. Most frequently benign ulcers were falsely diagnosed as early cancer, while early carcinoma type III seemed to look like a benign ulcer. The differentiation between early cancer type III and a benign ulcer is very difficult and sometimes even impossible, especially so in the active stage of the ulcer (FUCIGAMI et al. 1966; KASUGAI and AOKI, 1972; KAWAI et al. 1970; NAKAMURA et al. 1967; SAKITA, 1966). It should be possible to correct the false endoscopical interpretation by means of guided biopsy. In all cases of benign ulcer one should not only monitor the healing process by X-ray, but also by gastroscopic-bioptical means. This is necessary for the following reasons:

Owing to the small area of cancer infiltration around the ulcer, it is very difficult to obtein precisely representative material by biopsy. Since early cancer type III is a peptic ulcer in a carcinomatous mucosa, there is no clear contrast between the healing tendency and the malignant process. The endoscopical diagnosis is simplified by the IIc manifestation appearing in the area around the healing ulcer (KASUGAI and AOKI, 1972). The bioptical verification is rendered easy by the characteristical changes which allow a more precise excision of tissue. Healing and relapse of cases with early cancer type III and III + IIc are as common and well known as the fact that such carcinomas with changing endoscopic pictures, can remain limited to mucosa and submucosa for several years (KAWAI et al. 1970;MASUDA et al. 1970). The risk of overlooking an early cancer has prompted us to operate benign ulcers even more frequently than befor. In contrast to the alterations in type III and III + IIc, the mucosa in type IIc is altered so typically that

the biopsy of the changed area alone is sufficient for an exact diagnosis (FUCHIGAMI et al. 1966;KASUGAI et al. 1966). Histological confirmation of a suspected early cancer is not possible in any lesion without a detailed series of specimen preparations as suggested by KAWAI. This is essential not only for the detection of small carcinomas, but also for the exact determination of the degree of infiltration. With respect to screening and early diagnosis of suspicious lesions, an X-ray examination is of utmost importance.

SUMMARY

Among 26 cases of endoscopically suspicious early cancer our diagnosis was correct in 61%. The bioptical accuracy was 83%, but 5 benign ulcers were falsely diagnosed by endoscopy as early cancer, and 2 cases of early cancer type III were misinterpreted gastroscopically. A further source of misinterpretation is the ulcer scar. It seems that the guided biopsy is especially efficient. A definite correlation between size, type and depth of infiltration cannot be established; early lymphosarcoma does not differ endoscopically from early cancer.

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Discussions by Invitation

False Diagnosis in the Diagnostics of Early Gastric Cancer

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Radiology, gastrophotography, gastroscopy with and without biopsy, "blind" and directed gastrocytology are some of the methods which aid in the early diagnosis of gastric cancer. It is understandable that attempts are made to compare the results of different methods or combined methods graphically as "success rates". We feel that the rate of success is often not due to the method employed, but to the experience of the examiner (ELSTER and KUDLICH, 1971). The determining factor for success or failure is, however, not so much technical proficiency as the examiner's awareness of the limits of his methods.

The following report deals with such "individual errors" which may lead to false diagnosis, either negative or positive, during the time between gastrobiopsy and the final detection of gastric cancer in the resected specimen. Based on our previous experience we made a survey on 8.000 cases of which more or less numerous particles had been taken in directed biopsy, and on 26 cases of early gastric cancer found subsequently in the resected stomachs.

The most common source of a false negative diagnosis is the failure to obtain or locate representative particles. With respect to quantity, this means in general that the number of excised particles is too small. Findings in which out of 6 to 8 biopsy specimens, only one shows carcinomatous structures, are in no way rare. Thus, a small number of samples increases the likelihood of a false negative diagnosis. This is especially true in the case of ulcerated carcinoma, type III. One sample of fibrinoid necrosis and a second particle with regularly structured mucosa would indicate a benign ulcer, unless an additional specimen revealed signet ring cells. As far as quality is concerned, representative biopsy specimens may be deficient if during excision, the macroscopic peculiarity of a lesion is not considered. The demand, in type IIc, to biopsy the central portion of flat ulcer-like lesions will overrule the oldfashioned scruple that an excision from the centre of an ulcerative defect might lead to perforation. A biopsy from the border of such lesions usually yields only very insignificant and easily overlooked findings.

When histological findings are rather uncertain, and when control biopsies are omitted or not recommended, we are facing another source of diagnostical errors. In cases of "scarred mucosa" short-term controls are indicated. In one such case we detected two months later a tubular carcinoma in the excision which, at first, appeared to be an atypical glandular proliferation in the resected specimen, located in the ulcer angle. In additional sections a type of dedifferentiated carcinoma could finally be identified, and all doubts as to whether this was virtually a carcinoma, were abolished.

False negative diagnosis can also be based on mistakes made by the pathologist. One has to consider in this context that type of dedifferentiated carcinoma which

forms neither solid dark stained nuclear strings, nor differentiation of the signet ring cells, and which spreads diffusely in a fibrous tunica propria. The feature of a fibrotic scar is thus simulated. Difficulties in distinguishing signet ring cells from xanthoma cells are encountered, when mechanical or erosive defects of the foveolar relief are present. PAS-staining will not solve the problem, because the "fibrinoid veil" of the erosion is sometimes PAS-positive. However, we have to say it once more that the lack of representative particles, in terms of both quality and quantity, will be frequently responsible for the misinterpretation of histological findings.

A borderline case may even be overestimated in order to give the clinician a clear-cut diagnosis; such a false positive diagnosis, too, is not to be excused. In pathological histology one has the analogous problem of distinguishing between processes which are still proliferative and those which are already blastomatous. Glandular neck proliferation with cell atypia is a classical example (ELSTER, 1972). Japanese authors have already classified these problems (SUGANO et al., 1971). The definition of five groups of so-called cellular atypia is certainly of high theoretical value, but in Germany at least, we need greater practical experience, especially in the differential diagnosis of tubular early gastric cancer. Two false positive diagnoses, where we suspected a carcinomatous lesion judging from the biopsy specimen, were provoked by alterations of the kind we call foveolar hyperplasia with atypical epithelium. In both samples the biopsy was taken in the vicinity of an anastomosis.

A new and intriguing type of false positive diagnosis results from the heterogeneity of our material. If the examination of the biopsy material and of the resected stomach is not done by the same pathologist, it is possible that the second examiner will not be able to confirm the carcinoma diagnosed after the biopsy specimen. This may arise out of insufficient examination of the surgical specimen, or from ignorance of the classification and types of early gastric cancer. It is certainly not necessary in every case, to use the subtle techniques invented by our Japanese colleagues, but we will have to accept higher costs in order to attain a more reliable diagnosis of early gastric cancer. We need, however, the cooperation of the clinician and, in this phase, also of the surgeon. He must be able to rely on the endoscopic-bioptical diagnosis. A gastrotomy with or without exploratory excision in a frozen section will bring no new information but make, by virtual mutilation of the specimen, the examination more difficult with regard to surface and deep growth of the carcinoma.

Expert handling of the surgical specimen is indispensable for a precise examination, and would eliminate another cause of intrusive false positive diagnosis. For an audience of scientific experts this may sound like a mere banality, but we are convinced that our efforts towards early diagnosis of gastric cancer are often seriously impeded by such banalities. Moreover, we wanted to point out the many imponderables which make an objective comparison of the efficacy of different methods very difficult.

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Early Gastric Cancer

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Early gastric cancer (i.e. cancer limited to the mucosa or mucosa and submucosa, regardless of its extent and the occurrence of regional node metastases) is to be considered as a very rough entity, even biological nonsense, because submucosal blood and lymphatic vessels' network significantly enhance the metastatic spread. So "Superficial Carcinoma" in the sense described by MASON and SCHADE, is biologically an entity entirely different from "Early Cancer" and is, in addition, a much more useful one, especially at present when such lesions can be fully diagnosed by endoscopy and related techniques, or by blind lavage cytology. The diagnosis of carcinoma in situ is less common but it is possible (Fig. 1, 2, 3) for lucky researchers and lucky patients, especially when "cancer minded" clinicians look out for suspicious cases as a matter of routine and on the basis of high risk parameters.

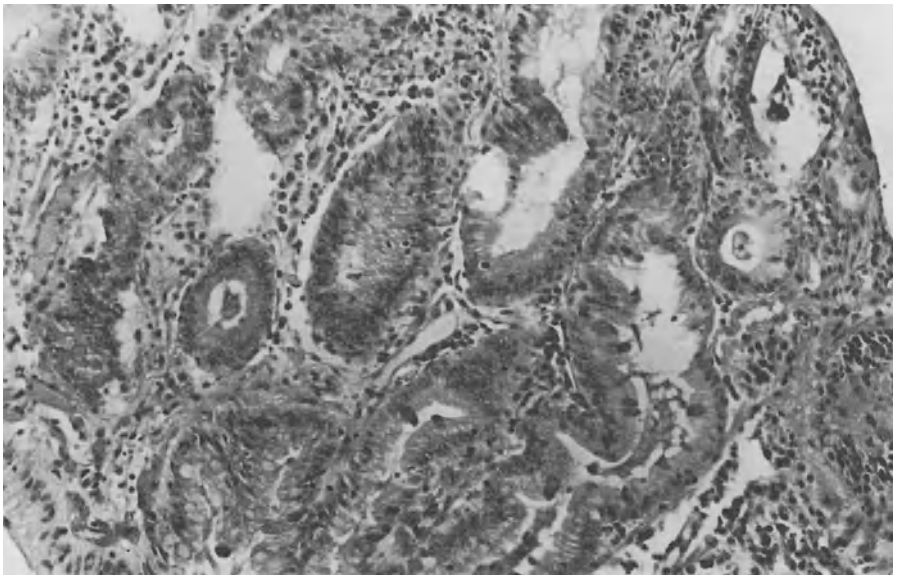

Fig. 1. Carcinoma in situ of the stomach, x 100. Loss of polarity of the glands, intestinal type metaplasia, multiple mitoses

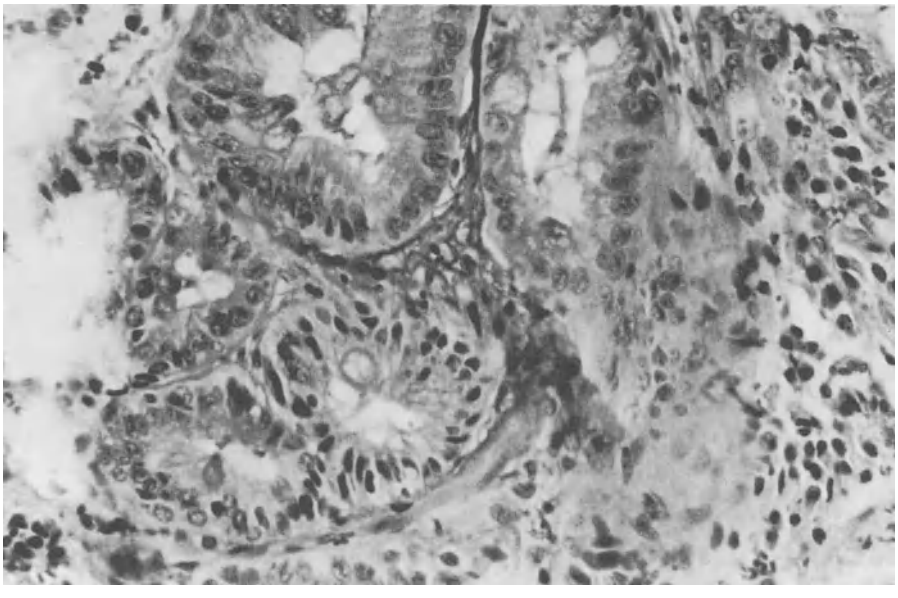

Fig. 2. The same case, x 250. On this field the architectural disorder is clearly evident

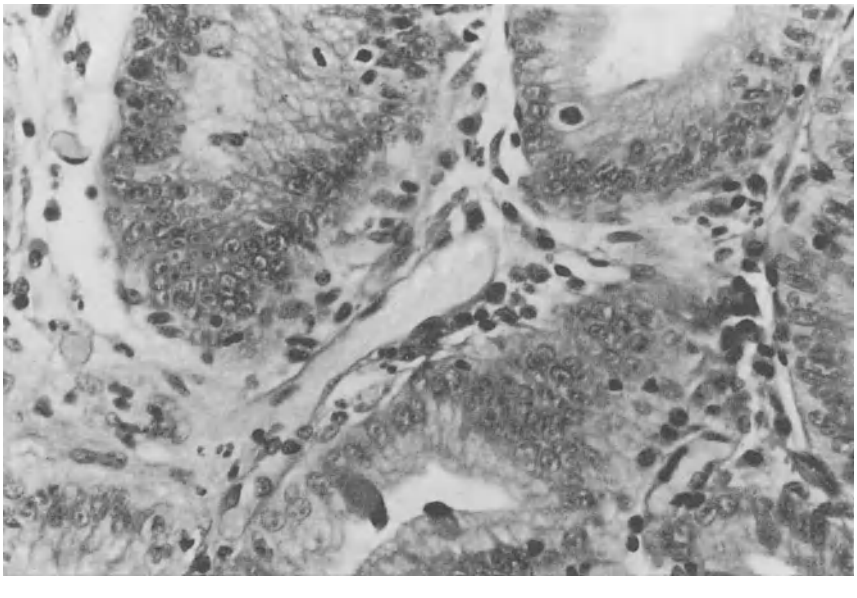

Fig. 3. The same case, x 250. Cellular polystratification and multiple mitoses are clearly distinguishable

For the purpose of comparing statistics and results from different research projects, which is the main aim of any stage classification, "Early Cancer" is,

therefore, completely unreliable. This is clearly pointed out by the results obtained by the American Joint Committee on Cancer Staging (KENNEDY 1970), in which, even though slightly different criteria were employed, very scattered five years survival patterns were obtained in cases which could all be classified as "Early Cancer".

Thus, the only value of "Early Cancer" is in clinical diagnostic work, that means in orientating by endoscopy or by high level X-ray examination, the surgeon towards expecting an involvement of the stomach into a malignant process.

A critical review of the different classifications employed in various countries - (and even within the same country) - and a much mor detailed and precise handling of tissue specimens by pathologists are, therefore, the most urgent priorities today in cancer research.

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Evaluation of Early Gastric Cancer from the Clinical Point of View

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The gastric cancer involving mucosal or submucosal layers is called an "early gastric cancer". We should like to say that an early gastric cancer is the initial stage of an advanced one. However, this is difficult to prove from a clinical point of view. It can only be proved by the retrograde follow-up study of clinically misdiagnosed cases.

Onthe other hand, many authors have already reported that gastric cancer is apt to arise in hypoacid or anacid stomachs. This paper aims to study early gastric cancer from a gastric acid secretion view-point and also from our retrograde follow-up study, to investigate the cancerous development.

Table 1. Gastric acid secretion in early gastric cancers in reference to their macroscopic types. (stimulated by AOC tetrapeptide 4γ/kg)

Type of cancer	case	M. A. O. (mEq/L)
I, I + IIa, IIa	3	3.74 ± 0.99
IIc + IIa	1	0.12
IIb	1	4.07
IIc, IIc + III, III + IIc	25	7.65 ± 0.96

(m ± S.E.)

Table 2. Gastric acid secretion in early gastric cancers in reference to the site of lesions (stimulated by AOC tetrapeptide 4γ/kg)

		Antrum	Angle	Lower body	Upper body
Normal			14.3 ± 2.07 (n = 13)		
Gastric ulcer			19.9 ± 2.11 (n = 22)	17.4 ± 1.61 (n = 29)	7.95 ± 2.33 (n = 6)
Carcinoma	mucosal	8.50 ± 2.60 (n = 5)	8.80 ± 2.55 (n = 5)	8.92 ± 1.68 (n = 3)	6.10 ± 2.42
	submucosal	8.46 ± 1.77 (n = 8)	4.78 ± 2.10 (n = 5)	3.17 ± 1.15 (n = 2)	
	mean	8.48 ± 1.48 (n = 13)	6.84 ± 1.78 (n = 10)	6.62 ± 1.68 (n = 5)	6.10 ± 2.42 (n = 2)

(m ± S.E.)

MATERIALS AND METHODS

1. Gastric acid secretion in early gastric cancer. After the stimulation of AOC-tetrapeptide 4γ/kg and taking into account types, locations and histological patterns (Tables 1, 2, 3), we investigated the rate of gastric acid secretion per hour in 30 cases of early gastric cancer.

2. Growth of gastric cancer. In 14 cases of early gastric cancer and in 4 advanced gastric cancer cases, we worked on the retrospective radiological follow-up studies and by calculating the tumor mass radiographically (Table 4), were able to investigate their doubling time.

In mucosal gastric cancer, two dimensions were calculated radiographically. The diameter of the cancer was measured without taking into account the depth of the cancerous invasion. However, in an advanced one, the volume was calculated as an ellipsoid. The results are shown in Table 5.

Table 3. Gastric acid secretion in early gastric cancers in reference to their histological pattern (stimulated by AOC tetrapeptide 4γ/kg)

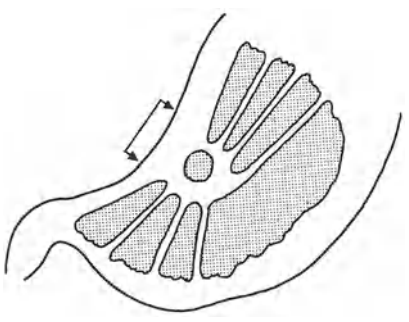
	Adenocarcinoma	Undiff. carcinoma	Mucin producing carcinoma	Scirrhous
No. of cases	28	24	4	7
Mucosal	6.68 ± 1.27 mEg/h (n = 8)	9.25 ± 2.28 (n = 6)	5.30 (n = 1)	
Submucosal	5.45 ± 2.21 (n = 6)	7.11 ± 1.75 (n = 8)	8.37 (n = 1)	
Pm or deeper than pm	3.31 ± 0.78 (n = 14)	5.06 ± 1.13 (n = 10)	4.40 ± 1.56 (n = 2)	2.23 ± 0.84 (n = 7)
Mean	4.73 ± 0.77 (n = 28)	6.79 ± 1.06 (n = 24)	5.61 ± 1.14 (n = 4)	2.23 ± o.84 (n = 7)

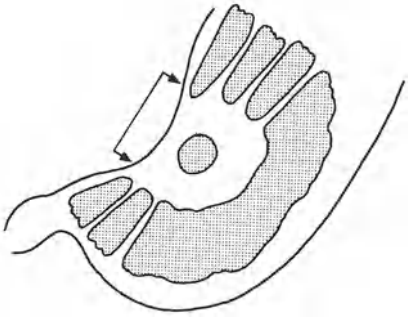
Table 4. Doubling time (t_D) of early gastric cancer

Type	t_D (days)
IIc + III	3462
IIc	2309
IIc	1385
IIc + IIa	1154
IIc	989
IIc + IIb	865
IIc	769
IIc	769
IIc	577
IIa + IIc	865
IIa + IIc	769
IIa	989
IIa	3462 a)
I	769
I	1385 a)

a) = polypoid cancer

Table 5. Radiological measurement of early gastric cancer





Type		days	
IIc + III	30 x 27.5mm	290	32 x 28 mm
IIc	46 x 46	370	50 x 46
IIc	19 x 16	113	20 x 16
IIc + IIa	13 x 15	390	16 x 16
IIc	14 x 11	240	14 x 13
IIc + IIb	7 x 5	240	7 x 6
IIc	19 x 16	136	20 x 17
IIc	15 x 8	145	17 x 8
IIc	18 x 18	204	22 x 19
IIa + IIc	11 x 11	210	13 x 11
IIa + IIc	35 x 35	120	37 x 36
IIa	22 x 15	302	22.5 x 16 a)
IIa	7 x 9	365	9 x 9
I	24 x 15	970	32 x 26
I	23 x 15.5	263	26 x 15.5 a)

a) = polypoid cancer

DISCUSSION

The difference of gastric acid secretion stimulated by AOC tetrapeptide 4γ/kg was proved in various types of early gastric cancer and also in the degree of cancerous invasion into the depth or locations of gastric cancer.

The close correlation of gastric acid secretion and the locations of gastric cancer cannot be observed as they can be in benign gastric ulcers, but it is very interesting to note that the level of gastric acid secretion in mucosal gastric cancers is high. Furthermore, a close connection was noticed between gastric acid secretion and the histological patterns of gastric cancers.

In these mucosal gastric cancers, the doubling time amounts to 3 years or more. These long doubling times are considered to result from the desquamation of carcinoma cells into the gastric lumen by the digestion of gastric acid.

Gastric cancer occurs not only in the stomach of hypo- or anacidity, but also in that of normo- or hyperacidity. Nevertheless, we must pay attention to the fact

that gastric cancer occurs in gastric mucosa with a high gastric acid secretion, and that the level of gastric acid secretion is high in almost all depressed types (IIc, IIc + III, III + IIc) of early gastric cancer.

CONCLUSION

From our radiological follow-up studies, it was emphasized that mucosal gastric cancer remained in high frequency in its original form for a long period. Furthermorem as far as gastric acid secretion was concerned, it was proved that the gastric acid secretion differed according to the degree of depth of the cancerous invasion.

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Present Results in Early Detection of Stomach Cancer by Radiologic Means

Forty Years of Early Diagnosis of Gastric Cancer

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The Ulcer-like Cancer

The first series of 15 gastric cancers, limited to the mucosa and detected between 1932 and 1937 by radiological interpretation, was presented by me at the International Congress of Gastroenterology in Paris 1937. Five of them had been operated on without the surgeon either feeling or seeing anything during laparotomy. Until March 1945, this series increased up to 19 cases. Of the 15 first cases, 13 were still living approximately ten years after gastrectomy; one died from a liver abscess, and another was never seen or contacted again. Two years ago, three of them, having reached the age of nearly 80, were still alive. To me, the so-called five-year-survival seems to be insufficient because gastric cancer can reappear after this time.

Although I have employed all diagnostic methods, now perfected by means of new instruments (gastroscopy using the rigid tube; washing cytology according to LOEPER and BINET; gastrophotographic techniques; the radiologic technique of thin-filling and compression), my early diagnoses were all performed without these additional methods. Several radiological aspects, such as the "niche en plateau", "niche encastrée, "niche sur fond plat", "racine de la niche" etc., were described by me, forty years ago, as very suspicious with respect to early malignant lesions of the stomach.

The history of one of my 15 pre-war patients is given as an example of my diagnostical methods:

A 26 year-old policeman who was on duty at the door of my hospital, had epigastric pains starting in March 1935. A small unsuspicious gastric niche at the angulus was discovered after an X-ray examination (Fig. 1). After undergoing active medical treatment, he felt better and did not attend a second X-ray examination two months later, as he hab been advised to do. In October 1935 he began to suffer again and now a much larger niche was apparent. In spite of continued treatment, the niche showed the same shape during three following radiographic examinations. The patient, feeling again in perfect health, did not accept the repeated advice that he should undergo an operation. The gastric juice was hyperchlorhydric.

In June 1936, the niche showed a lacunar appearance, but the patient still suffered no pain (Fig. 2). The patient was even more strongly advised to have himself operated on, but he asked for another short time treatment to be carried out for the last time. However, three weeks later the lacunar appearance revealed by the X-ray film was still apparent, and now the patient was willing to undergo surgical

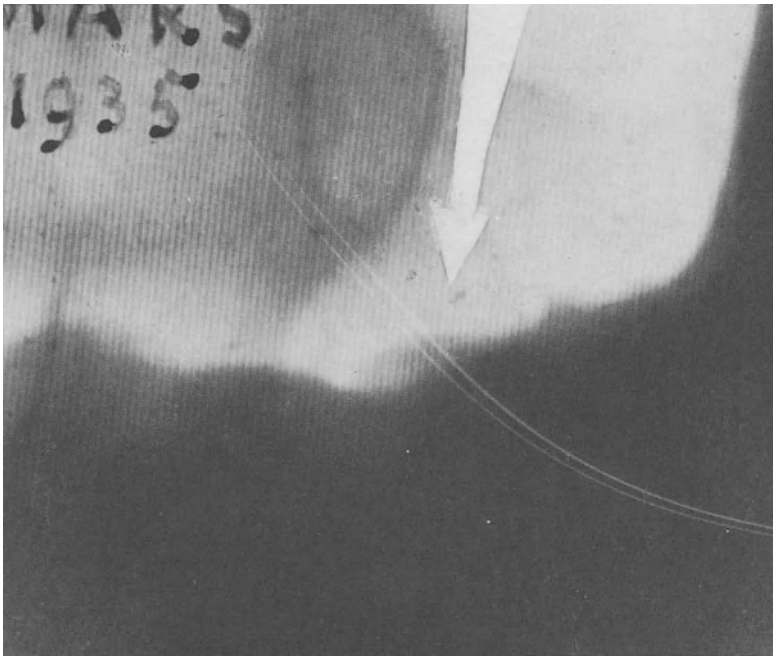

Fig. 1. 26 years, male, March 1935. Smal banal niche on the lesser curvature. Treatment of ulcer

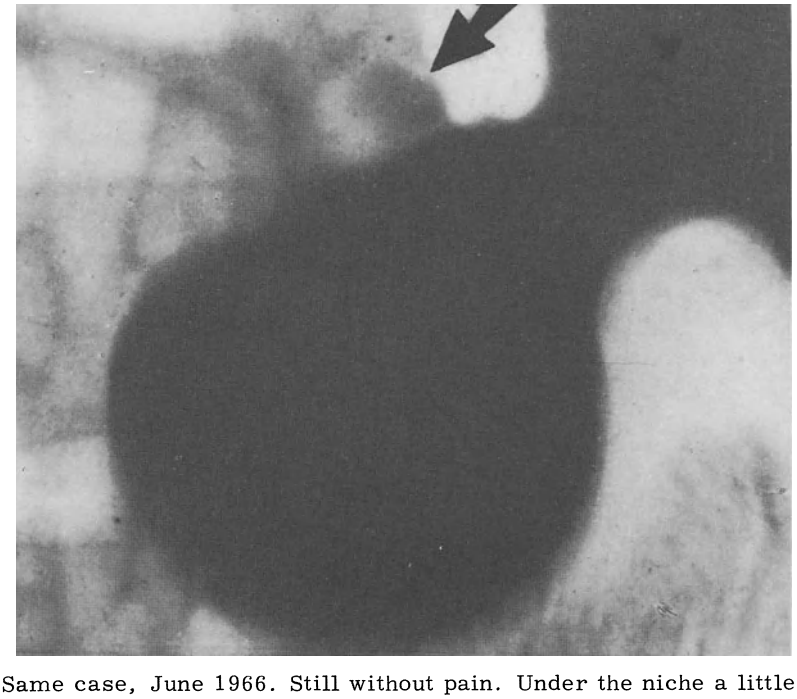

Fig. 2. Same case, June 1966. Still without pain. Under the niche a little lacunar appearance can be seen

Fig. 3. Same case. Resected stomach with a little ulceration, converging folds and a limited protruding area next to the ulcer

Fig. 4. Same case. The mucosa is entirely degenerated, but the degeneration does not invade beyond the mucosa

treatment. An ulceration with the macroscopic appearance of a benign ulcer with stellar folds was discovered (Fig. 3). Microscopically, the mucosa was entirely cancerous tissue. The cancer was limited totally to the mucosa (Figs. 4, 5).

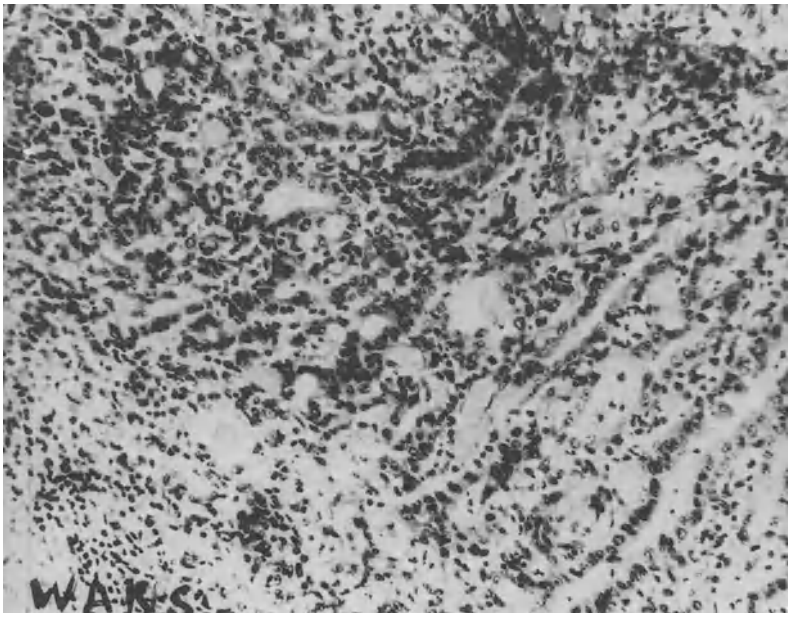

Fig. 5. Same case. Glandular atypia and an epithelioma which is trabecular and pseudoglandular

After gastrectomy the patient was still alive in 1965, despite the fact that he had been badly wounded afterwards and even lost a leg, and that he had to undergo lobectomy after becoming tuberculous.

These observations and other, later ones, the last of which were published in 1972, led me to the following conclusions:

1. The clinically favourable evolution of a niche is of no importance.
2. It is impossible to judge the real nature of an ulceration on the basis of its macroscopical aspects. This is true for radiological and gastrophotographic pictures as well as for the gross morphology of the resected stomach.
3. Simple measuring of gastric acidity is diagnostically worthless. Most of the small ulcer-like cancers have hyperacidic values.
4. The therapeutic test introduced by me before the war, has great diagnostic value. If after one or two months of active therapy, a niche will not diminish considerably on the vertical part of the stomach, or will not disappear entirely on the angulus, horizontal part, or pylorus, surgery is recommended. This differentiation between the two parts of the stomach is based on my observations : I have never seen an ulcer become a cancer in the vertical part. All graftings of cancer upon benign ulcers were seen by me on the angle or on the horizontal part.
5. The fiberscopic biopsy has the advantage of giving an immediate answer when positive. It has sometimes been alleged that the therapeutic test causes a loss of time. However, considering how slowly cancer is developing during its early stages, a delay of one or two months is of nō real consequence for the final result. It is easier to become a skilful fiberscopist than to learn radiographic interpretations. But in practice both methods, the radiological and the different endoscopic techniques, are not opposed, but should, if necessary, be used together.

The Transformed Benign Ulcer

The relation between a benign ulcer and a cancer, although still under discussion, seems easily resolved. The long pre-existent typical ulcer history is no proof, since it can be seen in an ulcer and in ulcer-like primitive cancer as well. But when, in the resected stomach, one finds a typical ulcer with all the well-known macroscopic and microscopic signs, and when one sees groups of cancerous cells on the upper outline of it, the existence of an "ulcère transformée" cannot be denied. In about a hundred actively treated patients with ulcerous niches in the angulus or in the horizontal part, and who had to undergo surgery, I found 50 benign ulcers persisting for various reasons, 40 ulceriform primitive cancers, and 10 undoubtedly benign ulcers with cancer grafting. The patients in the two last groups were never radiologically healed.

The Infiltrated Cancer

The infiltrated cancer spreads without signs of "corroding" or "elevating". It manifests itself by a limited rigidity which was explained by G. ALBOT as a reactive sclerous thickening of the submucosa under the cancerously transformed mucosa. This rigidity may continue at the level of the curvature or beneath it; it remains constant in all radiographs taken in the same position. Its inclination varies according to the peristalsis and to the erect or horizontal position of the patient, like "driftwood on the waves". It is at the same time "rigid and relatively flexible" (Fig. 6). The angulus, a very frequent location for cancer, reveals a "rigid and broadened" appearance instead of its normal acute and supple form. There are transitional forms between a normal and a pathological angulus.

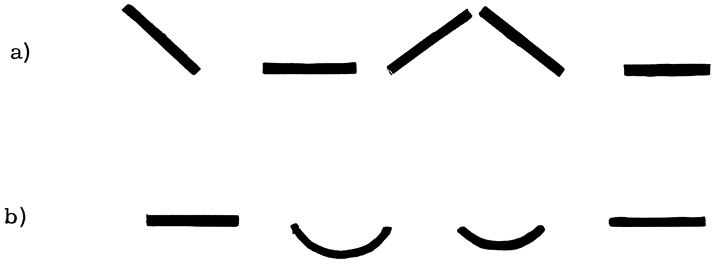

Fig. 6 a. The rigidity on the radiographs may vary in its orientation according to the peristaltic waves or the position of the patient. b The rigidity may bow itself according to the peristaltic motion

The embedded appearance ("aspect encastré") is a steep-sided depression caused by an infiltrated lesion where the cancerous mucosa is not interrupted.

All these signs can be observed in every part of the stomach. On the pylorus only one side can be affected in early stages. More frequently the growth is circular and a limited rigid lengthening is apparent.

Forty years ago I published the first recognized cases of the "muco-erosive" cancer which is now frequently found. This is a cancer which, despite its long clinical evolution ang progressive local growth, remains strictly confined to the mucosa. The patients were cured after undergoing gastrectomy.

"En face", it is necessary to use the double contrast method in order to discover an area deprived of rugae. Sometimes it is possible to see the en-face-lesions when the stomach is turned in a very oblique position.

The diagnosis of rigidity meets with some difficulties, as it may escape the attention of an inexperienced radiologist. An ulcer that is already healed may leave a rigidity possessing all the characteristics of cancer. Some localized forms of gastritis, cicatrised or, more often, still in activity, are also causing localized rigidity. In such cases the help of fiberscopic biopsy is often needed.

Forms of Tumors

The tumors are rarely primitive. More often they grow on primitive and non-operated ulcerous or infiltrating forms. If they are indeed primitive, they are usually not painful and, therefore, discovered rather late. Many malignant forms are due to the degeneration of benign tumors. There are also widespread tumors the diagnosis of which evolves around "polypoid gastritis", "Ménétrier's disease" etc. Fiberscopic biopsy can be misleading when a tumor is still intramural and not extended to the mucosa, or when it consists of a partly transformed benign tumor.

Mass Survey

Mass survey after the Japanese system is, for several reasons, not practicable in France and would not promise any scientific profit. Considering French conditions we have, instead, to examine selected cases only. My collaborator G. ALBOT organized a concentric "filtering" adapted to digestive cancers in general. The Insurance Societies, big organisations with medical staff, send patients suffering from "digestive ailments" to a so-called second stage, where non-cancerous, well determined cases are eliminated. Patients "suspected" of having cancer are then sent to the third stage, the "Centre de Dépistage systématique des Cancers Digestifs". ALBOT had the following results:

1. Between 1946 and 1965, 11.592 subjects were examined and the following cancers were detected: esophagus 33, stomach 60, rectum and anus 107, colon 26, pancreas 1, liver 8. This means a total of about 20 pro mille of all the examined patients.
2. During 1955-1965 in 972 examined cases, 37 with gastric cancer were detected. (4,2 0/00).
3. In the same period, 84 cases of rectal cancer were found in 8.793 examined patients (9,5 0/00).

Results of Operations Performed too Late

Thirty years ago we collected 85 cases of our last operated gastric cancers and studied the length of the evolution prior to the diagnosis, when we saw the patient.

Table. The evolution of 85 cases with operated gastric cancer

	less than 1 year	1 to 2 years	2 to 4 years	more than 4 years	total
Early cancers	3	5	1	4	13
Small cancers	4	5	4	4	17
Big cancers	5	9	7	5	26
Inoperable	8	5	6	10	29

While 13 cases had early cancer and 17 cases were in "good condition", 55 patients had been operated on "too late". However, out of those 55 cases, a retrospective study of the series of radiographs showed that in 26 of them clear radiological signs were present which had been missed or misinterpreted at the time when the diagnosis should have been made; at that stage, the tumor would not have been inoperable. Thus, in only 29 cases a correct diagnosis was (theoretically) impossible for different reasons, such as lack of radiographs, persistance of medical treatment despite a radiologically persisting deformation, symptoms neglected by the patient, or finally, a cancer in absolute clinical latency. Apart from the last reason, the other "pitfalls" could have been avoided if both patient and physician had been better informed.

The conditions are better now; the old causes, however, are still persistent. Moreover, it is not impossible that another cause for errors may be added in the future as a tribute to new methods : for example, the responsibility of untrained fiberscopists or cytologists and an exaggerated confidence in their negative results which may bear the risk of being false negatives.

Early Radiologic Diagnostics of Stomach Cancer

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The following report is an attempt to define the task and status of diagnostic radiology in the early diagnosis of stomach carcinoma. Moreover, it presents an evaluation of radiological examination techniques and of the limitations impeding the early diagnosis of stomach cancer.

A description of the status of diagnostic radiology may provide a basis for the discussion of different radiological examination techniques. This will necessarily imply a judgment regarding the relationship between radiology and endoscopy. As we learnt from various congress discussions in recent years, competition between radiological and endoscopical methods has been reanimated as a consequence of progress in fiberscopy. It has even been asserted that only the endoscopist is able to diagnose stomach cancer, because endoscopical biopsy alone produces histological proof. We feel, however, that such an attitude fails to realize that diagnostical methods have to be differentiated according to their various functions.

The first step in stomach cancer diagnosis is the detection of a lesion. The choice of examination method depends on the following criteria:

1. The best possible precautions must be taken to detect and localize a lesion.
2. Inconvenience to the patient must be minimalized.
3. The time involved and the cost of instrumentation must be kept at a tolerable level.

There is no doubt that, at present, the efficiency of radiology in the detection of stomach lesions is more or less equal to that of endoscopy. Preference for one or the other of the two methods will depend more on the ability of the available examiners and on the limited comparability of the material, than on the method itself. With respect to the frequency of cancer detection, radiology is indeed equal to endoscopy.

The risk of damage by radiation exposure is sometimes mentioned as an argument against radiology by supporters of other examination methods, but various other aspects of the problem have to be considered as well. The genetic risk can be neglected on account of the average age of patients undergoing an examination for stomach cancer detection. The somatic risk - induction of additional cases of leukemia or other neoplasms - can also be discounted for single examinations of patients where clinical suspicion of a tumor is evident. Our present notion of somatic late effects - expressed in linear dose-response-relationships - is derived from whole body irradiations with high dosage. It is improbable that the same relationship should be true for cases where repeated exposures of smaller parts of the

body are made with low dosage. Even supposing an extreme condition : a linear dose-response-relation upon repeated diagnostic radiation exposures, one would see that the number of additional tumors (induced e. g. by stomach mass screening) would be much less than 1% of all detected stomach cancers. On the whole, the real somatic risk is probably much smaller, and the radiation risk should bear no weight when a method of stomach cancer detection is chosen.

The subjective discomfort to the patient in X-ray examination is, today, even less than that caused by gastroscopy or gastrocamera examination. For both methods the examination cost is comparable. The time required for an X-ray is, on the average, shorter than that for an endoscopy.

We may conclude that, at present, X-ray and endoscopical examinations are of approximately the same value for the detection of suspicious stomach lesions. It can be said that an X-ray examination should be normally the first special diagnostic measure.

The detection of a suspicious lesion is followed by a second diagnostical step, the exact determination of shape, size and surface structure. The purpose of this step is to approach a definite diagnosis as near as possible. Approximately 70% of all small stomach lesions detected during a first X-ray examination show sufficiently pronounced macroscopic signs, to prove or exclude a stomach cancer with very high probability. This percentage can be increased by 10 to 15%, when a second intensifiedX-ray examination is conducted. The macroscopic appearance of the remaining 15 to 20% small lesions does not indicate a state of malignancy. Endoscopical methods have approximately the same percentage of efficiency. These 15 to 20% small lesions will require intensive co-operation between radiologist and endoscopist. In this context, radiology is useful not only in detecting suspicious lesions, but also in their macroscopic evaluation.

In order to arrive at a correct and just evaluation of efficacy for different diagnostical methods, we have to consider the histological proof by means of biopsy as a third diagnostic step. It should not be confused with a possible endoscopical detection and identification of a lesion. Pre-operative biopsy should be done in all cases of macroscopically suspicious lesions detected either by radiology or by endoscopy. Nevertheless, it has to be pointed out that radiological signs of early cancer have, in many cases, such a diagnostic importance that surgery will be indicated even if the ensuing biopsy fails to prove the presence of cancer.

The problem of an adequate technique for radiological examination in search of small stomach cancers, has been intensely discussed for more than 40 years. The controversy of diagnostical positions between GUTMANN (1933) and PREVOT (1937) delayed methodological progress for more than 20 years, although both authors claimed to have obtained good results by employing their respective diagnostical procedures. We have stated in 1957 (FRIK, 1958) that only a combination of different radiological examination techniques would ensure satisfactory diagnostical efficiency.

Radiographs of the filled stomach (GUTMANN et al. 1939) give in a surprising percentage of cases, a distinct indication that a tumorous lesion is present, but details of the lesion itself are identifiable only in a restricted number of them. In mucosal studies the surface of a lesion can be observed in a high percentage of cases (PREVOT, 1957). The most important information gained from mucosal studies, however, concerns the reactions of the mucosa in the vicinity of a lesion. This is often

the first and sometimes the only indication that a very small lesion exists at all. The best way to a direct and total demonstration of a small tumorous lesion is, depending to its type, either the compression technique or the double contrast study (FRIK, 1958). We wish to emphasize, however, that good fluoroscopical techniques including TV-fluoroscopy are indispensable for an exact demonstration of tumorous lesions with small- or largesize spotfilms.

Ten years ago, Japanese authors (SHIRAKABE et al. 1963) emphasized the importance of double contrast studies; to a certain degree, they neglected the other radiographical techniques and even, during the first years, fluoroscopy. ICHIKAWA et al. (1972) stated that double contrast examination provides a leading method of detection for early stomach cancer. They suggested, therefore, that it should be used in all stomach examinations. But as far as the complete double contrast study with insufflation by air-tube is concerned, we cannot agree with them for the following reasons:

1. 80 to 90% of all small suspicious stomach lesions can be detected in a careful stomach examination without artificial enlargement of the air contents. Air insufflation is therefore not necessary for detection in these 80 to 90% of cases.
2. Important advantages connected with the use of X-ray examination will be lost when th stomach tube is employed : a lower degree of discomfort to the patient, and a much shorter time needed for the examination.

Nevertheless, the double contrast examination which is known and accepted for more than 60 years (see v. ELISCHER, 1911; VALLEBONA, 1926, and many other authors) deserves a notable place among radiological stomach examinations for the following reasons:

1. Double contrast studies are decisive for the detection of lesions in a rather restricted number of cases. In many others, however, they are useful for improving the macroscopic evaluation of lesions that have already been detected.
2. Most parts of the stomach can be shown in double contrast by shifting the natural air bubble; but this method does not allow to change the degree of stomach distension, a procedure which often gives useful information.

When we search for an early cancer our standard examination method will be, therefore, a combination of fluoroscopy and radiographs, using complete filling, mucosal studies, compression techniques and double contrast studies with the natural air bubble. In the majority of cases this procedure is sufficient for an adequate demonstration of small tumorous lesions. If exact determination of a suspected or detected lesion is not obtained by these means, then a second intensified X-ray examination is performed. This second examination is directed on the suspicious region specifically. It includes - if necessary - an additional insufflation of air p provoking different grades of stomach distension (SHIRAKABE et al. 1966).

As far as the Japanese propositions are concerned, we do not wish to reject their method of double contrast studies, but we are reluctant to accept their rather dogmatic and exaggerated opinion of its value. In our opinion the procedure is unnecessary in many cases. Considering the small percentage of lesions that can be detected by the insufflation method alone, one has to ask whether the additional time and the possible discomfort to the patient are justifiable in all other cases.

Even in Japan, the emphasis on double contrast studies has been moderated in recent years. SHIRAKABE (1971) and his co-authors who represent the most experienced Japanese research group, underline in their last book the importance of a

combination of several radiological examination techniques. This means that between Japanese and German groups, differences of opinion are on the decrease. The remaining dissent may depend partly on the different tumor incidences in Germany and Japan, partly on differences in habits and tolerance of patients and doctors.

It should, however, not be forgotten that some rarer localizations of early stomach cancer require the use of specialized examination techniques; this is particularly true for the anterior wall of the stomach body.

Differential diagnostic problems cannot be discussed in this short report; but we have to mention the macroscopic classification of early cancer proposed by the Japanese Gastroenterological Endoscopy Society in 1962 which is one of the most important contributions of Japanese stomach cancer research. For younger and less experiences examiners, this classification makes it much easier to decide whether a detected lesion suggests the presence of cancer or not. Moreover, it enables us to distinguish with considerable probability, between early and advanced cancers according to macroscopic criteria. The final decision whether a cancer is still in an early stage or not is, however, left to histology.

One of the most grave limitations for early cancer detection results from the fact that many patients with early cancer will not go to the doctor because they overlook or underestimate the early symptoms. The only way to overcome this problem would be to organize gastric mass surveys (IRIE, 1953; MURAKAMI, 1971; and many other authors). The value of mass surveys will be related to the stomach cancer incidence in the respective countries. The average stomach cancer mortality in Germany is about half that of Japan. TREICHEL et al. (1972) established, however, that the incidence of stomach cancer in Germany is in the sixth decade of life the same as in Japan in the fifth decade. The mortality curve for stomach cancer in Germany has therefore the same shape as in Japan, but is shifted to the right for one decade of age. This leads to the conclusion that gastric mass surveys in Germany would be as effective as the Japanese surveys if age groups with a comparable cancer incidence were examined, e.g. the German population over fifty. In order to cover those age groups completely by radiological mass survey, it would be necessary to install at least 1.500 X-ray screening units all over Germany. Even if the technical organization were possible, and sufficient staff available, we doubt that the expenditure involved would be authorized. Japan is facing similar problems. Gastric mass surveys in that country involve, at present, less than 10% of the endangered part of the population per year. Experimental mass surveys with gastrocameras have shown that they are threatened by the same kind of problems as the X-ray mass surveys.

Another limitation of an effective radiological search for early stomach cancers lies with the personal experience of the examiner. This is true not only for mass surveys, but also for single X-ray examinations of the stomach in the doctor's practice or in a hospital. The average examiner can perform approximately 2.000 X-ray examinations of the stomach per year. In Germany the mean percentage of detected stomach cancers in clinical material of X-ray examinations is about 1,5%. Early cancers constitute at most 20% of the total number of stomach cancers. This means that the individual examiner will find at most 5 or 6 early stomach cancers per year, of which perhaps one or two are really hard to detect. Thus, opportunities for widening one's diagnostic experience remain rather restricted (FRIK, 1970). Psychological statistics and the results of vigilance research are revealing that the detection of concealed findings will be less and less probable (FEGER, 1971). This limitation by psychological factors is true for both X-ray examinations and endoscopical methods.

Let me summarize the above discussion of the position of diagnostic radiology in early stomach cancer diagnosis, of radiological examination techniques, and of the limitations involved in early cancer diagnosis : X-ray examination is as yet the most suitable "first step" of a series of examinations aimed at the detection of tumorous stomach lesions. In many cases radiology is able to furnish macroscopic evidence of a lesion of such quality as to render unnecessary the other methods of macroscopic definition. Moreover, in an increasing number of stomach examinations it is possible to make cautious assumptions about the stage of the tumor and, in particular, to establish the probable existence of an early cancer. An X-ray examination can be expected to give positive results in more than 80% of all stomach cancers. The successful use of X-rays for this purpose requires a combination of different radiological examination techniques, as we are able to confirm from our own experience. We could demonstrate that the rate of small lesions (less than 4 cm in diameter) among all detected tumors in our material, was approximately the same as the percentage of diagnosed early cancers in Japanese publications (FRIK, 1966). In recent papers (FRIK, 1971) and in the present report, we have evaluated some 30 early cancers detected by X-ray examination. The limitations of early stomach cancer detection result not so much from the respective examination methods used, as from more general difficulties including psychological factors.

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Discussions by Invitation

Present Results in Early Detection of Stomach Cancer by Radiologic Means

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It is needless to say that a combination of both radiological and endoscopical examinations is superior to the application of one single method, when we are hunting for good and correct results in the diagnosis of early gastric cancer (Table 1).

Table 1. Relation of radiological and endoscopical diagnosis of early gastric cancer

Type: / Diagnosis	I, IIa I+IIa	IIa+IIc	IIb	IIc, IIc+IIa IIc+III III+IIc	III	Total
Both correct	1	6		59	3	69 (48%)
Either correct	5	6		35	2	48 (33%)
Both suspected	2			1		3 (2%)
Either suspected	1			5	1	7 (5%)
Both erroneous	4		2	9	3	18 (12%)
Total	13 9%	12 9%	2 1%	109 75%	9 6%	145 (100%)

Furthermore, routine G-I series are still the first choice and first step in the diagnosis of esophago-gastrointestinal diseases. As yet, endoscopy can be only the second step. Despite the progress made in endoscopy, as far as gastric diseases are concerned, a radiological examination still remains the basis for localizing morphological lesions. Therefore, it does not seem appropriate to simply compare these two diagnostic techniques so different in character, and which are indicated at different phases of the patient's work-up. Diagnostic value of both methods and preference for one or the other technique will depend also on the extent, depth, type and localization of gastric cancer. The combination of both techniques may achieve a correct result in 80,1% or even 89,9% when suspicious lesions of final stage are included.

The radiologic examination is composed of four main techniques: Relief technique, filling technique, compression technique and double air contrast technique. Especially when we used the latter we were able to demonstrate the lesion precisely at the spot where it was confirmed later on in the resected stomach (Fig. 1).

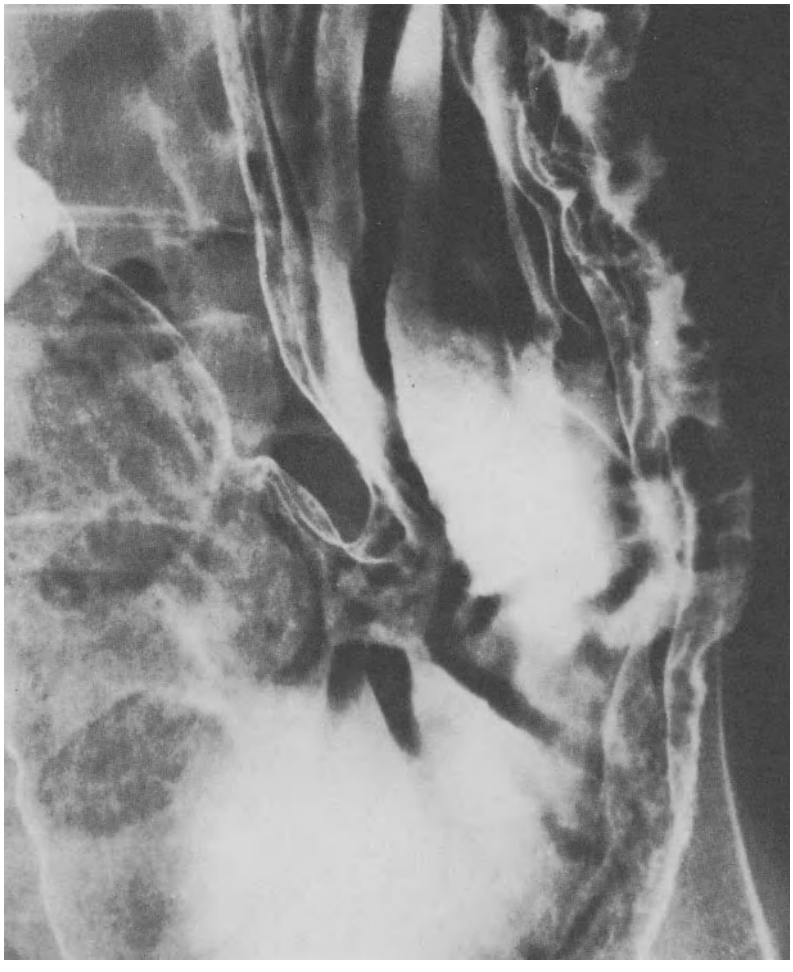
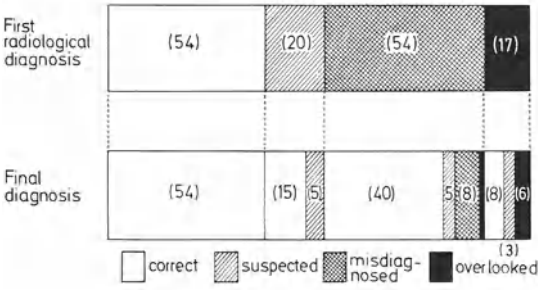


Fig. 1. Typical IIc type of early gastric cancer at the gastric angle (double air contrast study)

Five strong points of this method should be mentioned:

1. Minute lesions on the wall or the curvature can be seen in a wide area from the gastric cardia to the pyloric ring. Changing the patient's position and using a large amount of air are very helpful in making it possible to observe any part of the stomach.
2. Deformation of the stomach and marginal granules can be observed by using air and barium meal as in full filling techniques.
3. Features can easily be reproduced.
4. The quality of the picture is not affected very much by gastric juice or adherent mucus.
5. Double contrast technique is easy to handle, even for someone who is not an expert.

Table 2. Correlation between first radiological and final diagnosis of early gastric cancer

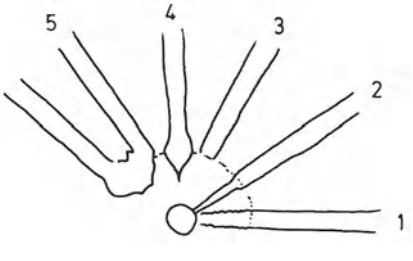


Two disadvantages of this technique should be mentioned:

1. At least 200 ml of air is needed for the double contrast picture.
2. It is difficult to analyse the findings properly if the shadow of the intestine or the spinal column interferes.

However, the most important point of this radiologic examination which has to me even some endoscopic aspects, is the indirect diagnostic way and the accuracy with which we are able to demonstrate lesions. Nevertheless, a radiological diagnosis without proof of histology remains always in the stage of probability. For example, a demarcated, depressed pattern is a typical sign of early gastric cancer of type II, which means an uneven central depression surrounded by abruption or thickening and confluence of mucosal folds (Table 3). However, this sign is not necessarily pathognomonic for malignancy. Abnormal mucosal relief patterns, such as stiffness, narrowing, abruption, thickening or confluence of proximal mucosal folds may also be seen in benign peptic ulceration (Table 4).

Table 3. Several phases of benign gastric ulcer of carcinomatous mucosa



1. Stiffness of mucosal folds,
2. narrowing of proximal mucosal folds,
3. sharp abruption of mucosal folds,
4. thickening of the proximal end of abrupted mucosal folds (clubbing),
5. confluence of abrupted mucosal folds

Table 4. Differentiation of gastric ulceration

	(1) rigidity	(2) narrowing	(3) abruption	(4) thickness	(5) confluence
Malignant ulcer Borr. II-III 40 cases	10 25%	10 25%	20 50%	31 78%	32 80%
Peptic ulcer of carcinom. mucosa 20 cases	16 80%	20 100%	13 65%	7 35%	2 10%
Benign ulcer (Ul. IV) 60 cases	9 15%	7 12%	4 7%	12 20%	3 5%

(Ul. IV = complete destruction of the proper mucosal layer)

CONCLUSION

As shown in Table 4, radiological examinations, especially those of double contrast technique, are very informative in routine and precise examinations. To anybody using this technique it is essential to know the abnormal pattern of mucosal folds or area pattern of early gastric cancer. Furthermore it is essential to know that only direct examination by biopsy study under direct vision or cytology will establish the final and correct diagnosis.

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Present Results on Early Detection of Stomach by Radiological Means

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Only in extremely skilful hands does radiology give the impressive results as reported by some French and Japanese authors. Normal routine examinations show very poor results (from 70% accuracy for invasive cancer to 14-20% in "early" cases.) Moreover, no valuable statistical data have been so far reported on the correlation between X-ray diagnosis, the histopathological staging of the lesion, and the parameters of the 5 year survival.

Of real interest in this connection are the results of a study made in Japan (SAKITA, 1972) on more than 18.000 cases in which screening procedure based on routine X-ray and gastrocamera, yielded much better diagnostical accuracy than that of a group of individuals screened by X-ray alone.

A substantial improvement of X-ray accuracy is strongly needed, for radiology today represents the only generally accepted diagnostic procedure in many countries. Closer cooperation, on a more routine basis, is also advisable between radiologists and endoscopists, in order to achieve better final diagnostic results in the early stages of disease.

But a main draw-back of X-rays will never be overcome: in borderline lesions of a very limited size, the lack of morphological evidence will never convince a surgeon to perform a major intervention, at least in Europe and in the USA, and pathology by frozen section during surgery is quite unreliable in early stages of a gastric malignant transformation.

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Present Results of Gastrocamera Technique in Early Detection of Stomach Cancer

Experiences with Gastrocamera Examinations as a Screening Method of the Stomach

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In accordance with the subject of point VI we would like to describe the experiences made by us on using the gastrocamera for stomach mass surveys in Germany.

The Distribution of the Method

Present results can only be assessed if the distribution of this diagnostical method is taken into account. As shown in Fig. 1, the distribution of this endoscopical method in Japan rose rapidly within the years of 1958 and 1960. In 1965 more than 10.000 instruments were already in use (SAKITA, 1967) (Fig. 2.). Up to 1971, this number had increased more than twofold (OSHIMA, 1972).

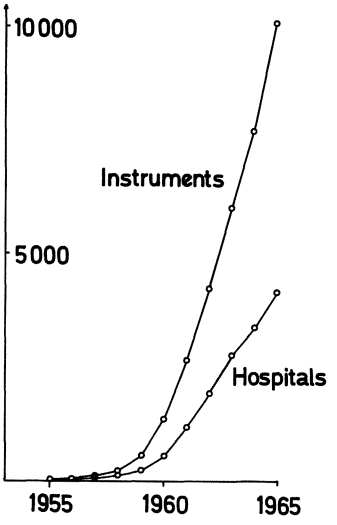

Fig. 1. Time trend of the number of gastrocameras in use and hospitals adopting gastrocamera examination in Japan (SAKITA 1967)

When these distribution patterns are compared, development seems delayed for 10 years in Europe, although - as can be seen in Fig. 2 - to a much smaller extent. While the distribution of the so-called blind gastrocamera is still increasing in Japan, the increase in the use of this method in Europe is very slow (OSHIMA, 1972).

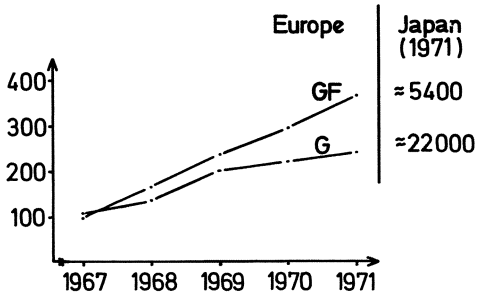

Fig. 2. Time trend of the number of gastrocameras (G) and gastrocameras with fiberscope (GF) in Europe as compared to Japan (OSHIMA 1972)

There was a widespread distribution pattern of endoscopic methods, as was statistically recorded for Japan by ARIGA in 1966 (Table 1). Three quarters of all instruments used in Japan were, at this time, in use in small hospitals or in general practices (ARIGA, 1966; OSHIMA, 1969a).

Table 1. Number of Japanese hospitals and practices where gastrocamera examinations were performed in 1966 (ARIGA)

University hospitals	60
Government hospitals	111
Municipal hospitals	119
Other hospitals	699
Practices	406

An enquiry made by the European Association of Gastrocamera Diagnosis about the latest status of gastrocamera examinations in Europe included also the results of early carcinoma detection; 215 endoscopists or examination sites were counted (NAVA, 1972). Nearly 75% of the answers were from the Federal Republic of Germany. Table 2 summarizes the result of the enquiry.

Table 2. Results of enquiry (Europe 1972) concerning the distribution of endoscopical methods and the number of cases of early gastric cancer detected during recent years (NAVA 1972)

	No. of instruments	predominantly used instrum.	cases of early ca.
Gastrocamera	239	100	206
(gastrocamera with fiberscope)	(144)	(81)	
("blind" gastrocamera)	(95)	(19)	
Gastrofiberscope	235	91	152

All of the persons questioned had the same number of gastrocamera models or fiberscopes. Examination with gastrocamera had slight preference over gastroscopy. However, there is a more distinct difference between the two methods when the number of early carcinomas detected is taken into account, and this speaks in favour of the gastrocamera technique. For details we refer to the evaluation of this enquiry (NAVA, 1972).

Statistical Basis for Mass Surveys in Gastric Screening in the Federal Republic of Germany

Since February 1968 a group under the leadership of OSHIMA has performed mass stomach surveys using the "blind" gastrocamera (OSHIMA, BERGEMANN, GALARZA, 1970). The statistical basis of these examinations were the well known facts about the prognosis of gastric carcinoma and early carcinoma as well as compared statistics on the frequency of gastric carcinoma in Germany and Japan with relation to age grouping (HAYASHIDA and KIDOKORO, 1970; OSHIMA, 1969b; SCHÄFER, MIKAT et al., 1970). On account of a difference of ten years in stomach carcinoma incidence, as it appeared in the mortality statistics (Fig. 3) it seemed advisable to focus mass surveys on patients aged 50 and more. In Japan they are carried out on patients of 40 and upwards (FUJITA, SAKITA et al. 1972).

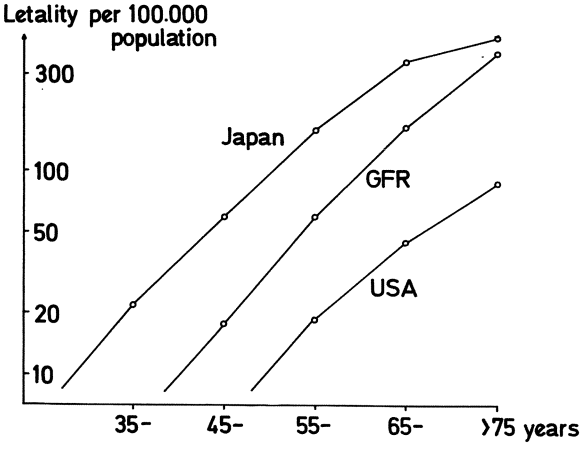

Fig. 3. Age-specific death rates for stomach neoplasms in the German Fed. Republic (1969), Japan (1969) and the USA (1968) (WHO 1971, 1972)

Mass Survey Program Carried out Stepwise

The concept of OSHIMA, shown in Table 3, was used for the rest of the project (OSHIMA, 1971b). Japanese statistics on symptoms of early carcinoma have shown that upper abdominal pains were present in approximately one half of the cases, and thatother symptoms pointing to epigastric diseases were also frequent (KUROKAWA et al. 1967; KURU, 1966; TASAKA, 1970). A recent enquiry in Europe about the symptoms of early carcinoma in about 200 cases corresponds with Japanese data (SCHÄFER, HEIDINGER and OSHIMA, 1972).

Table 3. Gradual procedure towards the screening of gastric cancer

Step I.	Patients older than 50 years suffering from pain or discomfort in the epigastrium
Step II.	Patients in the age of high risk for gastric cancer who are visiting the doctor
Step III.	All persons older than 50 years, in living areas and factories

Frequency of Circumscribed Pathological Findings in Gastric Screening by "Blind" Gastrocamera Examination

Table 4 shows a preliminary result of these mass surveys from the year 1970 (SCHÄFER, ASSHEUER et al. 1972). Firstly, outpatients suffering from epigastric complaints were examined (Group I). Patients with circumscribed findings detected by X-ray examination were not included. When localized findings were suspected by X-ray, we normally performed an examination using the gastrocamera with fiberscope. The age groups most frequently examined were those from 50 to 60 and from 60 to 70 years. The rate of carcinomas detected (among them one early carcinoma) was 1%, a rather high incidence rate.

Table 4. Screening with gastrocamera: results of examinations (July 1970)

Gastrocamera diagnosis	Group I	Group II
Cancer	10 = 1,0%	4 = 1,5%
Ulcer	31 = 3,2%	1 = 0,4%
Polyp	17 = 1,8%	24 = 9,1%
Total No. of examinations	974	265

A second group, similar to the above mentioned 3-step-project, consisted of patients from a geriatric hospital. For these cases examination with "blind" gastrocamera was the only screening method used. The mean age of these patients was 70 to 80 years. The preliminary result can also be seen in Table 4 (Group II).

The unexpectedly high percentage of carcinoma detected in Group I (1%) which was about 4 to 6 times higher than in Japanese mass surveys (OSHIMA, 1971b); OSHIMA, BERGEMANN et al. 1970), as well as the relatively high rate of other patients also needing observation or treatment, suggests the necessity of serious mass surveys at the level of step III (Table 3): This would mean to perform mass screening in factories or living areas, and to use television for pointing out the importance of medical check-ups. This method proved effective. In a third group, more than 1000 examinations have been performed as yet in Berlin, and the rate of circumscribed findings detected was 9%. Collectively more than 2. 800 examinations were performed in Berlin, and 3 early carcinomas were detected (BERGEMANN, RÖSSNER et al. 1973).

Table 5. Rate of early gastric cancer detected by mass surveys in Japan (OSHIMA 1969)

Authors	No. of examinations	rate of early cancer
GOTOH (1964)	23. 886	0,12%
TANAKA (1964)	7. 667	0,14%
NAGASAKO et al. (1967)	46. 794	0,04%
FUCHIGAMI et al. (1967)	22. 642	0,06%
KITAGAWA et al. (1967)	347. 921	0,04%
KAZATO et al. (1967)	39. 570	0,07%
YAMAGATA et al. (1968)	67. 134	0,05%
AIKAWA (1968)	23. 736	0,10%

As Table 5 shows, this detection rate of 0,12% for early carcinomas agrees with the data given in Japanese papers (OSHIMA, 1971b). It should be mentioned at this point that the groups I and III of our study included to a small extent, patients of less than 50 years. In the latter series, we had the opportunity to perform the survey by using a blind gastrocamera in combination with X-ray screening (TREICHEL, HEITZEBERG, FRIEDRICH, 1972). We consider this to be the optimal method.

The Practicability of the So-called Blind Gastrocamera in Mass Surveys

In the course of these examinations, the so-called blind gastrocamera proved appropriate in several ways for the use in mass surveys. Methods for this purpose have to be efficient in producing reliable diagnoses, they have to be without medical risk, and they should not be too uncomfortable for the patient (OSHIMA, 1971a)

a) Representability of the mucosa surface. First of all, a continuous evaluation of the representability of various stomach sections was done with different gastrocamera models. We found in the first series that 150 to 200 examinations were necessary for attaining an optimum (SCHÄFER, BERGEMANN et al. 1971). This period of testing could be considerably reduced later on (ASSHEUER and REINER, 1972; BAUMANN, 1971; HEIDINGER et al. 1972; REHS, BERGEMANN et al. 1970). Fig. 4 demonstrates how the main stomach sections can be recorded with two blind gastrocamera models (GT-Va and GT-P_{II}) (SCHÄFER, ASSHEUER, REINER et al. 1972). In addition to the fact that the upper stomach can be viewed only partly

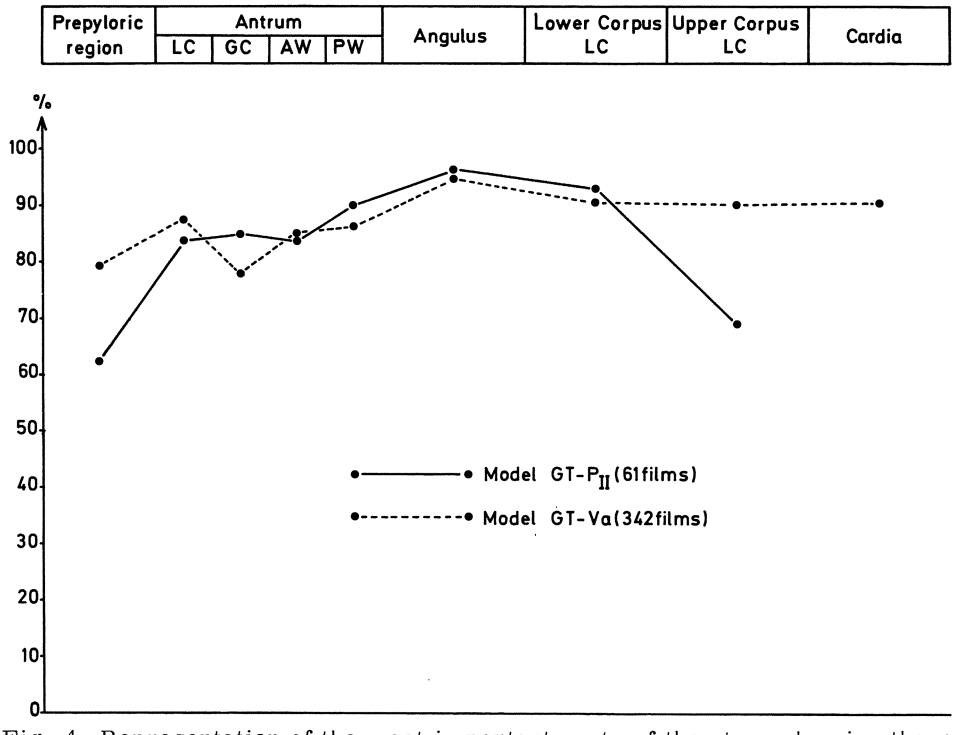

Fig. 4. Representation of the most important parts of the stomach using the gastrocamera. LC = lesser curvature; GC = greater curvature; AW = anterior wall; PW = posterior wall

because the model GT-P_{II} is unable to square off, it was proved that all main parts of the stomach can be viewed in approximately 90% of cases. In the meantime some of the examiners have achieved still better results (ASSHEUER, REINER, 1973; BERGEMANN, RÖSNER et al. 1973; HEIDINGER, SZEKESSY, ASSHEUER, 1973; REHS, BERGEMANN et al. 1970).

b) Duration of the examinations. Great store was set on an optimal presentation of th the entire stomach interior. It was equally interesting to note the number of patients who could be examined within a given time. Generally, only a few minutes were necessary to perform the examination. During the first screening of 150 patients with a model GT-P_{II}, the average time taken was less than 4 minutes per patient (ASSHEUER und REINER, 1972).

c) Subjective complaints. Immediately after examination, 671 patients were questioned about any possible discomforts (REINER and ASSHEUER, 1971): More than 75% of the examined persons said that the procedure was not unpleasant, or just a little, 12% said it was rather unpleasant, and only 1,9% said that the method caused great discomfort. Patients under fifty were especially sensitive to this discomfort. It was proved, however, that the psychological situation played a big role in this matter; anaesthesia of the throat considerably reduced subjective complaints.

d) Examination risks. There were no complications during our screening activities. According to the records of ARIGA (1966), hemorrhages, injuries or perforations are extremely rare during gastrocamera examinations. His statistics show that perforations occur 10 to 20 times less often than during examinations with different types of gastroscopes or fiberscopes (Table 6). Finally we examined also the cardiovascular functions in a large number of patients. This checking, which included ECG recordings, revealed no severe change (REINER and REHS, 1970)

Table 6. Frequency by perforations by different types of endoscopic instruments (ARIGA 1966)

Instrument	No. of examination	Rate of perforation
Several Gastroscopes	53.500	0,065%
Several Fiberscopes	70.400	0,030%
Gastrocamera	829.700	0,003%

Teamwork Based on Substantiated Findings

A fundamental and integral component of this method is the familiarity with the gastrocamera film on which diagnosis is based. It is an important prerequisite for any more extensive series of examinations, for two reasons: 1. In an extensive series of examinations the description of what was only seen is not sufficiently substantiated, and it cannot be reproduced objectively (OSHIMA, 1971a). 2. The examination technique is easier to learn than the endoscopical interpretation. A diagnosis is established independent of the examination itself, therefore this method gives the chance to organize a teamwork. The mass survey was performed mainly by beginners in endoscopy technique, e. g. by candidates for a doctor's degree. They were under supervision, and in any case the interpretation was always done under the guidance of an expert. When a control examination became necessary, it was always left to an expert who performed it with a "gastrocamera with fiberscope". Less experienced doctors were obliged to attend regular training courses (OSHIMA, 1972).

Thus, a final diagnosis was the result of several diagnostic steps, the combination of which ensured a maximum of examinations by the effective co-operation of experts and beginners.

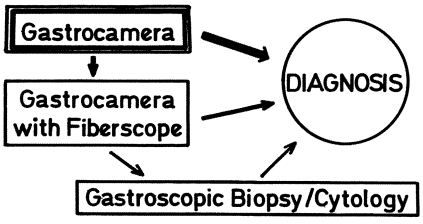

Fig. 5. Endoscopic procedure of gastric screening examinations

Fig. 5 is a rough diagram of the examination proceeding. For bigger endoscopy centres this system will offer an opportunity to compensate the scarcity of experienced endoscopists. Interested beginners in the field of endoscopy will soon be trained to examine larger numbers of people, and experienced endoscopicians will be available within a rather short time.

Discussion Concerning Certain Objections to this Method

Unfortunately there have been some objections against the use of the "blind" gastrocamera method in Germany. These objections appeared not justified, based as they were on easily misleading statistics about the frequency of gastric carcinoma which led to further speculations on the subject of medical check-ups (SCHÄFER, 1970). Moreover, this method was often abandoned on account of lacking experience (OTTENJANN and STADELMANN, 1971). Some doubts are still raised about the endophotographical quality of the instruments with respect to certain optical properties, e. g. the limited resolving power (FRÜHMORGEN et al. 1972). But this argument can also be refuted (SCHÄFER, HEIDINGER et al. 1972). For such reasoning, theoretical as it is, the good results of Japanese mass surveys by this method, seem to be nonessential. In fact, these surveys proved the diagnostic value of gastrocamera examinations to be in no way inferior to that of other screening methods e. g. the X-ray examination (FUJITA, SAKITA et al. 1972; KANO, YAMAGATA et al. 1972; SAKITA, 1967).

Recently SAKITA and FUKUTOMI (1972) were able to confirm this opinion on a large scale. The rate of early carcinomas detected was 0, 05% when the conventional X-ray method was used, which is in accordance with former results. But the detection rate for early carcinoma could be raised four- or fivefold when X-ray and gastrocamera examinations were combined and performed on the same day. In proportion to the total of carcinomas detected the rate of early carcinomas was also decisively increased by this method.

SUMMARY

The present status of gastrocamera technique in the early detection of gastric cancer can be judged only on the background of the distribution of this method. There is a considerable difference between the European and the Japanese situations. Analysis of statistical data reveals that in mass surveys the same frequency of

early gastric cancer is expected in Germany for people of 50 years and over, as for persons of 40 in Japan.

In mass surveys, stepwise proceeding is preferable. In the different groups examined we found an unexpectedly high number of circumscribed lesions, among which advanced carcinoma was particularly evident.

Investigations concerning the practicability of the gastrocamera method and including tests on several hundreds of patients, proved that it is indeed suited to mass screening in various respects. Moreover, the possibility of teamwork will bring even to big endoscopical centres, the chance for important steps towards the detection of early gastric carcinoma.

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Early Diagnosis of Gastric Cancer. Methods and Limits

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This lecture under the heading "Technique of Gastrocamera" was arranged because it is known that I advocate the gastrocamera. In my opinion, an optimal endoscopical routine examination of the stomach includes the use of an orthograde gastrocamera as photoscopy, and the inspection of the stomach with frontal viewing gastroscopes performed in one session. The necessary directed biopsies can be made during this examination.

I should like to mention first the X-ray method with which you are familiar. This subject will be dealt with by two experts in that field, Prof. Gutmann and Prof. Frik. The diagnosis of the early carcinoma, a more accurate term would be "early cancer", may be divided into two phases:

1. Recognition of suspicious lesions;
2. demonstration that a malignant process is involved.

The final definition of an early cancer with its excellent prognostic outlook, can be made only by the pathologist after examination of the resected stomach. Both the X-ray diagnosis and the gastrocamera are searching methods employed for the diagnosis of "early cancer".

In 1966, Japanese gastroenterologists asserted high certainty in early cancer diagnosis when the gastrocamera film was used; this feeling of safety seems to be lost nowadays. Histological proof is now requested as an indication that therapeutic resection of the stomach is necessary. This development favours biopsy. We are now facing the problem whether gastroscopy with biopsy alone is sufficient, or the "searching methods" can be abandoned. Unfortunately, we have not yet been able to evaluate our own material of more than 4. 000 simultaneous examinations by gastrocamera and gastroscopy, so that I had to ask for figures from other experts. In our group, 5 of 22 early cancers have been recognized by the gastrocamera after they had been overlooked during a simultaneous first gastroscopy.

I agree with COLCHER that gastroscopy as single method will not suffice for recognizing indistinct alterations of the gastric wall. While Colcher executes cinephotography and gastroscopy using the same instruments, we prefer gastrocamera examination and gastroscopy to be carried out in one course. Our own procedure and that of Colcher consist of the photoscopy in which diagnosis is based on a film or a series of pictures. Therefore, the whole stomach has to be photographed or filmed, not just the suspicious parts of it.

There is no study as yet which establishes with certainty that no lesions are overlooked during gastroscopy. We have had several cases where a circumscribed

finding was not recognized in gastroscopy because another alteration dominated, or because the lesion did not come into view. We have learnt from phantom-training that it is difficult or even impossible to examine the stomach systematically. This was proved by phantom examinations during which a series of electric contacts had to be released. In our opinion, this experiment "in vitro" is of great importance. Gastrocamera experiences "in vivo" support the combined examination method. With respect to the photographic documentation of the entire stomach, we shall have to ask whether gastrocamera diagnosis cannot be substituted by extragastrale photography, i.e. by photography through the endoscope. We are inclined to answer "no". The angle of view is smaller. In pictures taken from a distance of 10 cm and more, the visibility of details diminishes. An overlapping of pictures will be necessary to aid localization. Moreover, there are the small lesions that the surgeon should be able to identify on the basis of X-ray examination and/or gastroscopic data, especially when palpitation and inspection during the operation may become difficult. In that case, too, the gastrocamera film offers valuable proof. The anatomical sites of cardia, angulus and pylorus are usually good references.

On the other hand, one should not refuse additional extragastrale documentation of endoscopical findings. To me, it seems impossible to describe a finding so accurately that not only the diagnosis is verified, but that also the fine details are recognizable. Our team felt that on the basis of a mere description, no one could envision the real picture. Schürholz, a member of our group, said facetiously: "If you have never seen the smile of Mona Lisa, you will not be able to imagine it by the descriptions you get."

The reconstruction of a gastroscopic finding will be desirable whenever a discrepancy appears between the macroscopic and the microscopic picture, especially when a malignancy is suspected by endoscopy, but not proved by biopsy. External photography offers a method of choice in this field. Super-8-coloured films show more impressive pictures when infiltrations of the wall are of pronounced motility, e.g. in cases of "tumor simulating erosive gastritis".

In modern endoscopy the so-called blind procedure of "photoscopy" is smiled at and considered obsolete. In spite of that we have promoted the use of the GT-Va and, as I believe, we have got good results. Expert and critical examiners will, if they have really mastered it, often return to this instrument. When we analyse the reasons for rejecting blind endogastrale photography, a revealing of technical mistakes seems to be the most prominent one. No experienced endoscopist would like to see his errors demonstrated and the limits of his technical ability with them, as it may happen in photoscopy. Success is mostly taken for granted. - Indeed I do not understand why new gastrocameras should come to us from Japan if this method was really obsolete. Let me just mention the GT-Pa and the new GT-PF with an orientating fiberoptic bundle. Our experience with these instruments has already been favourable. A great advantage of photoscopy is that the responsibility for interpretation can be taken away from the examiner, especially when this person is a beginner. Such are the experiences of our team, but they have been confirmed by other physicians after an 8-day course of basic instruction.

Thus we have come to the main problem of how to recognize minimal lesions and how to interpret them correctly. Good training in the methods of gastrointestinal endoscopy is essential. From Stuttgart we have contributed various stomach phantoms for practice which are the basic material of the "Stuttgart training courses". An adequate propagation of these important endoscopy techniques will be guaranteed

only by a standardized training program including technical practice and audiovisual studies of endoscopical findings. Too little attention is given to the idea that the training of the operator should precede the purchase of an instrument. Only a widespread use of gastroscopy will make it possible to perform all the endoscopies that are needed for an accurate diagnosis of the "early cancer. Until then our rate of success will be inferior to that of our Japanese colleagues.

SUMMARY

For a routine endoscopic examination of the stomach we favour the combination of "photoscopy" with an orthograde gastrocamera, and "gastroscopy" with a frontal viewing pan-endoscope. Photoscopy is the basic diagnostical method as far as this procedure is concerned. It is supplemented by gastroscopy and directed biopsy in order to avoid examinations extended over several days. Such an optimal co-operation of examination and instruments is the only way to reach high standards of diagnosis, especially for the early stages of gastric carcinoma.

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Discussions by Invitation

Some Remarks About Gastric Biopsy Under Direct Vision

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Reports on the significance of biopsy studies in differential diagnosis of gastric diseases have been published by ourselves in the past. Some of the presuppositions for making a correct diagnosis are skilful eyes and experience in gastroendoscopy. Furthermore, diagnostic ability in detecting early gastric cancer is also related to the type, size and site of the lesion. One needs over 5 particles at least for biopsy studies. In addition, one has to know the topographic origin of cancer cells parallel to the type of early gastric carcinoma.

Table 1. Type of early gastric cancer and location of carcinoma cell - elevated type -

Type	No	Location			
		head of protrusion	eroded region	base of protrusion	surrounding area
I	8	8		5	1
I+IIa IIa+I	2	2		2	1
IIa	4	4		1	
IIa+IIc	11	5	11	2	

Table 2. Type of early gastric cancer and location of carcinoma cell - depressed type -

Type	No	Location					
		ulceration	depressed part	nodule in depression (Ca(+)	Ca(-)	margin of depression	surrounding area
IIc	24		24	4	1	24	7
IIc+III	26	9	26	8	4	26	8
III+IIc	6	2	6			6	3
IIc+IIa	7		7	2		7	

Tables 1 and 2 show the localization of carcinoma cells according to type and macroscopical findings.

We should make an effort to establish the specificity of cancer cell localization and refer such microscopical findings, to microscopical findings in all cases where cut serial sections of the lesions have been performed. For example, one should know that in the IIa and IIc types of early gastric carcinoma, it is more profitable for achieving positive results when the biopsy material is taken from the base of the depression and not from the marginal swelling. In the IIc pattern the biopsy material should always be taken from the discoloured depression and not from the protruded part of the depression.

The great advantage of such efforts may be not only to obtain some information on the abnormality of cell groups, but also to get an insight into the histo-architectural structure of the lesion. Particularly in the diagnosis of early gastric carcinoma, it is essential that the abnormal sites are discovered, rather than to identify the outstanding abnormalities. This needs skilled endoscopists. Having gained experience and a sharp eye, we could realize that we were able to get better results in minute carcinomas less than one centimeter in diameter.

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Early Diagnosis of Stomach Cancer with Special Reference to the Dye Scattering Method of Endoscopy

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Up to the end of 1971 we experienced 191 cases of early gastric carcinoma. This includes cases from affiliated hospitals, and cases diagnosed by gastric mass survey (Table 1).

Table 1. Yearly distribution of early gastric cancer

Period	Diagnosis	
	Stomach cancer	Early cancer
1958 - 1960	84	4
1961 - 1963	119 (2)	23 (1)
1964 - 1966	129 (20)	49 (10)
1967 - 1969	180 (50)	75 (33)
1970 - 1971	100 (14)	40 (14)

As we confined ourselves to 133 observations of our own clinic, it is evident that the rate of early gastric carcinoma among advanced carcinoma is always over 30% (Table 2).

Table 2. Frequency of gastric cancer in our clinic

		1958-1960	1961-1963	1964-1966	1967-1969	1970-1971
a)	Number of outpatients	8496	13791	11976	8031	5270
b)	No. of cases examined endoscopically	885	2719	2256	1556	1129
c)	cancer	84	117	109	130	98
d)	early cancer	4	22	39	42	26
	c/a x 100	1.0	0.8	0.9	1.6	1.6
	c/b x 100	9.5	4.3	4.8	8.4	7.6
	d/c x 100	4.8	18.8	35.8	32.3	30.2

Since 1964, of the 145 lesions observed in these 133 cases, 93 lesions were located in the M part (middle part of the stomach, according to the nomenclature of the Committee of the Japanese Gastric Cancer Association) especially on the lesser

curvature or the posterior wall. Furthermore, 76% of the lesions show a form (superficially depressed) that corresponds to types IIc, IIc + III, III + IIc or IIc + IIa (Table 3).

Table 3. Type and location of early gastric cancer

Type	cases	C				M				A			
		ant. wall	lesser curv.	post. wall		ant. wall	lesser curv.	post. wall	greater curv.	ant. wall	lesser curv.	post. wall	greater curv.
I, I+IIa IIa	13					4		2		2	1	3	1
IIa+IIc	12				1			1		3	1	5	1
IIb	2						1	1					
IIc, IIc+III III+IIc IIc+IIa	109	1	4		3	13	40	24	1	7	9	5	2
III	9					1	1	4		1	2		
Total	145	1	4		4	18	42	32	1	13	13	13	4
		9 = 6%				93 = 64%				43 = 30%			

Our major interest in gastric carcinoma is threefold:

1. How we can diagnose gastric carcinoma in early stages,
2. how we can discover small lesions and further, the correlation between advanced and early carcinoma,
3. how we can recognize the early stages of infiltrating carcinoma.

In order to make this problem clear from the endoscopical point of view, it is necessary to pay attention even to slight changes in colour, and to identify a very fine unevenness of the mucosa. It is, however, extremely difficult to recognize these changes by routine endoscopy. Two approaches in solving this problem appear possible, one is to improve endoscopic instruments, the other would be to use subsidiary means for enhancing endoscopically the fine unevenness of the mucosal surface.

As far as the latter method is concerned, TSUDA (1967) has already reported on the dye scattering method as an effective way of observing fine structures in the surface of gastric mucosa. This blue dye is directly scattered on the surface of the mucosa and makes a striking contrast against the reddish gastric mucosa in the endoscopical picture.

However, a clear view of the minute structure on the surface of the gastric mucosa is troubled by mucus. It is also difficult to scatter dye with a fiberscope under direct vision. However, when the dye solution is orally administered and the body of the patient appropriately rotated on a bed before the examination - as we reported at Prague in 1971, and in Paris this year - we notice that the solution accumulates on small concave surfaces such as the fine grooves surrounding gastric areas. This procedure enabled us to observe the stomach distinctly and throughout.

The technique which we applied is as follows:

1. An intramuscular injection of antispasmodic, twenty minutes before the examination.
2. An oral administration of 80 ml of tenfold diluted dimethylpolysiloxan solution mixed with 1000 mg of $NaHCO_3$ and 20.000 P. U. of pronase (proteinase) fifty minutes before.
3. An oral administration of 20 ml of 1.5% indigocarmine solution immediately before the examination.

All knowledge of the granular appearance of chronic gastritis must be at hand in order to clarify the specific granular appearance of the IIb type of early gastric cancer. In order to determine the boundary between fundic and pyloric gland areas a modification of the type classification of endoscopic atrophic patterns was employed for this study. The closed type, both, the fundic and the pyloric gland areas, are divided by the parabola. This falls symmetrically from the lesser curvature of the gastric body to the greater curvature of both the anterior and posterior walls. The fundic gland mucosa exists on the proximal side of the lesser curvature and in the open type, the pyloric gland mucosa exists on the side of the lesser curvature.

Table 4. The fine structure of mucosal surfaces of the fundic and the pyloric gland areas

	Fundic gland area	Pyloric gland area
Mucosal findings		
Thickness	thick	thin
Colour	reddish	yellowish
Gloss	lustrous	lusterless
Blood vessels	invisible	visible
Granular appearance		
Size	large	small
Variation in size	slight	remarkable
Shape	slender / round	polygonal
Contour	clear-cut	obscure
Density	close	coarse
Arrangement	continuous and regular	discontinuous and irregular

Table 4 shows typical findings of each area to which the indirect dye scattering method was applied. The mucosae in the pyloric gland area were mostly pale and thin, the submucosal blood vessels being occasionally visible through them, thus suggesting the discovery of atrophic gastritis. In contrast to this, the mucosae in the fundic gland area were red and thick, the blood vessels were not visible through them, thereby suggesting that there was no evidence of atrophic gastritis.

On the basis of these superficial granular findings of normal and chronic gastritis, we hope to clarify the superficial findings of mucosal carcinoma. Adapting this method we can easily detect not only the slightest change in mucosal folds, but also minute changes in the mucosal area pattern.

We investigated the effectiveness of this indirect blue dye scattering method in 18 cases of early gastric carcinoma. The results revealed an equal effect in two cases and a less favourable effect in two other cases (Table 5).

Table 5. Discrimination of superficial cancerous extensions using the dye scattering method

No. of cases	more clear	no change	less clear
18	14	2	2

However, we could obtain better information in 14 cases (77, 8%) as to the extent and depth of cancer infiltration during the time of the preoperative diagnosis. By apllying this method, two suspected carcinomas among 28 cases of gastric carcinoma (including advanced carcinoma) were diagnosed as malignant. One case, proven to be the superficial flat type of early gastric carcinoma, was still suspect after histological examination (Table 6).

Table 6. Endoscopical diagnosis with usual method and dye scattering method

	Usual method	Dye scattering method
Ca. +	25 →	27
	2 ↗	
Ca. ?	3 →	1

Based on the results of these mucosal appearances, a diagram of the superficial area pattern of early gastric carcinoma is shown in Fig. 1.

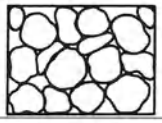
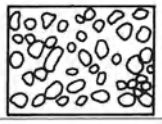
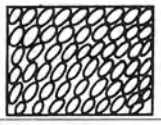
	Slightly elevated similar IIa	Slightly depressed similar IIc	Benign epithelium on carcinoma
cut section appearance			
face-on appearance			
Size	large, variable	small, variable	normal
Shape	polygonal, irreg.	polygonal, irreg.	round, regular
Contour	obscure, irreg.	obscure, irreg.	obscure, regular

Fig. 1. Granular appearance of superficial flat type (IIb) of early gastr. cancer

There are three types that can be distinguished in cases of superficial type of early gastric carcinoma:

1. A lower type than the usual IIa,
2. a shallower type than the usual IIc,
3. a type with healthy mucosa upon intramucosal carcinoma.

Our Figures 2, 3, 4 and 5 furnish some examples for the advantages of the dye scattering method.

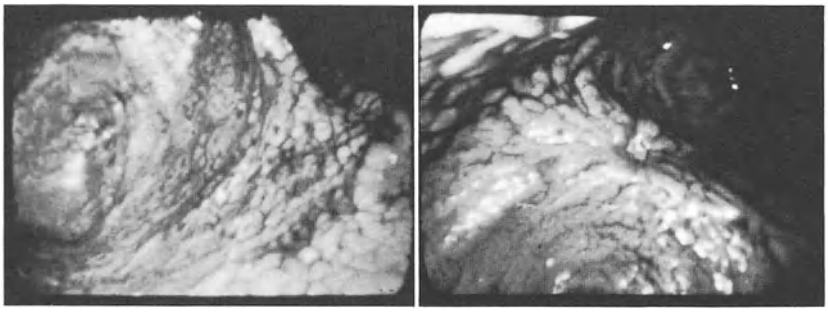


Fig. 2. Erosive gastritis, gastric ulcer and co-existent erosion in an angular postion

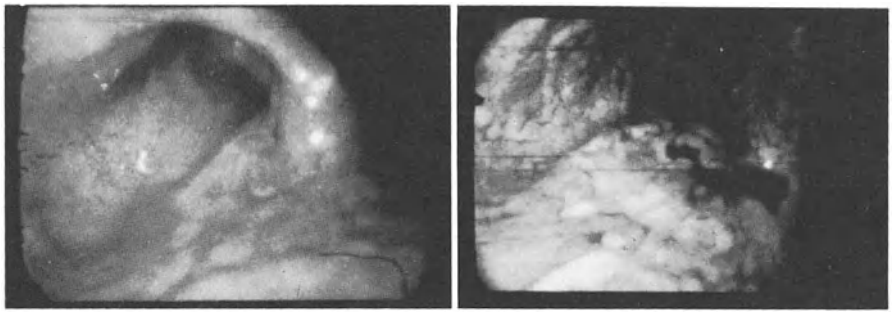


Fig. 3. Border of carcinoma infiltration is easily pointed out

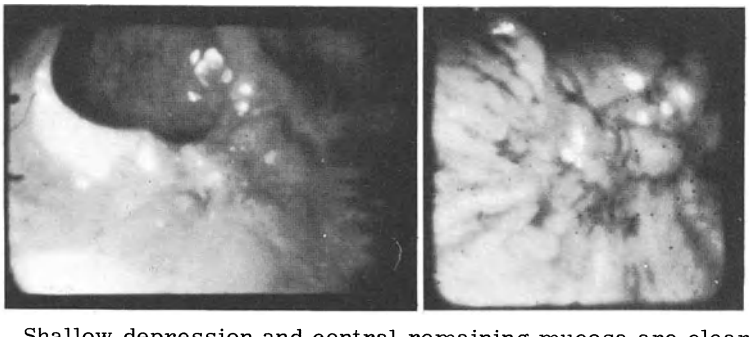


Fig. 4. Shallow depression and central remaining mucosa are clearly depicted (type IIc of early gastric carcinoma)

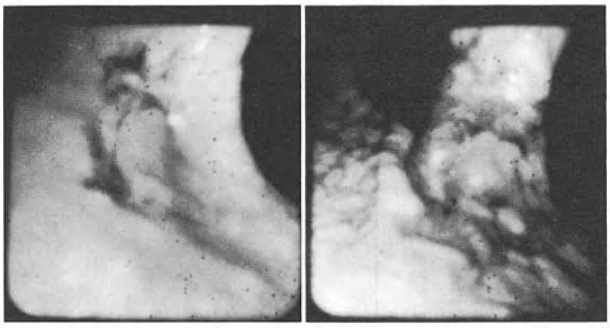


Fig. 5. Shallow depression and central remaining mucosa are clearly depicted (type IIc of early gastric carcinoma)

CONCLUSION

The application of the dye scattering method will enable us to diagnose minute changes in the mucosal folds. It will also simplify the detection of small ulcerated lesions.

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Gastroscopy, Biopsy and Cytology in Early Detection of Stomach Cancer (Comparison of Efficiency of Different Techniques and of a Combination of Techniques)

Gastroscopy, Biopsy and Cytology in Early Detection of Stomach Cancer

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Based on the endoscopical experience that even essentially benign looking alterations in the stomach - for example small polyps and round shaped ulcers - may prove to be malignant lesions, and that even completed scar formation may conceal a superficially spreading carcinoma, we advocate gastroscopic biopsy and cytology in all abnormal gastroscopic findings. Our personal experience with regard to early gastric cancer is based on 23 patients (3 recurrences, 1/3 advanced) with 25 singular or multicentric early carcinomas.

We perform gastroscopy usually with a prograde and, if necessary, with a lateral viewing instrument, for all patients with upper abdominal discomforts, even though the barium meal examination may show normal findings. The barium meal is an excellent screening method. The existence and benignity of gastric ulcers can be suspected radiologically in 80 to 85% of cases (ZBORALSKE, 1967) During routine radiology small carcinomas can be overlooked. Gastroscopy should therefore be performed for all patients with a probable or suspected higher incidence of gastric carcinoma, i. e. patients with multiple gastric polyps, pernicious anemia and partial gastrectomy for ulcer disease, when that operation was performed many years ago. Recent results indicate that the risk of developing gastric cancer will rise from 0, 5 within 5-14 years after operation, to 8, 4 after 35 years, compared with the normal population (STALSBERG and TAKDAL, 1972). In our series, 4 patients are included with early gastric cancer in a Billroth II stomach; two of them had been resected because of duodenal ulcer.

The macroscopic aspect of an early gastric cancer is a diagnostic hint for the experienced endoscopist: broad based irregularly shaped polypoid lesions, irregular, sometimes multiple ulcerations, or simultaneously prominent and excavated lesions. Differential diagnosis between scar formation and neoplastic infiltration, however, is usually impossible on macroscopic grounds. KOBAYASHI et al. (1972) reported that 29, 4% false negative diagnoses arose from gastrophotographs of 191 patients with early gastric cancer, most of them having been falsely interpreted as benign gastric ulcers. (Table 1) The diagnosis of early gastric cancer is neither an endoscopical nor a bioptical one : only the pathologist can decide the extent of infiltration in the resected specimen, and which classification has to be applied. According to the above mentioned Japanese authors, a diagnosis of advanced cancer was made for 13, 6% of their patients, while in fact there was a superficial carcinoma. On the other hand, in 10, 6% of 585 cases of advanced cancer, there was a false diagnosis of early cancer on account of the macroscopic aspect. KAWAI (1970) diagnosed early gastric cancer in 88% of 50 patients by means of endoscopy : in 9 cases the diagnosis was false positive.

Table 1. Initial endoscopic diagnosis of early gastric carcinoma (KOBAYASHI)

Endoscopic diagnosis		No. of cases	percentage
Malignant	early	101	52,8%
	advanced	34	17,8%
	total	135	70,6%
Benign[a)]	ulcer	35	
	polyp	8	
	gastritis	8	
	submucosal tumor	1	
	others	4	
	total	56	29,4%
Total		191	100,0%

a) includes inconclusive diagnosis

Table 2. Distribution of endoscopic variables in 20 benign and 20 malignant gastric ulcers (GABRIELSSON)

		benign ulcers	malignant ulcers	probability
Ulcer crater:	necrotic and dirty	1	7	
	bleeding	1	4	
Ulcer shape:	regular	12	1	0,05
	irregular	6	7	
	asymmetrical	2	12	0,05
Ulcer edge:	not totally visible	9	8	
	sharply demarcated	11	2	0,05
	blurred	0	10	0,01
	with small extensions	1	6	
	with stepwise depression	0	5	
	bleeding	7	7	
Marginal wall:	steep	1	11	0,01
	asymmetrical	2	10	0,05
Folds:	absent	3	3	
	reach crater	16	1	0,01
	disrupted	0	11	0,01
	disruption inconclusive	1	5	
	radiating	17	7	
	with abnormal appearance	3	10	
Surroundings:	capillary ring	3	1	
	rigid	15	15	
	nodules	1	8	0,05
	angular deformity	7	0	0,05
	incisura opposite the ulcer	7	0	0,05

Biopsy will only give optimal results when at least 6 particles are taken from ulcerative lesions (ISHIOKA, 1971). Although the malignant transformation of a benign gastric ulcer cannot be excluded, many Japanese endoscopists deny this possibility (cit. in RÖSCH, 1971). They recommend biopsies to be taken from the ulcer ground as well as from the ulcer edge, since type IIc lesions may be detected by this method. Necrotic, dirty or bleeding ulcer crater, stepwise depression of the ulcer edge, disrupted or fusing folds and an interrupted capillary ring in the healing stage, are macroscopic findings which point to a malignant ulcer and indicate the site from which the biopsy sample should be taken. GABRIELSSON (1972) found it difficult to differentiate between benign and malignant ulcers after comparison of endoscopic criteria. He regards endoscopic findings as a supplement to gastric biopsies. (Table 2).

Endoscopic polypectomy has shown that histology of the biopsy specimen and histological examination of the totally removed polyp are not identical at all (CLASSEN et al., 1972). 2/49 of gastric polyps removed in our series were carcinomatous. One of them was partly covered by hyperplastic mucosa. Polypectomy will, therefore, prove helpful in identifying localized carcinomatous growth within a polyp. There are increasing reports that malignant ulcers will temporarily heal (HAZZI et al., 1971; RÖSCH, 1971). SAKITA et al. (1971) gave an excellent report on the life cycle of the malignant ulcer, based on a group of 122 cases of early gastric cancer in which 51 (70, 8%) out of 72 malignant gastric ulcers showed significant healing. In our group of 25 early cancers, three ulcers healed completely. The malignant growth found in the biopsy specimen was an ulcer scar, in one instance at least, the recurrence proved to be a malignant ulcer. We recommend, therefore, that all ulcers should be followed-up with guided biopsy during the healing phase and in the scar stage.

Brush cytology is a very valuable procedure especially for the ulcerative type of early gastric cancer. The best results are obtained when the brush procedure is performed separate from the biopsy (WITTE, 1970). In 7 cases of early gastric cancer for which WEIDENHÜLLER from our group did guided cytology, cancer cells were found in 6 cases. (Table 3).

Table 3. Accuracy of endoscopy, biopsy and brush cytology in 52 cases of advanced carcinomas and 7 cases of early cancer of the stomach in our own series. (+) = positive, (?) = suspected or questionable, (-) = negative

	Diagnosis by								
	Endoscopy			Biopsy			Cytology		
Type of stomach Ca.	(+)	(?)	(-)	(+)	(?)	(-)	(+)	(?)	(-)
Advanced Ca. (52)	36	15	1	48	0	4	45 a)	1	6
Early Ca. (7)	3	4	0	7	0	0	6	0	1

a) Out of 45 cases, 3 were diagnosed by cytology only, 8 were initially found by cytological means, and were later confirmed by biopsy

When endoscopy, biopsy and cytology are combined, optimal efficiency can be attained. KASUGAI (1970) reported a diagnostic accuracy of 97, 7% by performing endoscopic examinations, 96% by gastric biopsy, and 95% by gastric cytology. By combining all three methods almost every early cancer will be detected. In our

small group, endoscopy was successful in establishing the diagnosis of early gastric cancer in 21 cases (84%), and biopsy was positive in 23 cases (92%).

In five of our patients suffering from early gastric cancer (20%), a multicentric origin was found either by endoscopy or by histological examination of the resected specimen. This figure exceeds by far the reports on multicentric gastric cancer (0, 61% to 3, 42% according to WIENDL and PIGER, 1970), but it agrees with the findings of COLLINS and GALL (1970), who demonstrated a multiplicity of early gastric cancer at the rate of 22%. Therefore, one should always look carefully for a second cancer in all patients with malignant lesions. Therapeutical conclusions have to be discussed.

In a follow-up study after partial gastrectomy for early gastric cancer, 17 patients were reexamined until now. Three patients (17%) showed once more a carcinoma in the gastric remnant not connected with the anastomosis; two patients had a new carcinoma of the early type limited to the gastric mucosa, one and two years respectively after surgical intervention. In the third patient the new growth was far advanced three years after the operation.

Many reports from several European countries have shown that early gastric cancer is by no means an uncommon disease, if one is familiar with the diagnostic problems. In a previous paper, we were able to show that of all gastric cancers operated on and resected in Erlangen during recent years, almost 20% were in an early stage (FRÜHMORGEN et al., 1972).

CONCLUSIONS

1. Multicentric early gastric cancers are not infrequent.
2. The high recurrence rate of early gastric cancer after partial gastrectomy in our series underlines the necessity of follow-up studies.
3. The highest detection rate of early gastric cancer is achieved by the combined use of all diagnostic measures, namely radiology, endoscopy, biopsy and cytology, for all patients with gastric alterations.

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The Results of Cytology Using the Technique of the Gastroscopic Cell Brush, in Comparison with Biopsy, Endoscopy and Radiology

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During the last four years we have performed examinations of 600 catamnestically secured cases of patients suffering from localized processes of the stomach and lower oesophagus. After a conventional X-ray examination, endoscopy was done with Olympus-models. As a first step we biopsized several times and finally obtained cell material by using a cell brush (WITTE, 1970). We then withdrew the brush sample into the mouth of the instrumental channel and finished the gastroscopy. After that, we cleaned out mucus from the channel's mouth, pushed the brush forward again, and rinsed in physiological saline solution of 5-10 ml; the cells were then collected by centrifugation.

Among these 600 examined cases 96, that is 16%, were catamnestically secured malignomas (Tables 1 and 2), this suggests that the cases were selected.

Table 1. The results of endoscopic brush cytology as compared with biopsy, endoscopy and radiology in 600 catamnestically secured cases

Tumor cases	96
Radiology false negative	82
Endoscopy false negative	-
Histology false negative	20
Cytology false negative	10
Benign cases	**504**
Radiology false positive	43
Endoscopy false positive	48
Histology false positive	2
Cytology false positive	7

By using cytological means the tumor was not revealed in 10 cases; this figure, however, was doubled when the bioptic-histologic method was applied, i.e. 20 tumors remained undetected. in two cases cytology as well as histology were false negative. These two cases were big tumors in a state of decay which could already be safely recognized by endoscopy. When we compared the success rates of both microscopical methods in the detection of tumors, cytology showed its obvious diagnostical superiority. For 10 cases which histologic examination proved to be negative, cytology was positive for tumor cells, whereas only 4 cases of negative cytology, were proved to be positive by histology.

Table 2. Comparison of endoscopic cytology with endoscopic biopsy in 96 gastric tumor cases

Cytology	Histology	No. of cases	%
positive	negative	10	10,4%
negative	positive	4	4,2%
negative	negative	2	2,1%

In all 96 cases of malignoma the endoscopist described them as suspected or real tumors when surveying the endoscopic picture macroscopically, whereas the radiologist classified 14 cases as non-suspect. The reliability of different methods, however, can only be safely evaluated when the circumstances under which catamnestically benign processes evolve, are also considered. In these 504, all of which showed circumscribed alterations of the stomach, there were 43 "tumors" falsely suspected by means of radiology, 48 even by using endoscopy, but cytology had only 7 false diagnoses, and biopsy only 2. For one case of chronical ulcus ventriculi, both the cytologist and the histologist assumed the presence of a tumor, but it was not found in the resected stomach.

Summing up all false "positives" and false "negatives", we find that the radiologist and the endoscopist were incorrect in 20% and 8% of cases, respectively. The histologist was incorrect in a little less than 4%, and the cytologist in a little under 3% of the cases. As to both microscopical methods used together, the definition was incorrect in three cases only, that is in 0,5%.

We may conclude that it is necessary for microscopic investigation to secure the macroscopic evidence provided by radiology and endoscopy. Biopsy misses existing tumors twice as often as cytology which, of all methods, has the highest rate of success in the detection of tumors. Its false positives range from 1 to 2%. When both microscopical methods are applied together, erroneous decisions could be prevented almost completely.

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Diagnosis of Stomach Cancer Today

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The advent of biopsy fiberscopes has literally revolutionized today's diagnosis of gastric cancer (GC). The three basic methods of diagnosis are:

Roentgenography
Gastroscopy
Guided gastrobiopsy and guided cytodiagnosis

Roentgenography is still the main initial examination method. Its advantages are evident: it is painless and easy to repeat, the films are of excellent quality, and their interpretation is now far more precise than it has been.

But there are also disadvantages: it cannot show the histological nature of a lesion and it often overlooks small lesions of the anterior and posterior walls of the stomach.

Gastroscopy has some disadvantages too. It is an unpleasant examination which cannot be repeated as easily as the roentgenographical one. It requires a considerable amount of equipment and, most important, well trained specialists.

But there are considerable advantages:

At present, the whole of the stomach cavity can be explored.
The appearance of a lesion is often suggestive of GC.
Very small lesions which are roentgenographically invisible, can be detected endoscopically.
Finally, bur most important, it allows the biopsy of the entire suspicious intragastric region.

Guided gastrobiopsy (GGB) and guided cytodiagnosis. GGB represents today's major victory in the diagnosis of gastric cancer. Only this kind of examination (together with cytodiagnosis) can provide histologic evidence of GC in 80 to 90% of cases. There are no "false positive" results with GGB. Today, it represents the clinician's main arm for positively confirming the presence of GC.

But it is not always easy to perform. It requires excellent equipment and perfect endoscopical, bioptical and pathological techniques. Naturally, a negative GGB result does not exclude the possibility of cancer, only positive results are of value. Some authors associate GGB with guided cytodiagnosis. The positivity rate of the latter is high, but a few errors (false positive results) are also involved.

Practical Management in the Diagnosis of Gastric Cancer

From a roentgenographic examination, there are three possible results:

I. The roentgenographic diagnosis of GC is very probable.

II. Roentgen-pictures are doubtful.

III. Stomach X-rays are normal.

I. GC roentgenographically very probable. Even when GC appears very probable on X-ray films, we feel that it is preferable to perform endoscopy and biopsy with regard to the following facts:

a) There is no roentgen-picture characteristic of a malignant lesion.

b) Endoscopy makes a precise recognition of the lesions of the mucosa which are often more extensive than suggested by a roentgenographic examination.

c) GGB which is usually positive, enables the surgeon to make all necessary preparations for an extensive gastrectomy.

In that case, i.e. when a diagnosis of GC is roentgenographically very probable, endoscopy-biopsy will be only an improvement on previous diagnostic methods.

II. Doubtful X-ray picture. Things are different when the X-ray picture is doubtful and the diagnosis hesitates between benign lesion or cancer. Before the endoscopy-biopsy era, the radioclinical therapeutic test devised by R. A. Gutmann was used most frequently, and sometimes complemented by endoscopy. This test involved several series of X-ray films taken several weeks apart. If the lesion persisted, gastrectomy was performed upon the probable diagnosis of cancer. This radioclinical test is open to criticism:

a) It cannot provide certitude of cancer but simply a fair degree of probability.

b) It is time-wasting (several months pass before the decision to perform gastrectomy).

c) It entails considerable expenses both for the patient and for society in consequence of the successive X-ray examinations and of the continuous medical treatment.

d) Finally, but most important, it happens often that we lose track of some patients who do not seek medical advice again for one or two years; by that time the cancer has spread and is no longer curable by surgery.

When there is a roentgenographic suspicion of GC, our present policy is to make the diagnosis "while it is still hot". If there is a suspicious picture on the films, endoscopy-biopsy is performed as soon as possible, without a therapeutic test. The advantage of this method lies in that endoscopy specifies the appearance of the lesion (benign, malignant or doubtful) and, more important, that it permits GGB which provides histologic evidence of cancer in 8 or 9 cases out of 10. The patient then undergoes surgery immediately.

The therapeutic test is only used when GGB proves negative. After intensive treatment, the patient is reassessed clinically, roentgenographicylly and endoscopically. If GC is present, the lesion persists and, more important, the second series of GGB performed during endoscopy is usually positive; for that, the gastroscopist can take a large number of fragments and can also make a guided cytodiagnosis.

III. Normal roentgenographic examination of the stomach. If a roentgenographic examination of the stomach is normal in spite of alarming general and functional signs, we feel that endoscopy is still indicated. Some GC are in fact invisible on X-ray films and are only discovered by endoscopy. Moreover, even if but a tiny endoscopic abnormality is discovered, endoscopy makes it possible to perform systematic GGB.

The Problems of Early Diagnosis of Gastric Cancer

Delay in seeking medical advice is in fact the stumbling block for early diagnosis of GC. Indeed, although it is now relatively easy to diagnose GC, this diagnosis is seldom made early enough, because the patient sees his doctor too late, when the tumor is already at an advanced stage. This delay in seeking medical advice is due either to the patient's negligence, or even more often, to the absen ce of symptoms, certain gastric cancers being particularly latent.

There is only one way to overcome this delay, and that is systematic detection. Unfortunately, attempts in this direction by using conventional methods, namely in Japan, have proved disappointing. The number of GC cases detected at an early stage is low. The investigations are complex and onerous, they are also unpleasant and therefore refused by people who are apparently in perfect health. The only solution, at present, will be to limit the investigation to high-risk patients:

Pernicious anemia, Menetrier's disease, single or multiple benign tumors of the stomach, descendants of GC-patients and previously gastrectomized patients should be registered. In these people the risk of cancer is higher than in others. It must be admitted, however, that many of these patients still escape medical supervision; they will not come back to seek medical advice owing to the fact that they are in good health.

Detection of GC at an early stage has at present reached a dead end. It will only be effective when we really do have at our disposal sure biological methods making it possible to recognize the existence of a GC or, at least, the existence of a cancer of the gastrointestinal tract in general. In this field the use of embryonic extracts as an antigen (alpha fetoproteins for primary liver cancer, carcinoembryonic extracts for the colon) will perhaps open new horizons to the immunology of gastric cancer.

Operated on early at the stage when the lesion is anatomically small, and when only the mucosa is involved, or when there is only a slight involvement of the submucosa, GC is a "good cancer". Patients recover in the majority of cases. Survivals beyond 5 years are common for these early gastric cancers : 90% according to FUCHIGAMI (1966), 77% according to KAWAI (1969).

Personal Statistics Concerning the Diagnosis of Gastric Cancer

Out of 3.200 patients having undergone fibroscopy from the beginning of 1967 until March 1971, 650 patients had also GGB. There were no incidents. The number of gastric cancers detected in this way was 324, and these are the material of our report. Out of these 324 cases, 251 (77, 4%) had a positive biopsy. This figure is lower than in other statistics (LIGUORY, 1971). That is due to the fact that when we started our work in 1967, the equipment we used was less perfect and the operators had less experience. Now, our percentage of positive results reaches 90%.

All regions of the stomach can now be examined with the endoscope and biopsied.

Table 1. Positive biopsy results according to the location of gastric cancer (263 cases)

Location	No. of cases	Biopsies +		Biopsies -	
		No.	%	No.	%
Cardia and greater tuberosity	58	42	72,0%	16	28,0%
Corpus of stomach	81	65	80,2%	16	19,8%
Angle	44	37	84,0%	7	16,0%
Other	57	47	82,4%	10	17,6%
Postoperative stumps	23	19	82,6%	4	17,4%
Total	263	210		53	

In our statistics we have stated that although 50% of GC is located in the corpus of the stomach, 17, 9% (58) is located in the upper part of the stomach (greater tuberosity to cardia) and 23, 8% in the antrum. Lastly, 7, 4% (24) occur in stomachs operated on for ulcers (11 cases) or for cancer (13 cases). Out of 263 cases collected from March 1969 until March 1971, biopsy was positive in 80 to 84% of cases with GC of corpus, angle, and antrum. The same figures were found in gastrectomy stumps. GC of the cardia and of the greater tuberosity yield a slightly lower number of positive results with GGB, that is 72% only. This is due to the fact that a certain number of these cancers lead to stenosis of the cardia making endoscopy or biopsy difficult or impossible.

It is evident that the greater the number of fragments taken, the better the chances of obtaining a positive result.

Table 2. Positive biopsy results according to the number of guided gastrobiopsies performed (308 gastric cancers)

No.of fragments	No. of cases	Biopsies +		Biopsies -	
		No.	%	No.	%
1 fragment	61	36	59%	25	41%
2 fragments	81	58	71%	23	29%
3 fragments	98	81	82%	17	18%
4 fragments	27	24	88%	3	12%
5 or more fragments	41	39	95%	2	5%

Out of 308 GC, cancer was histologically recognized in 59% of cases if only one biopsy fragment was taken, in 71% of cases if there were three biopsy fragments, and in 88% of cases if there were 4 biopsies. With five or more biopsy fragments, the percentage of positive results reached 95% of cases.

In 1o3 cases of GC, we took three fragments and found that 2 biopsies out of 3 were negative in 36% of cases; only in 15% of cases, all three fragments were positive. Thus, it is indispensable to do several biopsies, 5 or 6 being a minimum; some authors believe that 8 or even 10 should be taken. (Table 3)

Table 3. Guided gastrobiopsy-proved GC in 103 patients who had three biopsy samples taken

	No. of cases	%
Only one fragment out of three was positive	37	36%
Two fragments out of three were positive	50	49%
All three fragments were positive	16	15%

The number of positive results increases as a result of the equipment and of the operators experience. With a semi-rigid biopsy gastroscope, we obtained only 60% of positive biopsies in 1964. With the fiberscopes in 1967 and 1968, this percentage rose to 69%. In 1968 - 1970 it rose to 75%, and from the beginning of 1970 until March 1971, 95 out of 111 GC-biopsies (85, 6%) were positive.

Table 4. Positive results of guided gastrobiopsies according to the equipment used and the experience of the operator

Examinators and equipment		No. of cases	Biopsies + No.	%
Ch. Debray and P. Housset semi-rigid biopsy gastroscope	1964			60, 0%
Ch. Debray and P. Housset fiberscopes	1967-1968	61	42	69, 0%
	1969-1970	152	114	75, 0%
	1970-March 1971	111	95	85, 6%
Fuchigami et al.	1962			45, 5%
	1963			73, 0%
	1964			86, 3%
	1965			88, 3%
Kasugai	1968			86, 4%

These figures confirm those of FUCHIGAMI et al. (1966) which also show striking progress : 45, 5% of positive results in 1962, 73% in 1963, 86, 3% in 1964, 88, 3% in 1965. The figures of KASUGAI (1968) are similar, i. e. 86, 4%. It seems that under favourable conditions we may expect something like 85% of positive results. Some authors give even higher figures, close to 100%.

The value of GGB compared to roentgenography and gastroscopy has been proved by statistics covering 251 GC for which biopsy was positive (Table 5). The diagnosis of cancer was made by roentgenography and endoscopy in 59% of the cases (148 patients). In these cases biopsy only confirmed a diagnosis which was highly probable; thus, it was only of moderate interest. On the other hand, in 30% of cases (76 patients), it was impossible to differentiate between a benign lesion or a malignant lesion by means of roentgenographie and gastroscopy. It was GGB alone that made the diagnosis of cancer. Lastly, in 11% of cases (27 patients) the roentgenographic and gastroscopic diagnosis was that of a benign lesion, whereas biopsy showed that it was really GC. In these last two groups involving 41% of the patients, GGB was of fundamental importance since it rectified an incorrect

diagnosis or confirmed a diagnosis which was only suspected. It should be pointed out that among these last two groups of patients (103), 19 cases were GC at the intramucosal stage, that is in an excellent surgical form.

Table 5. Value of guided gastrobiopsy compared to roentgenography and gastroscopy (251 gastric cancers with positive GGB)

Roentgenographic and gastroscopic diagnosis	Gastrobiopsy diagnosis	No.	%	
Cancer	cancer	148	59%	
Doubtful benign or malignant lesion	cancer	76	30%	a)
Benign lesion	cancer	27	11%	

a) = 19 cases of GC at intra-mucosal stage

CONCLUSION

In view of our findings and those of other teams who have worked on the subject, we consider it evident that today, the diagnosis of gastric cancer should be made by combining three methods : roentgenography, gastroscpy and biopsy. Thanks to these methods, definite pathological evidence of GC can be obtained in 8 or 9 cases out of 10 within a very short time, and the patient can undergo surgery immediately. The therapeutic test should not be used except when GGB is negative.

Gastroenterologists and general practitioners should be familiar with recent progress in the diagnosis of GC, and they should not hesitate to suggest endoscopy-biopsy. In fact, today as before, the stumbling block for early diagnosis of gastric cancer remains the fact that GC patients who have few or no complaints, will see their physician too late and only when the gastric cancer is already at an advanced stage.

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Advantages of Combined Cytological-Histological Examinations in Guided Biopsies of the Stomach

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Cytological examination of samples taken under direct vision in gastroscopy seems to be another method beside histology, for diagnosing tumors of the stomach. (FUKUDA et al., 1967; SHIDA et al., 1967; SMITH FOUSHEE et al., 1969; YOSHI et al., 1970). The purpose of the present paper is to determine the diagnostic accuracy in cytology by using two different morphological methods of examination on the same specimen for interchange control; in that manner, errors caused by one of the methods should be clearly demonstrable by the other.

During the last three years simultaneous cytological and histological examinations were performed on guided biopsies of the stomach and oesophagus, in order to test the validity of both methods. The technique of cytology was simply the printing or gentle rubbing onto slides of all fresh biopsies (about 5 per patient); after air-drying they were May-Grünwald/Giemsa stained. Brush-cytology was renounced in order to avoid distorting the mucosa for later histological examination, and also because printing is easier to perform. Moreover, when using the brush-cytology method, there is always the danger of cell-loss, and of soiling the instrumental channel by repeated samplings.

The guided biopsies of 1.400 patients were examined. Whenever a contradictory diagnosis occurred, the negative one was re-examined. Histologically graded sections were carried out. Classification of cytologic results referred to Papanicolaou. showed that doubtful cases (i. e. Pap. III) were rare. (Table 1)

Table 1. Results of print-cytology in 1400 patients examined by guided biopsies from 1970 - 1972

Papanicolaou	I	II	III = %	IV	V	No. of patients
1970	8	136	31 = 13,6	12	40	227
1971	93	338	38 = 6,5	31	87	587
1972	96	340	13 = 2,2	37	100	586
Total	197	814	82 = 5,8	80	227	1400

The quota of Pap. III decreased from 13% in 1970, to 2,2% in 1972. This decrease was a result of improved diagnostic experience; the final low quota proves that heavy cell atypies are rare when not malignant.

Malignant tumors were found in 286 out of 1.400 cases; they were mainly adenocarcinomas, with 5 malignant lymphomas and 34 squamous cell carcinomas of the lower oesophagus. In agreement with previously published results in print-cytology (YOSHI et al., 1970), a comparison of these histological and cytological results proved that the latter method by which 91,9% of the tumors were detected, was 4,5% better than histology. (Table 2)

Table 2. Detection of malignancy by histology and print-cytology in 286 provided tumors of the stomach and oesophagus

Method	positive	missed
Cytology	263 = 91,9%	23
Histology	250 = 87,4%	36
Cytology and/or histology	283 = 98,9%	3

In cytology 8%, and in histology 12,6% of the tumors were not diagnosed, and 98,9%, i.e. 283 out of 286 tumors, were detected only with the combination of both methods. This is slightly better than the results recently published by YAMAKAWA et al. (1971). In spite of graded sections we have found that 36 out of 286 tumors (12,6% false negatives) were not diagnosed by histological examination alone. This clearly shows that in those cases the tumor examined in the biopsies, was so tiny as to be lost by taking prints for cytology. As there is no early carcinoma which is so small that it cannot be diagnosed by histology, the specimens had to be taken from the periphery of the tumor.

As regards the three false negative cases, the biopsies were probably not taken from the tumor; the indication for surgery was based exclusively upon endoscopic findings. The false negative cytology results may be attributed to errors in printing or processing.

Table 3 . Results in relation to type and location of 56 tumors

Type	No. of patients	Biopsy positive	Biopsy missed	Cytology positive	Cytology missed
Early carcinoma	5	4	1	4	1
Polypoid	9	7	2	9	-
Ulcerated/infiltr.	35	35	-	32	3
Mucous producing	3	2	1	3	-
Location					
Antrum	30	28	2	27	3
Corpus	17	16	1	17	-
Cardia	5	4	1	4	1
Oesophagus	4	3	1	4	-

Attempts to relate macroscopic appearance and location of tumors to false negative diagnoses were unsuccessful with exception of the lower oesophagus. Table 3 shows that there is no correlation between macroscopic and microscopic appearance and location. Tumors of the lower oesophygus are less frequently diagnosed by histology than tumors of the stomach. However, better results are obtained by cytology.

It is impossible to assume a difference in diagnostics in comparison to advanced carcinomas, since only 7 out of 8 early carcinomas were examined by cytological/histological techniques. However, there is an evidence based on cytological criteria whicht might allow the separation of early cancer from advanced tumors (Table 4).

Table 4. Probable and useful criteria for separating early cancer from advanced carcinoma

Cytologic criteria	Early carcinomas	Advanced carcinomas
Anisokaryosis	limited	heavy
Chromatin pattern	fine	coarse
Nucleoli	increased, small	increased, large
Cytoplasma, quantity	scarce	plenty
vacuoles	small, rare	numerous, signet-ring cells
Cell pattern	groups, solid	groups, rosettes

Comparison of both forms shows clear progress in anaplasia in the advanced carcinomas. Nevertheless, further examinations are needed to prove the reliability of this assumption.

SUMMARY

1. Print-cytology shows the same results as brush-cytology, but with the advantage that only one specimen has to be taken, and without the disadvantage of cell loss and of soiling the instrumental channel when several brushings are done.
2. Errors in single techniques, histology as well as cytology, are considerable, whereas by combination of both, a 98, 9% success can be reached.
3. Squamous cell carcinoma of the lower oesophagus is more frequently missed in histology than gastric carcinoma.
4. Atypic epithelium beyond gastric cancer (analogous to severe dysplasia of the squamous epithelium of the cervix uteri) is very rare in cytology.
5. There are evidences suggesting that early carcinomas can possibly be separated from advanced carcinomas by cytology.

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Gastroscopy, Biopsy and Cytology in Early Detection of Stomach Cancer

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There is no doubt about the superiority of gastroscopy in the diagnosis of gastric carcinoma in its early stage, and about the necessity of combining X-ray diagnosis with endoscopy. Even with subtle techniques - practised as a matter of routine by by only a few very experienced radiologists - malignant processes of the early gastric cancer type may be overlooked. Based on our experience of more than 2. 000 hospitalized or amulant gastroscopies we believe that guided biopsy is an essential part of the endoscopic examination. The limitations of blind gastrocamera examination are that one can rely on the macroscopic aspects only, thereby reducing the chance of recognizing the patient's cancer in its early stages.

RESULTS

This concept should be demonstrated by the endoscopic-bioptical results gained within 15 months after examining 580 outpatients with undetermined upper gastrointestinal discomforts. All end ›scopical examinations were performed by myself using the fiber-gastroscope GF-BK or the panorama-endoscope (ACM). Four particles at least were taken from each circumscribed lesion. Gastroscopy was performed within 10 to 15 minutes under local anaesthesia and without any premedication. For histological examination I have to thank professors ELSTER and REMMELE.

Our collection of 26 polyps shows very clearly the problems of macroscopical classification for diagnostical purposes. Differential diagnosis between hyperplastic and adenomatous polyps is impossible without histology. Mesenchymal polypoid lesions may be distinguished from epithelial neoplasms by their macroscopic aspect, but the final diagnosis - leiomyoma, lipoma, fibroma, neurinoma or sarcoma - is uncertain. Nowadays the optimal diagnostic method for gastric polyps is the endoscopic polypektomy with almost no complications. The polyp must be exa mined in toto by serial sectioning of its whole body.

A malignant ulcer - also type III of early gastric cancer - may resemble a benign peptic ulcer. Biopsy may reveal malignant structures despite the benign aspect in about 5% of cases. Malignant ulcers may even heal completely for some time, as was proved by us and by other authors.

Positive biopsy was correct in 90% of our cases of advanced gastric cancer. In our series, we had 3 early gastric cancers which were diagnosed preoperatively by a directed biopsy. In one of them, 2 lesions of early cancer type could be found: one at the pylorus , the other at the anterior wall of the antrum. Apparently, a more

successful biopsy is possible in early gastric cancer than in extensive malignant ptocesses; this paradoxical fact is most probably due to the greater accuracy observed when biopsies are taken from tiny lesions.

DISCUSSION

The results of gastroscopic biopsy cannot be improved by the use of a deeper-cutting biopsy forceps that would penetrate the muscularis mucosae, because the cancer originates from the epithelium. The risk of bleeding is not increased by taking as many particles as possible.

Of three early gastric cancers, two were already suspected during the X-ray examination. During gastroscopic examinations of 580 outpatients with upper abdominal complaints, we therefore detected only one early gastric cancer that had not been discovered previously by other methods. This experience supports the opinion that screening with gastrocamera or gastroscopy will not be possible in the German Federal Republic. It may be advisable for patients with complaints lasting over two weeks, but it seems still too expensive in relation to the rate of cancers actually detected.

I should therefore advocate control examinations of some groups whose increased liability to develop gastric cancer has been statistically proved: Patients who had undergone gastric resection more than 10 years ago, and patients with pernicious anemia; in adenomatous gastric polyposis, many authors are requesting gastrectomy per se. An increased cancer risk for patients with chronic atrophic gastritis has not been established unequivocally, and nobody has claimed as yet, that this proof could be furnished at a reasonable cost.

Gastroscopy, Biopsy and Cytology in Early Detection of Stomach Cancer

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The diagnosis of gastric cancer in a phase when it is still a curable lesion remains a most difficult problem. It is important to realize that only tumors confined to the mucosa or submucosa carry a 90% chance of a five-year survival. We found the Japanese classification of such tumors as "early gastric carcinoma" very useful, and it contributes to the recent progress made in endoscopic and radiological diagnosis. This improved macroscopic diagnosis is complemented at microscopical level by direct vision endoscopic biopsy and cytology.

GASTROSCOPY

The advent of the gastrocamera and of the fiberendoscopes has greatly improved the contribution of endoscopic examination of the stomach. The role of the gastrocamera, in some mass surveys conducted in Japan, is well known (ARIGA, 1967). Elsewhere in this symposium we shall discuss in more detail its possible greater use because of the limitations of photofluorography. The instrument combining a gastrocamera and a gastrofiberscope (GTF-A, Olympus Co., Tokyo) is quite adequate for routine clinical visualization and photographic documentation.

In 1969 we reviewed (KOBAYASHI, PROLLA et al., 1969) the gastroscopic diagnosis of early gastric carcinoma at two institutions: Aichi Cancer Center Hospital (Nagoya, Japan) and University of Chicago Hospitals (Chicago, USA). The results are shown in tables 1 - 3.

Table 1. Gastroscopic diagnosis in 85 provided early gastric carcinomas. Aichi Cancer Center (KOBAYASHI)

Gastroscopic diagnosis	no. of patients	%
Early gastric carcinoma	73	98%
Advanced carcinoma	11	
Benign lesion	1	2%
Total	85	100%

As we noted then, endoscopy tends to over-diagnose early gastric cancer, pointing to the need of complementary techniques at microscopical level. Interestingly enough, better diagnostic results have been reported in early, rather than in advanced tumors (KOBAYASHI, PROLLA et al., 1969)

Table 2. Histology of 120 gastroscopically suspected cases of early gastric carcinoma. Aichi Cancer Center (KOBAYASHI)

Histological diagnosis	no. of patients	%
Early gastric carcinoma	73	95%
Advanced carcinoma	41	
Other	6	5%
Total	120	100%

Table 3. Results of biopsy and cytology under direct vision in 85 proved early gastric carcinomas - Aichi cancer Center (KOBAYASHI)

Result	Cytology	Biopsy
positive	75	73
negative	2	6
suspicious	1	-
unsatisfactory	3	-
not performed	4	6
Total	85	85

The vast majority of early gastric carcinomas are ulcerated and we consider the criteria of KIDOKORO (1963) quite reliable:

a) A definite depression confined to the margins of the ulcer;

b) rigidity and clubbing of the tips of the converging rugea involved by the depression;

c) discoloration and adherent necrotic tissue and blood in the depressed zone, in contrast to the adjacent normal mucosa.

Polypoid lesions are far more difficult to differentiate from benign adenomatous or regenerative polyps on the sole basis of their macroscopical appearance. The histological characterization of atypical borderline lesions is far from established, and the views of CASTLEMAN (1962) are well known.

BIOPSY AND CYTOLOGY

The ultimate diagnosis of malignancy is based on histological criteria. Roentgenographic and endoscopic examinations are, therefore, only indirect diagnostic procedures at a macroscopical level which can provide only a presumptive diagnosis. On the other hand, cytology and biopsy can yield definitive information at a micriscipical level.

The modern fiberoptic endoscopes have been designed to incorporate a mechanism by which lesions may be directly brushed to exfoliate cells for cytological examination, or biopsied under endoscopic control.

However, we would like to emphasize, as we did elsewhere (PROLLA, 1971), the complementary role of these techniques: in all cases a radiographic study preceded the endoscopic visualization. This sequence greatly facilitated identification of the lesion and the planning of the direct vision techniques. They do not replace radiographic or endoscopic visualization of lesions, but rather help in determining the precise nature of the lesions.

In our series at the University of Chicago (PROLLA, 1971), the combination of cytology and biopsy provided a definitive preoperative diagnosis at a microscopical level, in all 50 cases of upper digestive tract malignant tumors. all but three of such cases were advanced tumors.

Table 4. Diagnosis of gastroesophageal malignant tumors by combined use of biopsy and cytology under direct vision (Univ. of Chicago)

Cytology	Biopsy	No of patients	
positive	positive	35	
positive	negative	10	
negative	positive	5	
negative	negative	0	
	Total	50	(Prolla)

Recently (KOBAYASHI, PROLLA et al. 1971) we reviewed the experience at the University of Chicago, with 16 early gastric carcinomas.

Table 5. Data on 16 cases of early gastric carcinoma seen at the University of Chicago (1955 - 1969)

case no.	type - depth		location	metastasis	gastric acid	X-ray	gastroscopy	cytology	survival (year)
1	I	sm	body	(+) liver	(-)	(-) 2 y. bef.	not done	not done	found at autopsy
2	I	m	antrum	(-)	(+)	(-)	(-)	(-)	dead, c.d.
3	I	sm	antrum	(-)	not done	(+)	(+)	(+)	11, alive
4	I	sm	antrum	(-)	(-)	(±)	not done	(-)	2, alive
5	I	m	fundus	(-)	not done	(-)	(+)	(+)	1, alive
6	IIa	m	antrum	(-)	(+)	(-)	(±)	(+)	5, dead
7	IIa+IIc	sm	fundus	(-)	(+)	(-)	(+)	(+)	postoper. death
8	IIc	sm	antrum	(-)	(+)	(-)	(-)	(+)	11, alive
9	IIc	sm	body	(-)	(+)	(-)	(±)	(+)	8m. alive
10	IIc	m	body	(-)	(-)	(-)	(±)	(-)	6m. alive
11	IIc+III	sm	antrum	(-)	(+)	(-)	(-)	(+)	14, alive
12	III+IIa	sm	antrum	(+) L.n.	(+)	(+)	(+)	(-)	9, alive
13	III+IIc	m	antrum	(-)	(+)	(-)	(-)	(+)	10, alive
14	III+IIc	sm	antrum	(-)	(+)	(+)	(-)	(+)	6, alive
15	III	sm	antrum	(+) L.n.	(+)	(-)	not done	not done	6, dead c.d.
16	III	sm	antrum	(-)	not done	(+)	(+)	(+)	6, alive

L.n. = Lymphnode m. = months c.d. = cardiac disease

Radiology was poor in properly demonstrating malignant features of the lesions, with only 4 correct of 15 cases studied. Endoscopic visualization was somewhat better with 8 positive or suspicious diagnoses in 13 cases studied, and gastroscopic biopsy was performed in only three more recent patients and was positive in all three. Cytology was the most accurate method, having a positive result in 1o of the 14 cases examined.

In conclusion, we think the modern fiberendoscopes allow exact and precise identification of the nature of all gastric lesions by the combined effect of improved visualization, direct vision biopsy and cytology, in the cinical context. There remains, however, the problem of the selection of individuals from a large asymptomatic population with preclinical lesions in number enough to substantially increase resection and five-year survival rates.

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Special Remarks Concerning Efficiency and Problems in Cytology

Endoscopic Brush Cytology in the Diagnosis of Gastric Disease. Comparision With Other Diagnostic Measures

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Examination of exfoliated epithelial cells from the gastric mucosa has now been in use for approximately 25 years. The aim of this method has been to help in the diagnosis of malignant disease, and particularly to try and reach a diagnosis of malignancy in the early stages of the disease where conventional methods of diagnosis often fail. However, in spite of many reports documenting the accuracy of gastric cytology in cancer diagnosis, the method is not widely accepted, and doubts exist among both clinicians (ACKERMAN, 1967) and pathologists (CHRISTOPHERSON, 1970) about the diagnostic value of gastric cytology.

The reason is that gastric cytology on material obtained by gastric washing is uncommonly difficult and has many pitfalls. Several factors contribute to this. The exfoliated cells disappear from the stomach through the pylorus, or they are rapidly damaged and destroyed by the gastric juice. It is, therefore, difficult to obtain a sufficient number of well preserved cells. Furthermore, the stomach also contains cells from the respiratory and proximal alimentary tract and the smears are usually heavily contaminated with these cells; thus, screening is made a time consuming and difficult task, and many specimens must be rejected as unsuitable for diagnosis. Even among expert teams of gastroenterologists and cytotechnicians the rate of unsuitable material runs as high as 10 - 18% (MAC DONALD et al. 1963; ACKERMAN, 1967; BRANDBORG and WENGER, 1968). The new flexible gastroscopes with movable tips have made it possible, not only to examine practically every region of the stomach, but also to take biopsies and cytological samples from any suspicious area. Cytological material can be obtained either by lavage after selective water jet washing (SHIDA et al. 1967) or by selective brushing (WILLIAMS et al. 1968; PROLLA et al. 1970; LIAVÅG et al. 1971). By these methods a diagnostic accuracy of malignancy from 80 to 100% is reported, and the rate of unsuitable material is below 1% (LIAVÅG et al. 1971). In our laboratory, the collection of cytological material by the brush technique has been in routine use since the second half of 1968.

MATERIAL AND METHODS

Our series comprises 347 patients referred to the gastroenterological unit of the Diakonissehuset Hospital in Oslo. (Table 1). All patients had a radiographic examination of the upper gastrointestinal tract prior to gastroscopy, and they had either radiological evidence of gastric lesions, or clinical symptoms suggesting gastric disease.

Table 1. Total material of our investigations

Diagnosis	Men	Women	Total
Benign gastric lesions, unoperated	108	72	180
Benign gastric lesions, operated	69	42	111
Malignant gastric lesions	39	17	56
Total number of cases	216	131	347

Among the total of 347 patients, 291 had benign diseases of the stomach (Table 2). In 111 of these cases the diagnosis was confirmed histologically by operation or autopsy (Table 3). In the remaining 180 cases the benign nature of the disease was based on repeated radiography, gastroscpoy with repeated biopsies, cytological examinations and clinical observation for a period from 6 months to 4 years. There were 56 patients with malignant diseases. In all of them the diagnosis was confirmed histologically by operation or autopsy (Table 4).

Table 2. Results of selective brush cytology in benign gastric diseases

Diagnosis	No. of cases	negative	suspected	positive
Gastric/pyloric ulcer	161	155	4	2
Stomal ulcer	10	10	0	0
Gastritis	74	67	6	1
Gastritis in res. stomach	39	39	0	0
Menetrier's disease	2	1	1	0
Polyposis	2	2	0	0
Lipoma	1	1	0	0
Leiomyoma	1	1	0	0
Amyloidosis	1	1	0	0
Total number of cases	291	277	11	3

Gastroscopy is performed after 12-hours overnight fasting. We used either the Olympus GFB or the ACMI mark "87" fibergastroscopes. A methodical survey is made of the whole stomach and biopsies are taken from any lesions seen. The brush for cytological sampling is then introduced through the channel of the gastroscope into the stomach, and the lesions are abraded several times under visual control. The brush containing the cell material is then withdrawn just inside the distal part of the channel, and the gastroscope is removed. The brush is then pushed out of the gastroscope and four smears are made by rubbing the brush directly against the slides. The smears are fixed immediately by spraying with a cytological fixative, and then stained after the Papanicolaou method. After the smears have been examined by cytologists experienced in gastric cytology, and after a full description of the cellular contents and quality of the smears is made, a cytological diagnosis is given: Negative for malignancy (Papanicolaou Grade I and II),

suspicious of malignancy (Pap. Grade III) and positive for malignancy (Pap. Grade IV and V). Unsuitable material has been submitted on three occasions only.

Table 3. Results of various investigations in cases of benign gastric diseases, histologically verified

Histological diagnosis	No. of cases	X-ray (-)	(?)	(+)	Endosc. (-)	(?)	(+)	Cytol. (-)	(?)	(+)	Biopsy (-)	(?)	(+)
Gastric/pyloric ulcers	87	67	18	2	64	17	6	83	3	1	84		
Stomal ulcers	5	2	2	1	5			5			4		
Extra gastric malignancies	12	8	2	2	7		5	11		1	11		
Ménétrier's disease	2		1	1			2	1	1		2		
Polyposis	2	1		1		1	1	2			2		
Lipoma	1		1			1		1			1		
Leiomyoma	1		1		1			1			1		
Amyloidosis	1		1		1			1			1		
Total	111	78	26	7	77	20	14	105	4		106		
		neg. 70%			neg. 69%			neg. 94%			neg. 95%		

(-) = negative, (?) = inconclusive, (+) = positive for malignancy

Table 4. Results of various investigations in cases of gastric malignancy

Histological diagnosis	No. of cases	X-ray (-)	(?)	(+)	Endosc. (-)	(?)	(+)	Cytol. (-)	(?)	(+)	Biopsy (-)	(?)	(+)
Borderline lesions (Ca. in situ)	4	4			2	1	1			4	1	1	
Early infiltr. Ca.	6	1	1	4			6	1	1	4	4		2
Advanced Ca.	38	4	10	24	3	2	33		2	36	12	2	19
Advanced Ca.in resected stomach	7	1	4	2	1	1	5	1	1	5	4		2
Malignant lymphoma	1			1			1			1		1	
Total	56	10	15	31	6	4	46	2	4	50	21	4	23
		pos. 55%			pos. 82%			pos. 88%			pos. 48%		

(-) = negative, (?) = inconclusive, (+) = positive for malignancy

RESULTS

Among the 291 patients with benign gastric disease (Table 2) the cytological diagnosis was correctly negative for malignancy in 277 (95%), false positive in 3(1,1%) and suspicious of malignancy in 11 cases (3,8%).

Among the 111 patients with benign conditions where the diagnosis was verified histologically on resected specimens or at autopsy (Table 3), the cytology gave a conclusive diagnosis of non-malignancy in 94%, whereas X-ray and endoscopic evaluation gave a conclusive non-malignant diagnosis in only 70% and 69% of cases respectively.

In the 56 patients with gastric malignancy (Table 4) the brush cytology was correctly positive in 50 cases (88%), false negative in 2 (3,6%), and in 4 patients (7%) only a suspicion of malignancy was diagnosed.

Compared to the other methods of investigation, the cytology gave a definite diagnosis of malignancy in the greatest number of histologically verified cases, and was the only method that revealed with certainty the early malignant changes occurring in 4 cases of chronic peptic ulcers (borderline lesions or carcinoma in situ).

COMMENTS

The false positive cytological diagnosis or unwarranted suspicion of malignancy have all been submitted on patients with gastric ulcers or severe gastritis. The diagnosis was made during the early stages of the series before we fully realised what considerable degree of deviation from the normal, including mitosis, may accompany these conditions (Fig. 1 and 2)

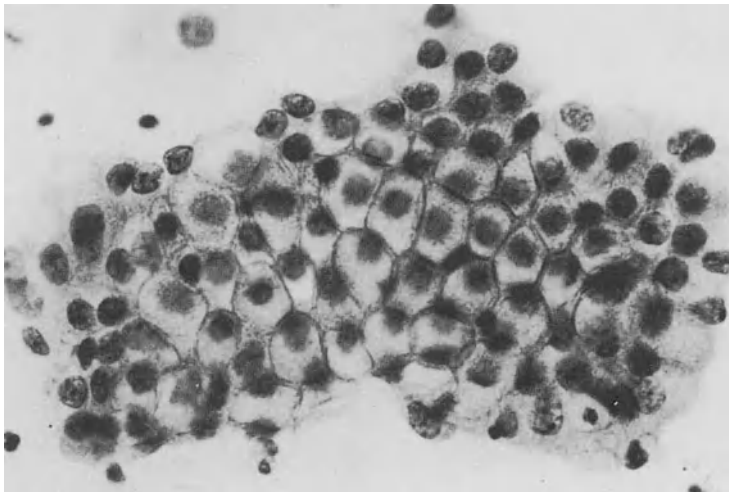

Fig. 1. Group of normal surface epithelium. Note well demarcated cellular outline, inactive regular nuclei and tightly packed cells. Pap. Grade I, Pap. stain x 525

With regard to false positive or unwarranted suspicion of malignancy, the cytology compares, however, very favourably with the radiological and endoscopic evaluation, where approximately 30% of the diagnoses submitted were inconclusive or positive with regard to malignancy (Table 3). The high rate of correct negative biopsies must be seen in relation with its high failure rate in cases with malignant disease, and consequently cannot be relied upon to the same extent as a negative cytological report. It should be stressed, however, that it was only through

the latter half of this series that we fully realised the necessity of taking a large number of biopsies in order to secure representative material.

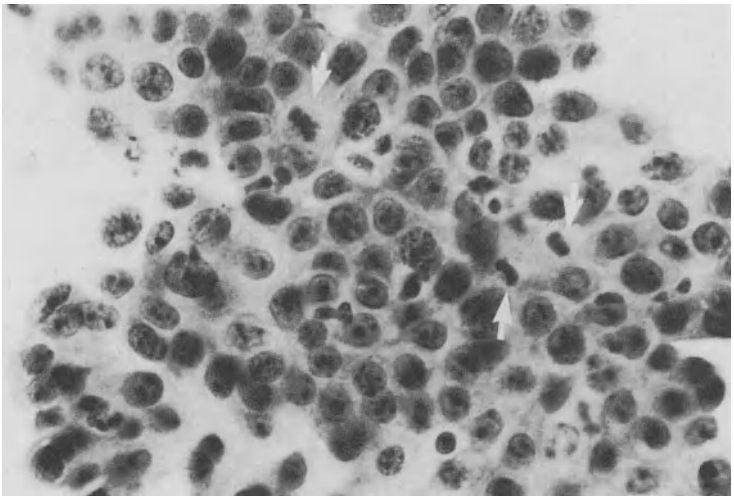

Fig. 2. Group of surface epithelium from edge of chronic benign peptic ulcer of the stomach. Note less well demarcated cellular borders than in Fig. 1. The nuclei have an active appearance with prominent nucleoli, often more than one, and several mitoses are seen (white arrow). There is also some degree of anisonucleosis, but not more than is commonly seen in smears from the edge of benign ulcers or in severe gastritis, Pap. Grade II. Pap. stain x 525

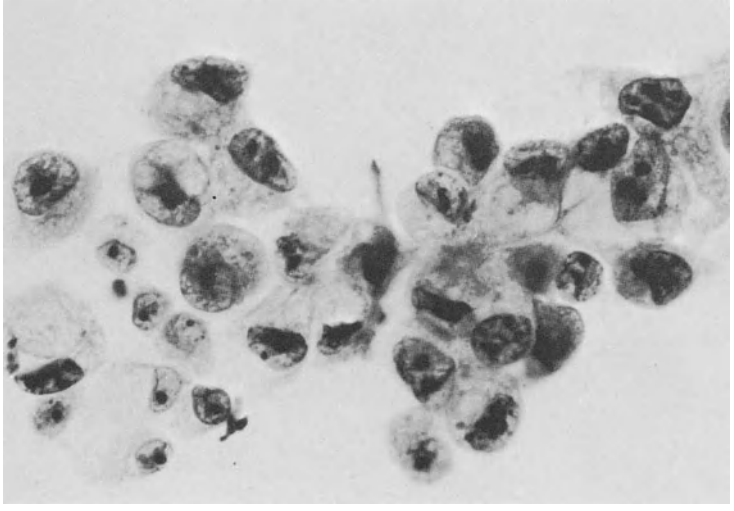

Fig. 3. Group of cells from an adenocarcinoma. Note loss of cohesion among the cells, many with indistinct cellular borders, marked anisonucleosis and nuclear pleomorphism, large and irregular nucleoli and coarse chromocentres. Note also the enlargement of most nuclei. Pap. Grade V. Pap. stain x 525

The false negative cytological diagnosis has been due partly to non representative material (2 cases) and partly to the fact that the tumors from which the cells originated, were highly differentiated with but moderate cellular atypism, so that only a suspicion of malignancy could be diagnosed on the smears (5 cases).

Non representative material is particularly likely to be submitted in cases with large necrotic tumors or ulcerating lesions where the ulcer floor is covered with fibrin (SERCK-HANSSEN, 1967), and also in cases of diffusely infiltrating carcinomas, because the tumors tend to grow under an intact surface epithelium and frequently exhibit only moderate cellular atypism (BACH-NIELSEN, 1966; BRANDBORG and WENGER, 1968; SERCK-HANSSEN, 1967).

From the diagnostic point of view, the most interesting cases in the present series are the 6 cases of early carcinoma, and the 4 cases with "borderline lesions" (i.e. carcinoma in situ), where the cytological diagnosis was positive in 80% (Table 4). KAWASHIMA (1966) using different techniques for cytological sampling, reported 78% positive tests in 40 cases of early carcinoma (i.e. carcinomas infiltrating only down in the submucosal layer), whereas SHIDA et al. (1967) reported positive cytology in all of 20 cases by the water-jet method.

The cases designated "borderline lesions" (carcinoma in situ) in the present series were all cases with chronic peptic ulcers where the histological examination revealed changes in the adjoining mucous membrane with very marked cellular atypism, sometimes associated with abnormal adenomatous or villous proliferation with minimal or no convincing evidence of infiltration of the lamina propria (Fig. 4, 5, 6, and 7). These early lesions are certainly too small to be detected by other than cytologic or bioptic means, and the brush cytology appears to be better than biopsy, probably because the cellular sampling can be done over a larger area than can be covered by biopsies.

Although too little is yet known of the natural history of the "borderline lesions" (carcinoma in situ), it would be fair to assume that a great deal will eventually develop into invasive lesions and because of the much better prognosis, the importance of diagnosing gastric cancer in the early stages cannot be over-emphasized.

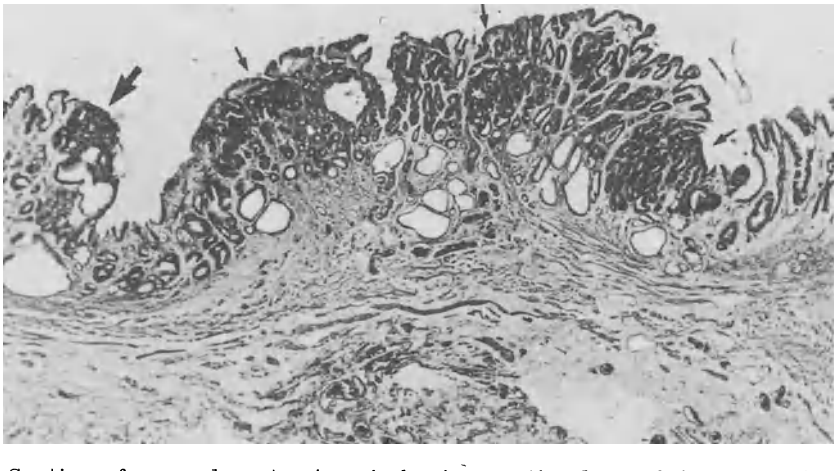

Fig. 4. Section of area close to chronic benign peptic ulcer of the stomach. Brush cytology revealed malignant cells. Note areas with hyperchromatic irregular adenomatous proliferation (arrows). See Fig. 5. HE x20

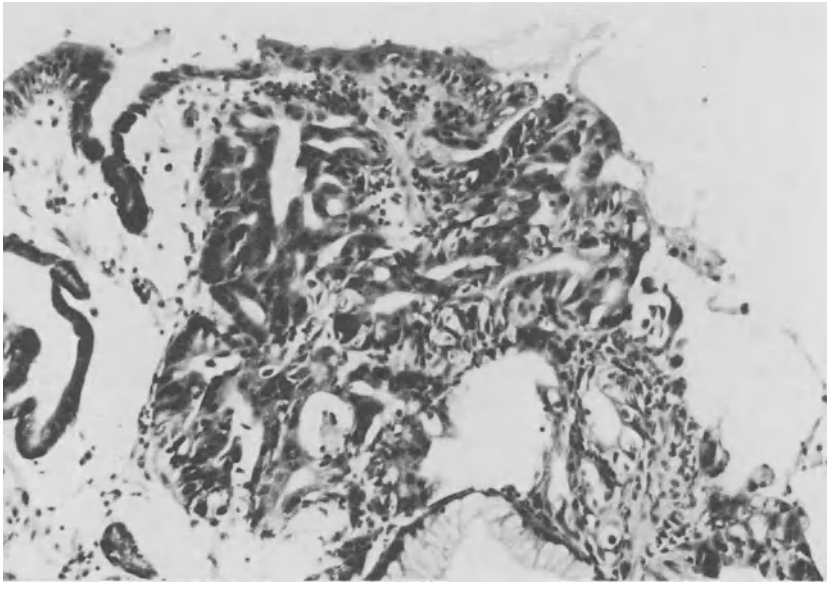

Fig. 5. Enlargement of area marked with large arrow in Fig. 4. Note irregular adenomatous proliferation with hyperchromasia and atypism. Probably also local invasion in lamina propria (intramucosal carcinoma) but diagnosed as a borderline lesion (carcinoma in situ). HE x 150

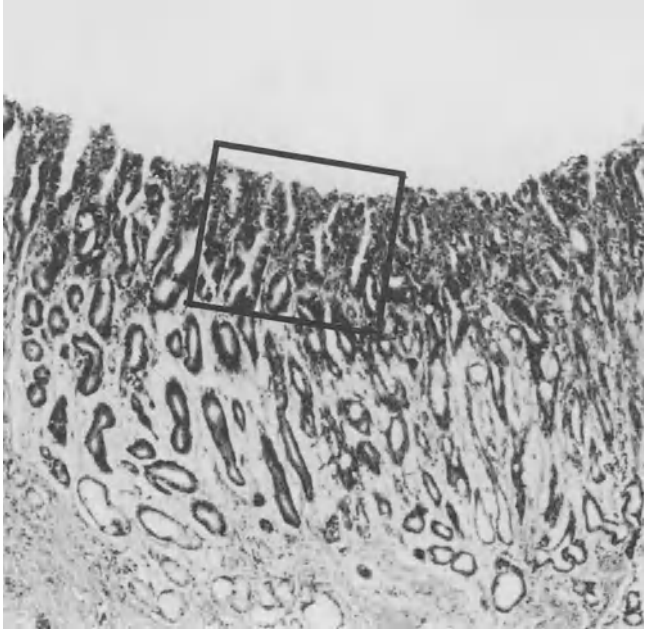

Fig. 6. Section from area close to chronic benign peptic ulcer of the stomach. Brush Brush cytology revealed malignant cells. Note villous surface with hyperchromasia of surf. and foveolar epithelium. Window see Fig. 7. HE x 65

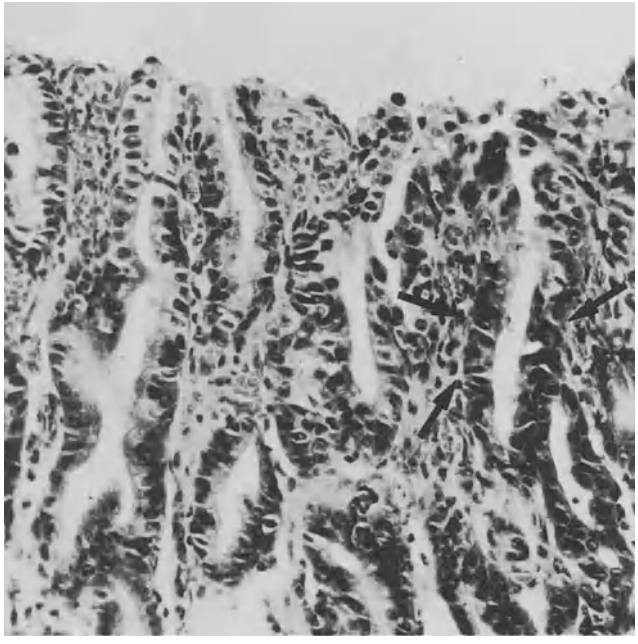

Fig. 7. Enlargement of area marked with window in Fig. 6. Note hyperchromasia and atypism of surface and foveolar epithelium, particularly area marked with arrows. No definite evidence of infiltration in lamina propria. Diagnosed as borderline lesion (carcinoma in situ). HE x 215

CONCLUSION

When properly done, with a trained gastroenterologist for collection of the cells and an experienced cytologist for the evaluation of the smears, the brush cytology is an accurate and reliable method in the diagnosis of gastric malignancy, including the very early cases, and also in differentiating between benign and malignant conditions. It is our experience that whenever a focal lesion is seen by the endoscopist, the selective brush cytology has three main advantages compared to the blind gastric washing:

1. The brush sample contains numerous well preserved cells,
2. there is little contamination with cells from the respiratory and proximal alimentary tract, which makes the screening of the smears more rapid and reliable, and
3. the smears have a locating value and make correlation possible with the endoscopic findings and the histology on bioptic and surgical specimens.

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The Place of Vital Microscopic Methods (Phase Contrast, Fluorescent Microscopy and Ultra-Violet Absorption)

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In cytology staining methods of fixed preparations are dominating. Their most important practical advantages are the easy microscopical recognition at little technical expenditure, and the durability of the slides which is essential for documentation. I regard as disadvantages the intricacy of handling implying the risk of artefacts, the possible loss of cells as well as the time spent for fixation and staining procedures.

The cytological "native" methods are always rapid procedures using unfixed and, if possible, native cell material, and the time spent is rather short. Another decisive advantage is that artefacts can be avoided, and that one is safe from cell loss during the staining procedure. Last but not least, new information about structure and constituents of cells can be gained by the native methods, which could not be obtained otherwise. A drawback for the native methods is the necessity of close contact between microscopical examiner and patient which makes it impossible to send the cell material by mail.

What, then, are the qualities and characteristics of the different native methods with respect to our problem? In the phase-contrast microscope we see the nucleoli and the nuclear membrane at an optimal degree, much better than with the standard Papanicolaou-staining. Cytoplasmic structures, such as granules, vacuoles or the cuticular border, are beautifully displayed (Fig. 1.). We are thus able to recognize very rapidly an intestinal metaplasia in the stomach. According to our experience, the nuclear membranes as much as the nucleoli, represent important tumor cell marks; they can be recognized under low power, and the slides may be scanned in a short time (HENNING and WITTE, 1970). By this, we have been able to increase the yield of tumor cells by a certain percentage because, otherwise, during the following staining the cells were either destroyed or drifted off and did not appear any longer by taking stain in a recognizable way (Table 1).

Table 1. Improving of tumor cell findings by phase contrast microscopy

Cases with tumor cell findings (gastric cell-swab-tube)	
Total	212 cases
only by phase contrast	15 = 7%
only by Papanicolaou staining	34 = 16%
both methods combined	163 = 77%

The limitations of phase contrast microscopy lie in objects or preparations which are too thick, thus leading to an overlapping of structures. Furthermore, nothing can be stated about cell chemistry, and the chromatin structure of the nucleus cannot be seen because it is obviously, to a large extent, a product of fixation and staining.

On the other hand, cell chemistry can be examined by fluorescent microscopy. Let me mention here the well-known acridine-orange method (BERTALANFFY et al. 1956) by which nucleic acids can be shown and distinguished (SCHÜMMELFEDER et al. 1957). When searching for tumor cells, one recognizes the richness of DNA in the cell nucleus, as well as the structures containing RNA, i. e. nucleoli and ribosomes. Moreover, general cytomorphological details must also be considered.

As a special fluorescence method we introduced the intravital staining with Atebrin or Acranil (WITTE, 1955 and 1968). The staining takes place in vivo after an oral dosage of the dye which has an affinity to tumor cells. Granular cytoplasmic structures are shown attracting attention by their intense sparkle and their compact and irregular storage of coarse granules (Fig. 2.).

While the normal epithelium in the oesophagus remains unstained, metaplastic epithelial cells or regenerating mucosal cells on the edge of an ulcus are granularly figuring in the stomach. Thus, we use this method only as a rapid scanning in order to sort out suspected cells from the entire unfixed material; after that, they are examined moreclosely in the phase contrast (Table 2).

Table 2. Results of intravital fluorescent staining with Atabrine in 399 cases of gastric diseases

	No. of cases	Fluorescence		
		strong	weak	negative
Tumor cells	165	71	16	13
Benign cells	234	9	50	41

This can be easily performed in the same microscope by the practical combination of phase contrast and fluorescent illumination.

A last method we are especially concerned about is the ultra-violet microscopy (WITTE, 1968). It serves for figuring the specific monochromatic absorption of cell constituents such as nucleic acids and proteins. Thus, with the help of an image converter, we can see the quantity and structural distribution of the most important cell contents in its native status. Moreover, the optical resolution is considerably improved because of the short wavelengths of the illumination : 263 nm for nucleic acids, 280 nm for proteins respectively. This method is particularly suitable for investigating the problem of differences in structure and quality of nuclear chemistry between tumor cells and other cells, differences not provoked artificially by the procedures of fixation and staining. At present this question is investigated by different methods in several laboratories, but it cannot be answered as yet. We are, however, surprised at the relatively poor structure of nucleic acids and proteins in the native cell nucleus (Fig. 3). Mr. SPRENGER just mentioned and showed a quantitative aspect of ultraviolet microscopy saying that here, fluorescent microscopy is much more satisfactory than measurements of the UV-absorption in the FEULGEN-reaction. Thus, cytology must try to choose from the broad and constantly widening spectrum of microscopical methods, the one that

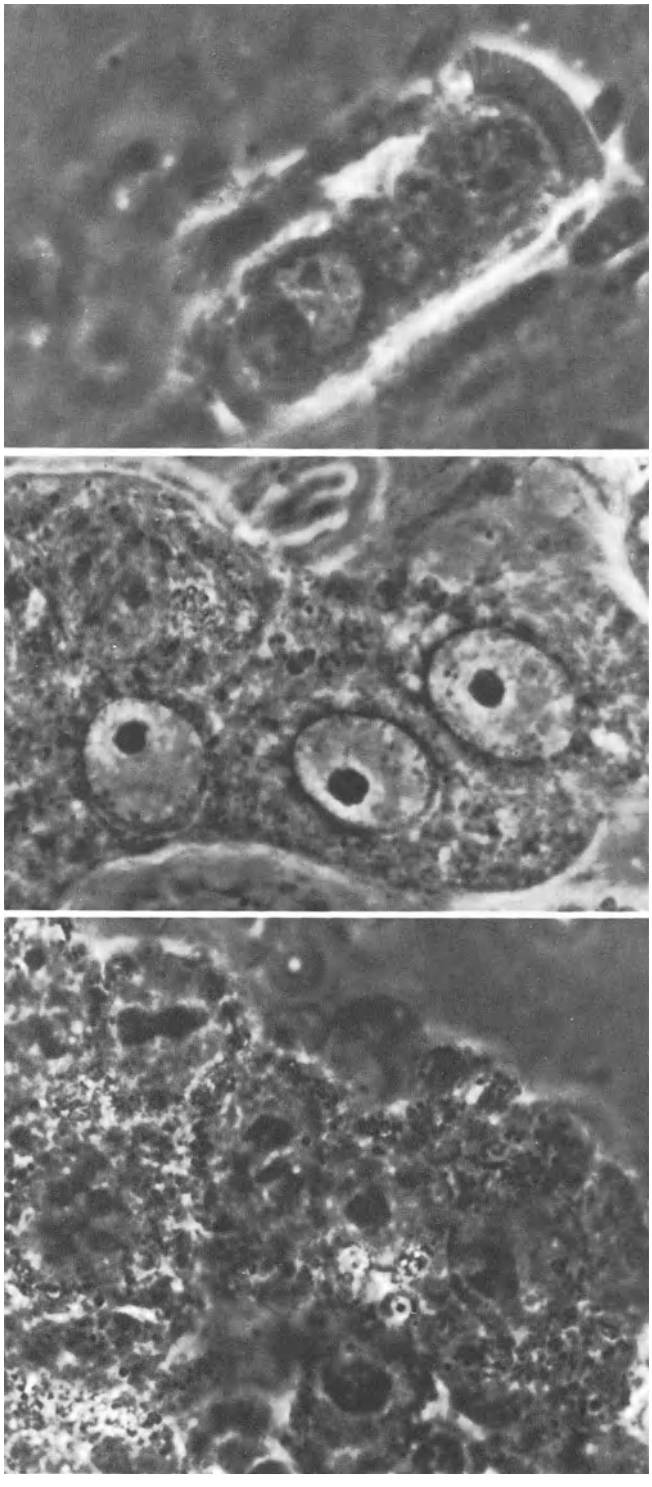

Fig. 1. a, b, c

is most suitable to its respective purpose. In consequence the intravital native methods should find more often an application in practice.

Fig. 2. A cluster of tumor cells under fluorescent light after intravital fluorescent staining with acranil. Material obtained by gastroscopic brush. Obj. 40:1, Oc. 12, 5x

Fig. 1. (Opp. page) Gastric cells obtained by endoscopic brushing under phase contrast view as unfixed wet preparations. Obj. 100 : 1, Oc. 12, 5 x . a) Epithelial cell with a brush border from case with intestinal metaplasia of stomach. b) Gastric epithelial cells from the border of a gastric ulcer, so-called "ulcer cells" with 1 single prominent nucleolus. c) Cluster of tumor cells from case with polypous gastr. carcinoma. Note enlarged and deformed nucleoli in heavily enlarged nuclei with a small rim of granulated cytoplasm

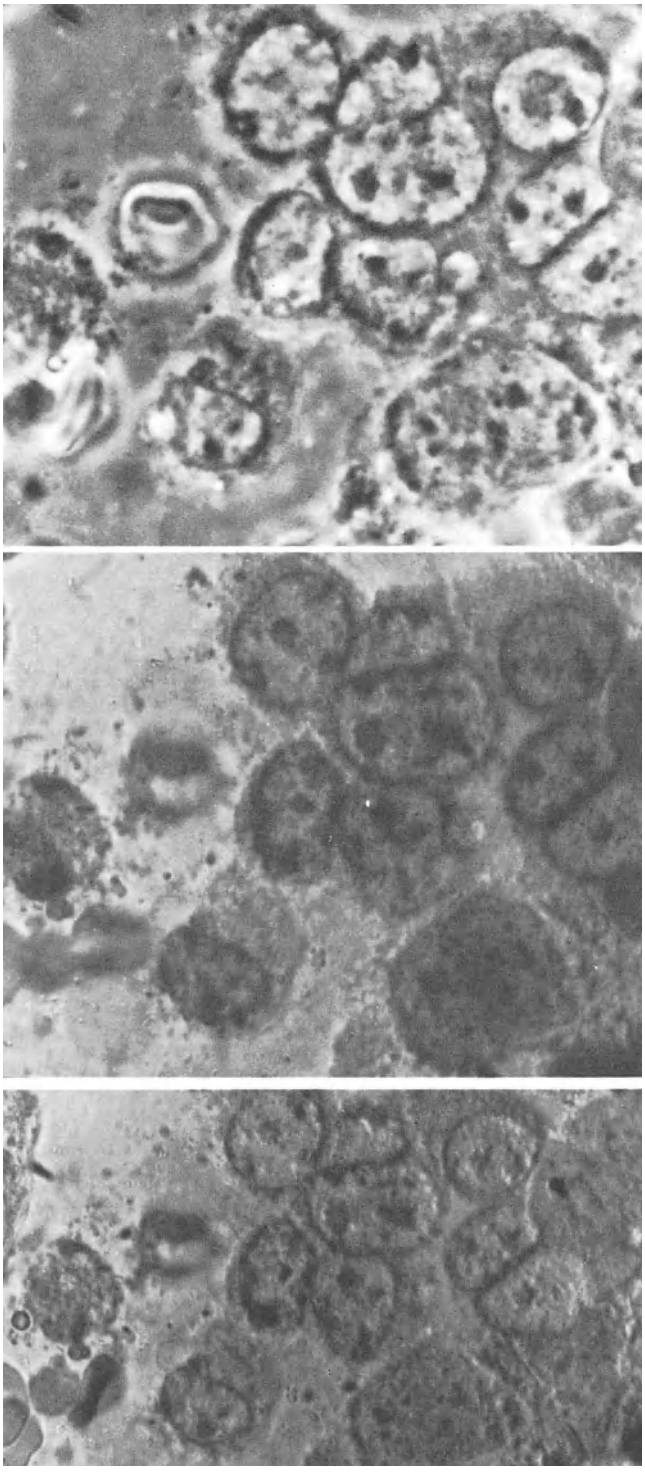

Fig.3. a, b, c

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Fig. 3. (Opp. page) Tumor cells obtained by gastroscopic brushing from a case of gastric cancer. Unfixed native preparation. Obj. 100 : 1, Oc. 3,5 x . a) Phase contrast. b) Same cells under monochromatic light (263 nm) in the ultra-violet microscope. Absorption of nucleic acids. c) Same cells under monochromatic light (280 nm) in the ultraviolet microscope. Absorption of proteins

The Differential Diagnostic Role of Nuclear DNA Contents in Gastric Cytology

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Cytologicyl material from the stomach was formerly obtained by gastric washings or by cell-swab-sounding. Using these methods we obtain exfoliated cells that have been in a hydrochloric milieu for a longer time. The hydrochloric acid in the stomach effects a prehydrolysis of the nucleoprotein complex in the cell nuclei, thereby rendering impossible exact cytophotometric measurements. After the introduction of fibreglass endoscopy it has become possible to obtain in vivo fresh cytological material which is suitable for cytophotometric DNA determination. In analogy to cervical cytology, the possibility of associating cytomorphological findings with characteristic DNA frequency distribution patterns has been investigated. In addition, the question has been raised whether flow-through cytophotometric nuclear DNA determination can be used for the diagnosis of gastric carcinoma.

MATERIAL AND METHODS

Single cell photometry allows the classification of cell morphology and the measurement of nuclear DNA contents of the same cell. Acriflavin-Feulgen stained cell smears (BÖHM and SPRENGER, 1968) are measured with a single cell fluorescence cytophotometer (SPRENGER and BÖHM, 1971). Flow-through cytophotometry allows the ultrarapid DNA determination of large cell populations (SPRENGER et al. 1971). The association of cell morphology and DNA contents is not possible by means of this method. Ethidiumbromide serves as DNA-fluorchrome (BERKHAN, 1972; SPRENGER et al. 1972). The peptic digestion of the cytoplasm, a process which is necessary for ethidium bromide staining, will separate the grouped gastric mucosa cells, thus forming a single cell suspension. The flow-through cytophotometric measurements are carried out on an impulse cytophotometre ICP 11 from PHYWE AG., Göttingen. Simultaneously, tissue specimens are examined histologically together with the cytologic material.

RESULTS AND DISCUSSION

Gastric mucosa smears from 41 patients are evaluated by single cell photometry. 27 cases show benign mucosal changes which are diagnosed cytologically as minimal gastritis, severe gastritis, atrophic gastritis, gastritis with enteral metaplasia and ulcus gastritis. 14 Cases show definite tumor cells or cytologically suspicious cells. The DNA distribution pattern of cells cytologically diagnosed as benign shows a peak in the diploid range. Cells with DNA contents exceeding the tetraploid value (4c) were not observed.

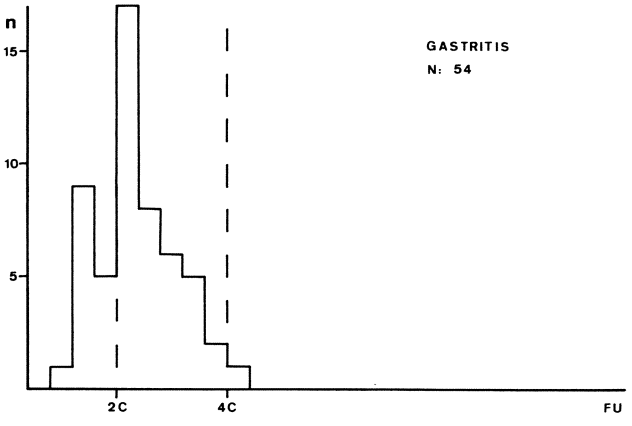

Fig. 1. DNA histogram obtained by single cell photometry of a gastric cell sample in a case of gastritis. FU = fluorescence units (relative amounts of DNA); n = number of nuclei; 2c, 4c = DNA contents corresponding to diploid or tetraploid chromosome set; N = total number of nuclei measured

Fig. 1 shows a typical DNA frequency distribution pattern of cells with benign changes. Cytologically as well as histologically, the diagnosis was that of gastritis. Cell smears with suspicious or well defined tumor cells will yield a DNA distribution pattern which is clearly different from that seen in benign changes. In addition

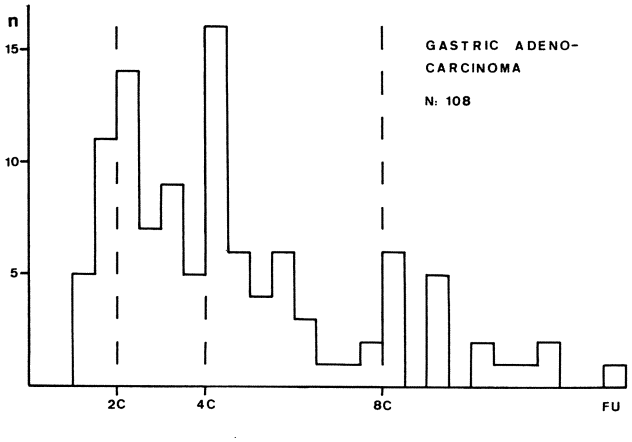

Fig. 2. DNA histogram obtained by single cell photmetry of a gastric cell sample in a case of adenocarcinoma. Abbreviations as in Fig. 1

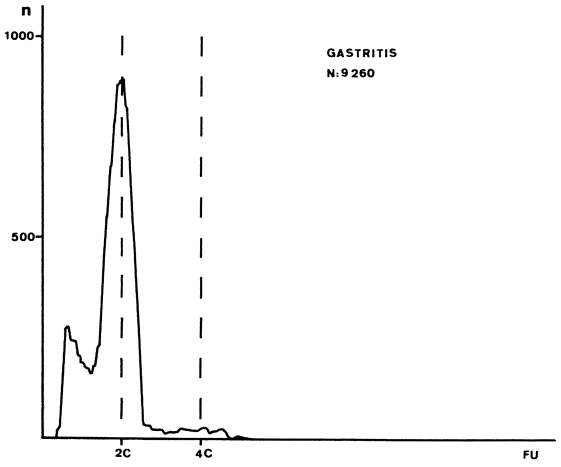

Fig. 3. DNA histogram obtained by flow-through photometry of a gastric cell sample in a case of gastritis. Abbreviations as in Fig. 1

to cells in the diploid range (2c) there are cells showing DNA values that exceed the octoploid value (8c) and have an aneuploid distribution. Fig. 2 shows a typical histogram of DNA value from a tumor cell population. The cytological and histolo gical diagnosis was adenocarcinoma of the stomach.

The results obtained by single cell photometry of nuclear DNA show that it is possible to distinguish normal cells or cells showing inflammatory changes from tumor cells. The possibility of differentiating between gastric carcinoma and nonmalignant changes by cytophotometric methods corresponds to results obtained from material of the cervix uteri (BÖHM et al. 1971; WAGNER et al. 1972). As yet, there are no results with regard to the detection of the preinvasive stages of gastric carcinoma.

Cytological material from 38 patients was examined by flow-through cytophotometry. 31 cases were cytologically diagnosed as benign, and 7 cases as malignant. The results of flow-through cytophotometric DNA measurements correspond, in principle, to the findings obtained by single cell photometry. Gastric mucosa with inflammatory changes shows DNA values mostly in the diploid range (2c), and a smaller proportion of tetraploid (4c) cell nuclei (Fig. 3). Material containing tumor cells, i.e. a mixed population of normal gastric mucosa and atypical cells, shows a diploid DNA distribution peak (2c) in addition to numerous polyploid and aneuploid nuclei (Fig. 4).

There is, however, an important difference between flow-through cytophotometry and single cell photometry. In the latter method, atypical cells appearing in the smear can be selected for photometric evaluation. Flow-through photometry monitors all components of a mixed population according to their relative frequency. If a smear contains only a small number of atypical cells and numerous normal epithelial cells, single cell photometry allows selection of the atypical cells and

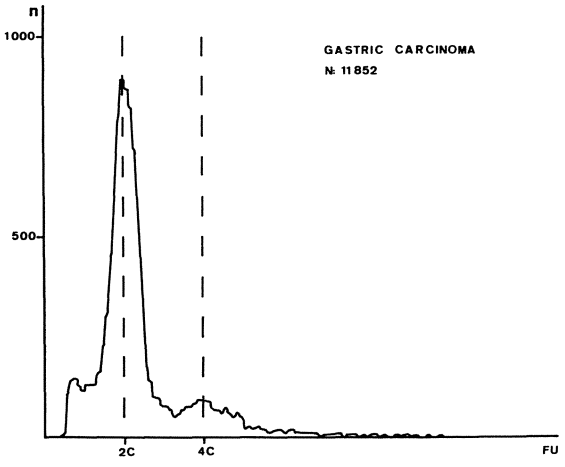

Fig. 4. DNA histogram obtained by flow-through photometry of a gastric cell sample in a case of adenocarcinoma. Abbreviations as in Fig. 1

demonstration of their DNA contents in the histogram. Flow-through photometry records only an insignificant number of tumor cells because of the relatively low frequency of atypical cells. The histogram can be misinterpreted as representing a benign change in the mucosa.
Therefore, cell preparations from 5 tumor cases were falsely classified as benign by flow-through cytophotometry. Only an enrichment of atypical cells will make it possible to avoid false negative results in flow-through photometry. A further development in cell sorting methods for enrichment of atypical cells, as suggested by KAMENTSKY and MELAMED (1967) and FULWYLER (197o), is the prerequisite for a successful introduction of flow-through photometry in the diagnosis of gastric carcinoma.

SUMMARY

Cytological material obtained by fibergastroscopy is suitable for the cytophotometric nuclear DNA determination. The DNA determination by single cell photometry allows a differentiation of normal or inflammatory cells from atypical cell populations. Flow-through cytophotometry records the DNA distribution pattern of all cellular elements according to their relative frequency in the smear.

A minimal relative frequency of atypical cells compared to that of normal cylindrical cells may lead to false negative results. The introduction of flow-through fluorescence cytophotometry in the diagnosis of gastric carcinoma will probably be possible in combination with cell sorting methods that allow the enrichment of atypical cells.

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Diagnosis of Gastric Carcinoma With the Aid of Brush Cytology

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It is often very difficult to diagnose gastric carcinoma, even when the lesion is not very small and exceeds the limitations of early carcinoma. The difficulties are particularly great when during an outpatient examination, the gastroscopist has to determine in a single session whether a lesion is benign or not, and whether the patient should be operated on. Since we have to do many gastroscopies on outpatients, we have tried any technique available to define the nature of the lesions observed. We have used brush cytology in gastroscopies since 1970; some 750 gastroscopies have been performed, using photographic techniques, biopsies and cytology.

During gastroscopy we push the brush through the biopsy channel and take a smear from the surface of the area suspicious for carcinoma. Recently, we fed the brush through a polyvinyl tube which is pushed through the operating channel of the gastroscope, because a tube is easier to cleanse than the operation channel itself. Then, the brush is rolled over a rough slide and either dried in air or immersed in a solution containing glycerol and isopropyl alcohol. The staining is done according to Papanicolaou or Pappenheim methods. The grading is as usual from I to V.

From our 750 gastroscopies we selected 87 patients who were examined between January and September. These patients were referred to gastroscopy on account of doubtful X-ray findings, or because the practitioner had suspected gastric carcinoma but could neither prove nor disprove it. One year after the gastroscopy, we wrote to the practitioners to ask what had become of the patients, particularly of those cases where the diagnosis had been a benign lesion.

Among the 87 patients we diagnosed, there were 36 cases of carcinoma, that is 41, 6%. The diagnostic results of these 36 carcinomas of the stomach were :

gastroscopy false negative	1 case (2, 8%)	of 36 cases
cytology false negative	3 cases (8, 3%)	
cytology & biopsy false negative	3 cases (8, 3%)	
gastroscop. & biopsy & cytol. false negative	1 case (2, 8%)	
cytology false positive (grade IV)	4 cases (4, 6%)	of 87 cases

Cytology grade V (malignant cells in connection, doubtless carcinoma) was done in one case in which we were not able to demonstrate a carcinoma with biopsy. The patient was operated on and the stomach resected; the lesion (a ventricular ulcer) appeared malignant only in one part of the ulcer wall, and was proved to be an early carcinoma. After this, we found another case in which a grade V cytology was the only diagnostic procedure, and the patient was successfully operated on. In 12 cases there was no follow-up, the practitioners had not replied. Among these 12, we found three with a grade IV cytology, but no positive biopsy.

We conclude from our results that a repeated gastroscopy is necessary in all cases with grade IV and V cytology. We are inclined to say that patients with grade V cytology should be operated on even if we are unable to prove the presence of a malignant lesion. We had two patients with grade V cytology; they were operated on, but the surgeon was unable to find the lesion, so there was no resection, but we keep a close watch on them.

The cytologic smears were read by Prof. Dr. Breinl of Rüsselsheim, Germany, and Dr. Beyreder, Amstetten, Austria.

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Special Remarks Concerning Efficiency and Problems in Cytology

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Today, we must clearly distinguish between aimed cytology and blind techniques. Aimed cytology represents the most powerful tool for achieving a morphological diagnosis of malignancy, especially when routinely combined with biopsy and visual data. We prefer brush sampling instead of direct washing techniques because of the better recovery of the sample. A special tube for retracting the brush during the passage through the endoscope avoids contamination and loss of the sample. Reported accuracy of the method ranges from 92 to 96% (KASUGAI, 1972; OKUI, 1971). When combined with aimed multiple biopsy, the accuracy goes up to 100% (PROLLA, 1971).

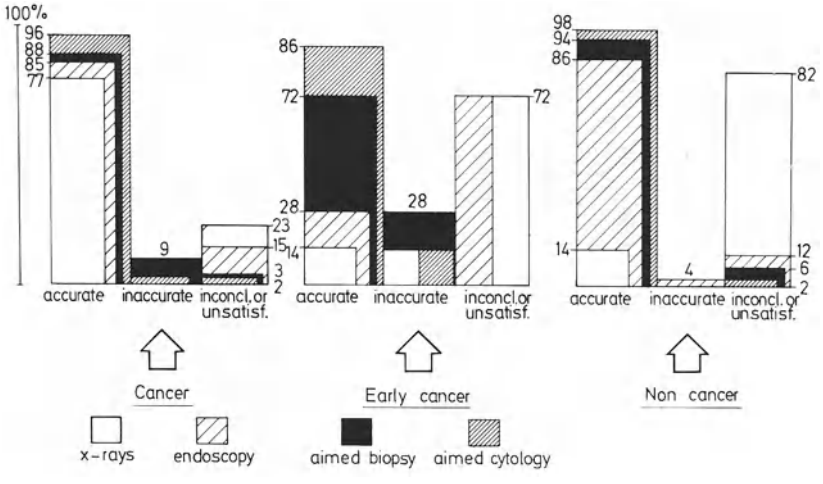

Fig. 1. Diagnostic accuracy of different procedures in 119 cases of suspect gastric cancer

Our data on 119 cases of suspected gastric cancer (Fig. 1) are in agreement with reports from other authors. Aimed cytology is nowadays considered to be the main diagnostic procedure in early gastric cancer; but, for a real effectiveness in improving the patient's survival, the problem is in submitting to the examination, people who would not be selected otherwise. The results for blind saline lavage cytology vary widely, but may be realistically estimated for an accuracy of around 60 to 70% in large series (ACKERMANN 1967). The generally poor preservation

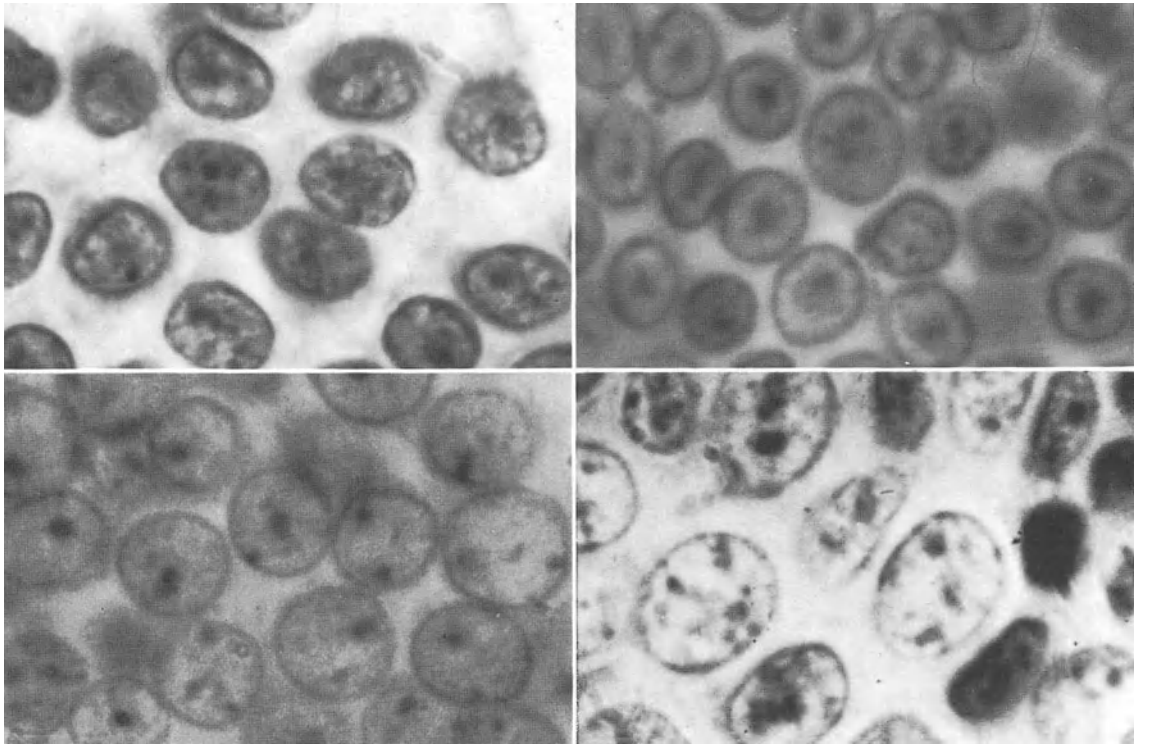

Fig. 2. Progressive alterations in cytological specimens of cases with chronic gastritis. Top left: Grade I. Top right: Grade II. Bottom left: Grade III. Bottom right: Grade IV

of cellular material impairs the fine structural studies and accounts for the 3 to 4% reported incidence of "false positives". For the same reason, it is also very hard to interpret on the base of such material alone, the degree of diffuse stomach diseases, such as chronic gastritis. However, saline lavage cytology is the only suitable means for a harmless, acceptable and low cost follow-up of high risk cases and may enable us to pick up initial stages of malignant transformation (LOUX and ZAMCHECK, 1969). No transitional forms, as exist in other organs, e.g. in the uterus, have been described so far, but it would be of considerable interest to establish the guidelines for future cooperative studies in this item. Phase contrast microscopy and other technological improvements could lead to new possibilities in this respect.

For the diagnosis of diffuse diseases of the stomach, blind abrasive gastric cytology has many advantages. The sampling is less time consuming and more acceptable for the patients, thus ensuring a better follow-up. The qualitiy of cellular material obtainable by brush sampling is excellent, and it is possible to study the fine details of nuclear structures. In chronic gastritis it is possible to make evident, depending on the stage of the disease, progressive alterations (NIEBURGS et al. 1963; VILARDELL, 1966; CRESPI, 1971). They consist of an increase in the average nuclear diameter and in the N/C ratio, and an increase and variation in nuclear size (anisonucleosis) (Fig. 2). The chromatin content is progressively decreased and the chromatin is irregularly disposed with numerous small chromocentres, connected by delicate chromatin bands outlining achromatic areas.

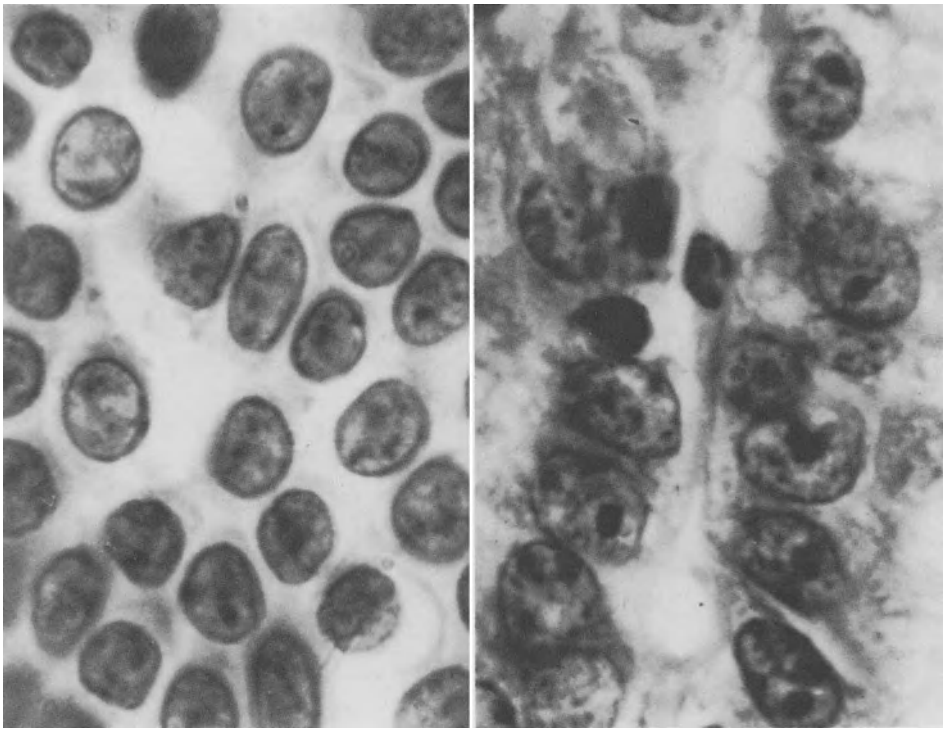

Fig. 3. The same nuclear features are present in cytological (left) and histological (right) specimens of cases with superficial gastritis. Cytology is Grade I

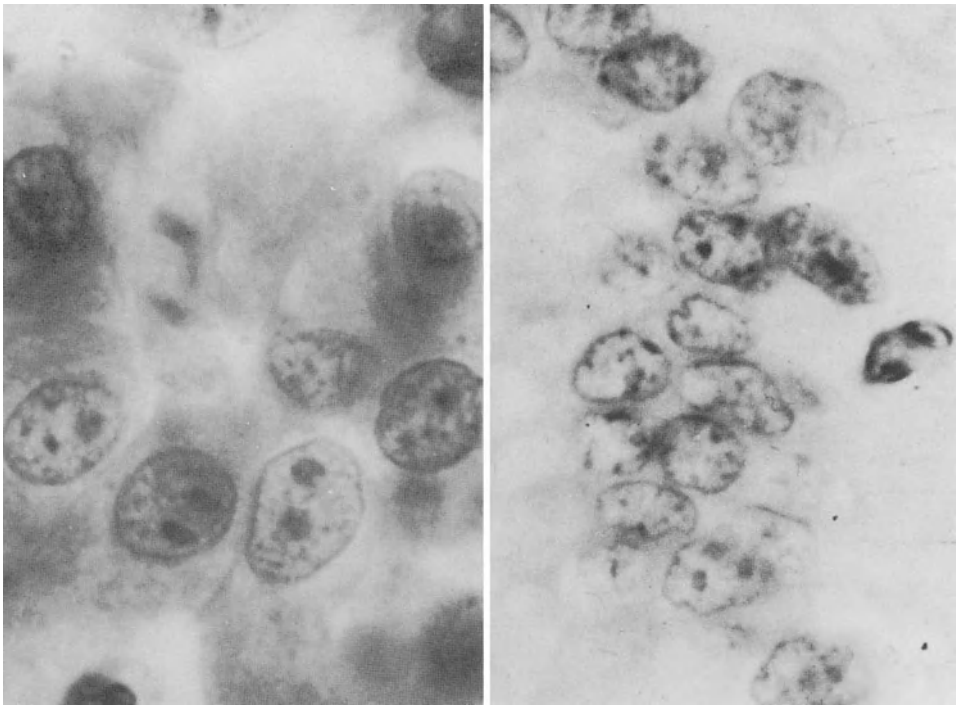

Fig. 4. The same comparison in a case of severe atrophic gastritis. Cytology (left) Grade IV

Nucleoli are multiple and usually progressively increasing in volume. Sometimes the nuclear membrane is broken. When clumped together in small groups, the cells tend to increase in size, working their way towards the periphery. The same features may also be seen by comparing histology and cytology at high magnification (Figs. 3 and 4).

The above described progressive alterations may be grouped into five grades, ranging from the normal to the pernicious anemia-like cell, and they correlate quite well with histological patterns obtaines by multiple suction biopsy of the gastric mucosa (Table).

Table. Comparison between histological classification and cytological grading

Prevalent cytological grading	No. of cases	Histological classification				
		normal	superficial gastritis	atrophic gastritis moderate	atrophic gastritis severe	gastric atrophy
0 (normal	29	29	-	-	-	-
I	56	51	5	-	-	-
II	125	4	78	32	11	-
III	129	-	21	45	60	3
IV	45	-	2	2	9	32
Totals	384	84	106	79	80	35

Nuclear structural changes may be interpreted in terms of cell kinetics, and recent evidence obtained by studying patterns of nucleid acid and protein synthesis in human gastric mucosa (DESCHNER, 1972), permits the interpretation of the whole process as a consequence of an impairment in the gastric columnar epithelial cell maturation.

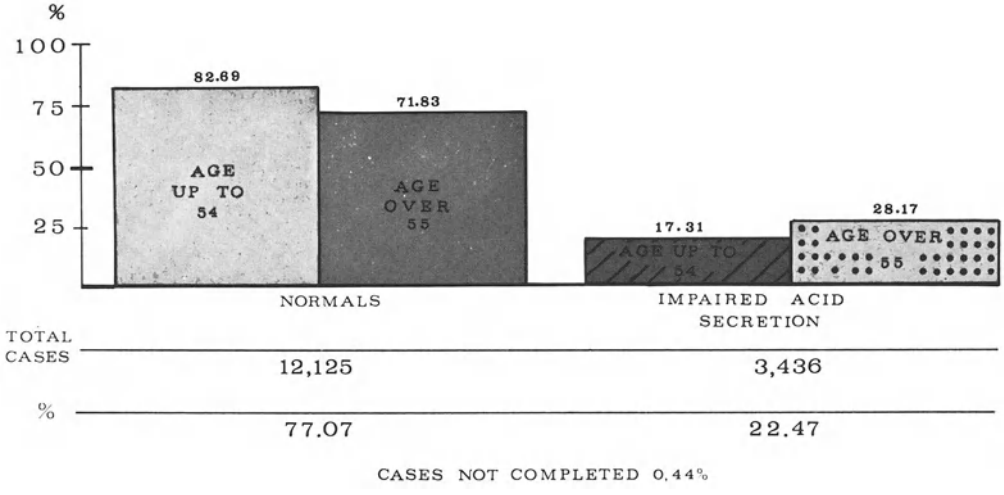

Fig. 5. Results of the dye urinary test for acid gastric secretion

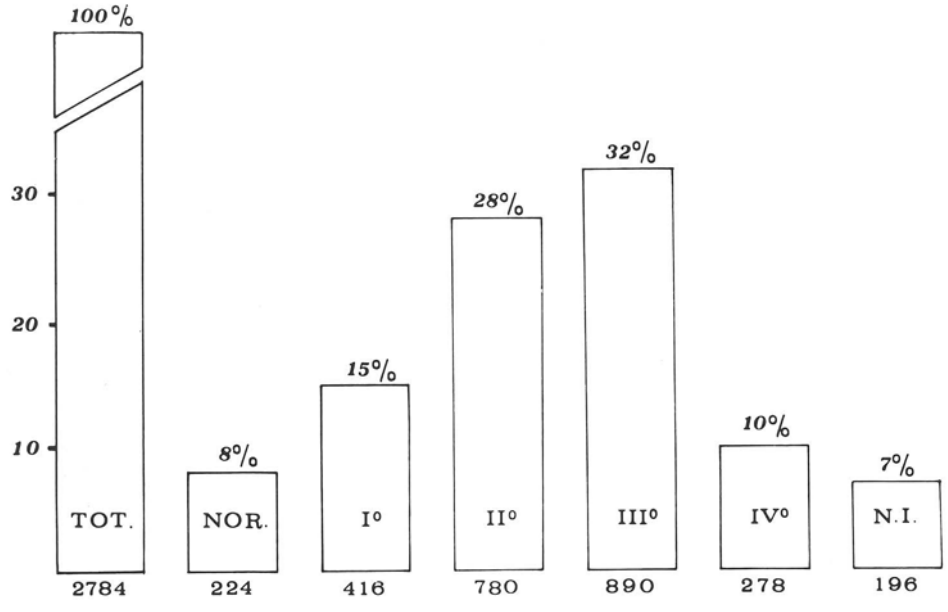

Fig. 6. Abrasive gastric cytology. Cytological grading at the first exa ination
grading at the first examination

Considering our lack of knowledge about a primary or secondary prevention of gastric cancer, our main task for reaching an early diagnosis will be, today, the selection of high risk groups. As pointed out by different research approaches to the problem, chronic gastritis is considered to be a condition strongly predisposing to stomach malignancies (MORSON, 1955; RUBIN, 1967). For a diagnosis of the degree of atriophy of the gastric mucosa cytology, as we have seen, may be of interest. To further reduce the group of individuals who should be submitted to cytology for such a purpose, a previous screening by tests furnishing a profile of stomach acid secretion will be very helpful. Our results with one of such tests on 15.731 persons over 45 (Fig. 5) showed 22% cases of impaired secretion; this represents the first step of our screening.

These cases, cytologically examined, were classified in different stages of cytoligical grading (Fig. 6.) and grades 3 and 4, suggesting atrophy from moderate to severe, represented our high risk group.

A close follow-up of these cases by means of double contrast X-rays, endoscopy, related techniques and blind lavage cytology, will ensure prompt detection of the earliest signs of malignant transformation within the stomach.

The long term results of this pilot study could prove of some interest for better establishing the potentialities and limits of selective screening for gastric cancer.

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Special Remarks Concerning Efficiency and Problems in Cytology

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Diagnostic cytology is primarily a cancer detection technique. In the evaluation of patients with upper digestive tract symptoms it is a very useful complementary technique, which helps to decide the exact nature of lesions discovered by radiology and/or endoscopy. At the moment, there are two main gastric cytology techniques: the blind washing method and the endoscopic aimed method. Meticulous technical care is of utmost importance in all the cytological procedures, and it is of much more importance than the selection of a specific cell collection or the staining method.

We agree with VILARDELL and the ACKERMANN survey (1967), and thus tend to support their view that gastrointestinal cytology should be orientated exclusively towards the digestive tract. It should also be part of any large Gastroenterology Department unless someone has a specific interest in a general cytology laboratory. However, the responsibility of collecting cells should at all times remain that of the gastroenterologist, and not the responsibility of busy interns or any other insufficiently trained member of the medical team.

Blind washing or abrasion methods. The main advantages are:

a) They can be performed by trained technicians;
b) the vast majority of the patients tolerates these methods;
c) the detection rate in ideal conditions is approximately 90%;
d) their potential applicability to mass surveys.

The main shortcomings of such methods are:

a) The shortage of well-trained technicians;
b) they are time consuming techniques, reading of the slides especially;
c) they are blind techniques and the site of origin of malignant cells is never completely known with certainty;
d) the rate of unsatisfactory examinations, even in the hands of the most trained teams, ranges from 7% to 10%;
e) in a national USA survey carried out by ACKERMANN (1967), a percentage of 60% to 90% was the median range of accuracy.

Aimed endoscopic methods. Direct vision is performed by either of two methods: brushing or washing. We prefer the brushing method, because:

a) It dispenses with a Levin intubation after endoscopy;
b) the smears are made immediately, thus rendering centrifugation unnecessary and thereby saving time;
c) screening is easier and quicker, due to the high yield of diagnostic cells and the clean background;
d) an antifoam agent can be used prior to endoscopy;

e) in cases of stenosis of the pylorus or cardia, lavage under direct vision is frequently unsatisfactory whereas brushing is more practicable;
f) three intubations are necessary when washing under direct vision, thus increasing the time spent and thereby causing a decrease in the patients willingness to co-operate.

When considering the direct vision brushing method, several advantages are evident (PROLLA, YOSHII, XAVIER et al., 1971; PROLLA, KIRSNER, 1972) :

a) Brushing and endoscopy are performed simultaneously making a second procedure for both physician and patient unnecessary. A biopsy is usually performed immediately after brushing.
b) The problem of trying to discover the origin of malignant cells is solved because the cells are obtained selectively and simply from the lesion.
c) The time spent in collecting cells and processing the material is very short.
d) There is no need to train cytotechnicians in collecting cells.
e) The smears obtained are rich in well preserved cells originating from the lesion itself; because of the very light and clean background, screening is easy and quick.
f) The detection rate of this technique is excellent; it is in the order of 90%, when combined with biopsy almost no case of cancer will go undetected.

However, endoscopic cytology has some shortcomings:

a) The instruments are expensive;
b) the patient must be willing to tolerate gastroscopy;
c) it has to be performed by trained physicians.

Mass Surveys and Cytology

When one considers mass surveys of gastric carcinoma, the main purpose of cytology or that of any other method is to select patients for tissue examinations at a minimum cost financially, and to take the minimum amount of time of the medical personnel. Cytology fulfils its casefinding role adequately, if it singles out for detailed clinical examinations or biopsy almost all malignancies of a large asymptomatic population, and produces a minimum of false-positives. The method should be simple, easy to perform, and reasonably well tolerated by most people. At present, lavage with saline (with or without alpha-chymotrypsin added) is the method which incorporates most of these requirements. The potential value of fluorescent or phase contrast microscopy in shortening the screening time should be considered.

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Doubtful Cases and Precancerous Lesions. (Indicative List for the Various Methods of Examination, for Surgery, for Observation and for Prophylactic Screening)

Doubtful Cases and Precancerous Lesions

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Chronic atrophic gastritis as diagnosed by suction biopsy is far too common to be selected as a high risk group (Fig. 1.), for according to SIURALA (1973), 50% of the population over fifty suffer from this ailment.

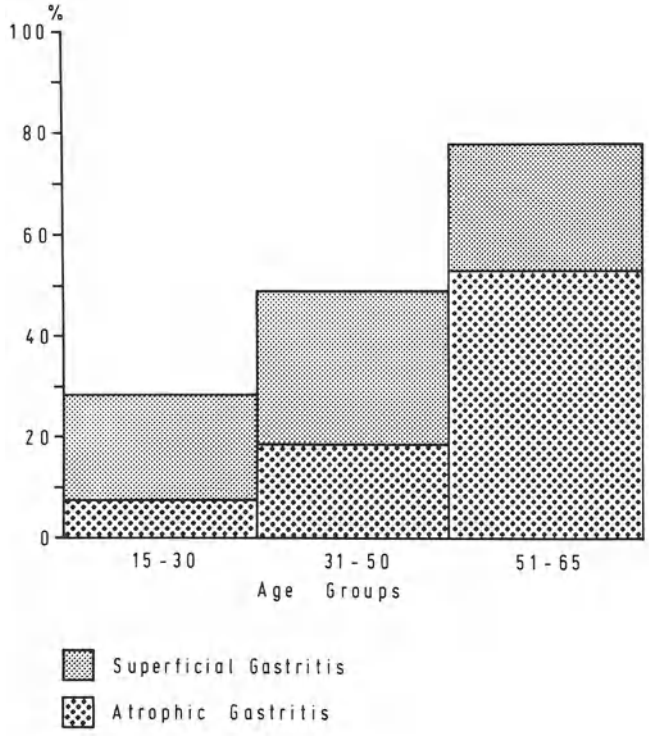

Fig. 1. Incidence of gastritis in various age groups in Finland (SIURALA)

A step-wise biopsy along the minor and greater curve - showing gastric atrophy with intestinal metaplasia - and a quantitative gastric secretion analysis demonstrating achlorhydria, would be mandatory for selecting these patients. According to HITCHCOCK, MAC LEAN and SULLIVAN (1957), the cancer risk is increased by 4,5% in this group. WALKER et al. (1971) found a cancer risk ten times higher in a group of patients with gastric mucosal atrophy as compared to the normal population, but according to TAYLOR (1969) a statistically significant correlation

between gastritis and cancer has not yet been clearly established.

Since only 20% of the patients with advanced gastric cancer show achlorhydria, gastric secretion studies cannot be used as screening procedures. Relations between size and malignancy of gastric polyps have been discussed. It is noteworthy that SAGAIDAK (1960) found malignancy in 18 of 152 polyps with a diameter smaller than 20 mm. Endoscopic polypectomy is therefore advisable in all cases with a solitary or only a few polyps. Whether big gastric polyps (2 cm in diameter) and gastric polyposis have to be regarded as precancerous stages, will depend on the type of polyp: in metaplastic polyposis malignant degeneration is probably very rare, whereas in adenomatous polyposis malignant transformation seems to occur. A difficult problem is that of the older patient with multiple or diffuse tiny polyps of less than 1 mm in size: should we observe this patient closely and remove growing polyps via diathermy snare, or should we advise early surgical intervention? A similar problem exists for the patient with pernicious anemia whose cancer risk is nearly 22 times higher than that of the normal population (HITCHCOCK et al. 1957). When such a patient develops several gastric adenomas: should we remove all adenomas immediately to prevent carcinogenesis, or should we perform a total gastrectomy because proliferation was already triggered? When we find a small gastric carcinoma in a patient with or without pernicious anemia, should we recommend total gastrectomy because this patient may have a multicentric growth (5 of 25 = 20% of the cases in our series)?

What are we to do with a patient who has had gastric surgery? Recent reports on carcinoma in the gastric stump indicate that the cancer risk increases considerably after 15 up to 35 years (STALSBERG and TAKDAL, 1972). When exactly do we have to submit this patient to a screening program in order to detect any early cancer as soon as possible? We have observed early gastric cancer in a resected stomach as soon as three years after a resection for duodenal ulcer.

There is some evidence that early gastric cancer may need years to grow to an advanced stage (MASUDA, 1970). The observation is somewhat consoling, seeing that the theoretically required screening programs cannot be carried out because of financial limitations. Therefore, the only reasonable proceeding seems to be close supervision of high risk patients: cases of pernicious anemia, gastric polyposis, and partial gastrectomy (on account of resectable cancer, and ten years after gastrectomy for gastric and/or duodenal ulcer).

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Discussions by Invitation

Doubtful Cases and Precancerous Lesions (Indicative List of Various Methods)

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The more problematic the evaluation of a histological diagnosis, the longer the pathologist's comment on it. This seems to be necessary in order to demonstrate the perplexing matter to the clinician. It remains, however, often doubtful whether a certain understanding is established or not. Everybody expects a "useful" diagnosis from his pathologist making room for therapeutic consequences and prognostic aspects. From the pathological anatomist's point of view, this is impossible in borderline cases; that is why we have to claim an accurately adjusted nomenclature. I am talking about alterations which are qualified by us as "proliferation of the glandular neck with cellular atypia", by others as "cell atypia" or "proliferative intestinal metaplasia". In simple words this would mean a diagnosis corresponding to Papanicolaou III in cytology. It depends on clinical findings what further diagnostic procedures or follow-up studies will be indicated.

Borderline cases as far as surgery is concerned, are those patients with whom multicentric foci are found in other areas of the resected specimen, beside the early cancer already identified. What clinical consequences have to be drawn? I have to confess that such questions embarrass me. May be Dr. Kawai can calm us by furnishing significant data from Japanese experience - or he may worry us even more.

Doubtful Cases and Precancerous Lesions

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Frequently we had difficulties in the differential diagnosis of gastric lesions. This demonstrates that we were not able to completely establish a correct diagnosis or even a basis for differential diagnosis by radiological or endoscopical means.

Table 1 . Result of scopic biopsy for gastric ulcerations

Period	No. of cases	Endoscopic diagnosis		Result of biopsy ca(+)	(±)	(-)
1964		benign ulcer	24			24
	85	malignancy cannot be ruled out	13	3	4	6
1966		suspicious of malignancy	2		1	1
1967		benign ulcer	111	2	8	101
	238	malignancy cannot be ruled out	22	2	5	15
1969		suspicious of malignancy	8	2		6

There were no diagnostic difficulties when the lesion showed a typical slight depression or protrusion in comparison to the adjacent healthy mucosa. And also low filling defects, the slight retention of the barium meal, or stiffness of the gastric wall, by using the filling or double contrast technique gave no trouble. In addition, such changes were endoscopically localized by slight changes of colour.

However, as we reported in the past, the most important point is that we still have difficulties in diagnosing type IIb, the superficial flat type of early gastric cancer, especially when the cancer cells are covered by healthy mucosa. In such cases, we are not able to see any abnormalities and although we are experienced in endoscopy, false negative results still occur in our series. Another problem is the diagnosis of multiple lesions. This problem arises from the fact that, psychologically, we are usually satisfied when finding just one stomach lesion.

All of our IIb type early gastric cancer cases were discovered after a histological examination. In order to avoid overlooking such cases we must, as a matter of routine, always examine all parts of the stomach from the pylorus to the cardia. Contributing to the problem of benign gastric ulcer being a pre-cancerous lesion, we may report on 408 lesions out of 1. 042 cases of benign gastric ulcers, followed in a peroid of 6 months. In this series we determined 8 cases of gastric cancer, five of them being particularly close related to pre-existing gastric ulcer. Otherwise, we did not find any gastric cancer cases among the follow-up study of 1. 501 cases of gastric ulcer scars. However, we can as yet not conclude from this fact

that benign gastric ulcers are pre-cancerous lesions. This is because Hauser's type of ulcer cancer and cancer infiltration restricted to the edge of a benign gastric ulcer, can also be seen after peptic ulceration of the carcinomatous mucosa. As reported in another paper, we were able to measure a long period of doubling time which the IIc type has. However, we do not know anything about the life history of this IIb stage. Influenced by follow-up studies, internists are still very reserved and worried about evaluating gastric ulcers as being pre-cancerous stages. For us, it is easier to understand that the origin of cancer is in a healthy mucosa which then besomes depressed, and that after peptic ulceration of the carcinomatous mucosa has taken place, the Hauser's type of ulcer-carcinoma is found. However, we cannot as yet deny the possibility that Hauser's type of carcinoma may occur after peptic ulceration of a scar carcinoma having developed from a benign ulcer scar itself.

We must always bear in mind that the niche of an ulcerating carcinoma heals under medical treatment in one or two months. Of 16 ulcer cases which we confirmed to be healed, the healing time depended on the depth of the "ulceration", the depth of the carcinoma infiltration, and the cancer cell density around the ulcer. (Tables 2 a+b and 3)

Table 2 . a) Healing time and depth of carcinoma infiltration

	1 month	2	3	3-6	6	total
mucosal	5	3				8
submucosal	2	3		2	1	8

b) Healing time and depth of gastric ulcer

	1 month	2	3	3-6	6	total
Ul II	4	2				6
Ul III	1	1		1	1	4
Ul IV	2	3		1		6

Table 3 . Healing time of gastric ulcer and carcinoma cell distribution

	1 month	2	3	3-6	6	total
thick	2	3		2	1	8
intermediate	3	3				6
spotted	2					2
circular	5	4		2	1	12
intermediate	2	1				3
partial		1				1

This shows that the healing process of such lesions depends on the regeneration of the remaining healthy mucosa. Therefore, the evidence of ulcer-carcinoma would not be based on the endoscopical picture alone.

As yet, there are no statistically significant differences between the number of cancer cases in stomachs with ulcers (5/ 171) and stomachs without ulcers(2/ 98). The author's opinion is that further knowledge should be obtained on the life history and biological behaviour of superficial flat type mucosal carcinoma or carcinoma

in situ, before coming to a conclusion on the problem of ulcer cancer.

With regard to the malignant changes in benign gastric polyps, we followed 35 out of 178 cases over a period of six months. One case of polypoid carcinoma was found three years after the first endoscopy. However, we cannot deny the possibility that this observation was evidence of the growth of a protruded type of carcinoma itself, from the very beginning. For the criteria of polyp-cancer one usually needs the presence of a spring-like elevation of muscularis mucosae, of localized distribution of carcinoma at the polyp, and of surviving pyloric glands. By studying 78 cases of polypoid lesions histologically, we observed in only one case a significant focal, atypical epithelium at the polyp, in combination with the other two criteria mentioned above.

Concluding from endoscopical follow-up studies, it is still difficult to postulate a malignant change of benign gastric polyps.

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Indications for the Various Methods of Examination. Clinical Context and Mass Surveys

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CLINICAL CONTEXT

In the clinical context, the first examination to be done should be radiology. If adequately done it rarely fails to detect any lesion present. Moreover, it has a good accuracy in predicting the exact nature of the lesion. However, there remains a relatively large number of lesions which are either over- or underdiagnosed as cancer by radiology. The most difficult are polypoid lesions between 2 and 4 cm in their largest diameter, the ulcer-cancers, antral mucosal lesions, and the previously operated stomach.

Endoscopic visualization. The preceding roentgenographic study facilitates both the planning of the procedure and the interpretation of the endoscopic findings. In addition to further delineation of the nature of lesions already detected by radiology, endoscopic visualization will detect a few lesions missed by radiology, especially small ones near the cardia or diffuse mucosal lesions. Another valuable indication for endoscopy is the follow-up of ulcerated lesions. The experience of Dr. SAKITA from Tokyo (1971) is particularly pertinent, and his study of the life-cycle of benign and malignant ulcers is very important.

Endoscopic cytology and biopsy. Diagnostic cytology followed by biopsy, should be done in every lesion visualized by endoscopy, no matter how benign they look. In a review of our experience (KOBAYASHI, PROLLA et al. 1970), almost 15% of upper digestive tract cancers were considered benign at the first radiological or endoscopic examination. If no adequate (and I mean excellent!) material is obtained in the first attempt, endoscopy should be repeated immediately for another collection of either cytological or biopsy material, or both.

Blind cytology. This technique should be reserved for the occasional patient who has contraindications for endoscopy or could not tolerate this procedure. A second indication is the lesion at the cardia, even if the preceding endoscopic cytology and biopsy were both negative. A third indication is the infiltrative lesion which is negative by using aimed techniques, especially if lymphoma is suspected.

Blind suction biopsy. It should be used in linitis plastica type of lesion, if all preceding techniques were negative.

Therapeutic test. Considering the progress in radiological techniques and in endoscopic visualization, coupled with the combined use of cytology and biopsy under direct vision, we feel that there is no longer a place or need for the so-called

therapeutic test. It is also clear now that routine radiology is an inadequate method of assessing ulcer healing rates. Again, the work of SAKITA (1971) shows the danger of taking less than total and durable healing as evidence that an ulcer is benign. If all techniques, namely radiology, endoscopic visualization, cytology and biopsy, are performed with meticulous care and are repeated if any doubt persists, we should like to maintain that there will be not one case of gastric carcinoma undetected. The very exceptional case where all methods have failed, will only prove that the possibility of human error is unavoidable at all times and in all circumstances. However, this is not the time for making repeated (and in my opinion quite unnecessary) roentgenographic studies after 4 or 6 weeks of medical treatment of an ulcer, because the solution of this problem lies elsewhere.

MASS SURVEYS

In countries where the incidence and death rate of gastric carcinoma is high, as is the case in Japan or Germany, the organization of mass surveys should be considered. As we all know, Japan has already started to do this. As we shall hear later on in this symposium, there are several very important preliminary points to discuss before deciding which technique should be used. I, personally, feel that a pilot study of about 10.000 cases should decide between cytology and gastrocamera examinations. Photofluorographic mass surveys are probably limited by the excessive number of false-positives or suspicious cases, and the possible genetic hazard of radiation should be completely excluded.

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Problems of and Recommendations for Organizing Early Stomach Cancer Diagnosis in Hospitals, Out-Patient Clinics, Doctor's Offices and in Mass Screening

Gastroenterological Welfare Centre and Early Gastric Cancer in Hungary

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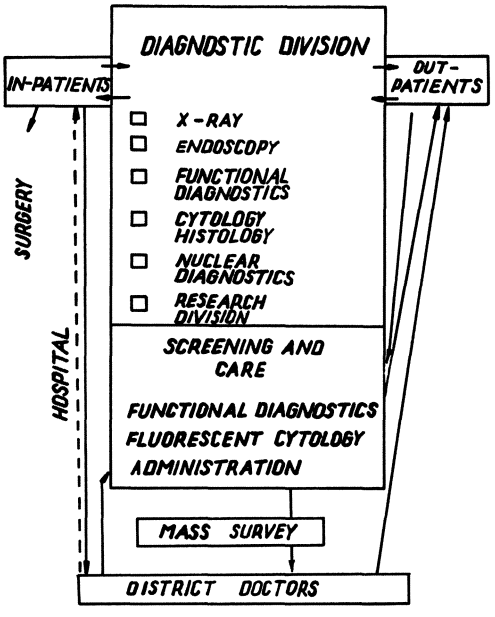
For the last few decades oncological screening tests have been receiving an increasing recognition in the Hungarian preventive health organization. With respect to this program as a whole, gastrointestinal disease as such has somewhat fallen back, not only in our country but throughout the world. This is due to the fact that financial and personal conditions of screening were limited or restrained.

In Hungary, cancer of the stomach occurs more frequently than cancer of other organs, although certain data indicate that mortality of stomach cancer has decreased over the past 30 years, or at least, remained the same. However, such gradual diminution is almost negligible, compared to the statistical figures of other countries. We are threatened by the sad outlook that in the near future, we shall come near or even overtake the countries actually leading in mortality statistics of gastric cancer. This prevalence of gastric cancer requires that this question be considered with special attention. The organization of complex mass surveys and gastroenterological centres is essential, because successful therapy will be possible only after recognition of early symptoms or lesions, timely diagnosis and immediate operation. In our hospital we have been trying to organize a complex screening centre since 1965. Fig. 1. shows the set-up of the welfare centre.



Three main problems emerged in the course of this work:

1. The correct definition, detection and follow-up of precancerous conditions of the stomach, in particular of gastric atrophy and intestinal metaplasia.
2. The selection of a simple and relatively inexpensive mass screening method for gastric cancer.
3. An increase in the detection of early cancer cases by means of complex check-up methods including X-ray, endoscopy, cytology, functional examinations.

The Clinical Significance of Precursory Stages of Gastric Cancer

Data published in many medical papers all over the world lead us to believe that gastric carcinogenesis is a process which may pass the following phases: normal mucosa - atrophic gastritis and intestinal metaplasia - early gastric cancer.

Gastric atrophy and intestinalization are common properties of clinical conditions that may be considered as precancerosis. The pre-neoplastic role of gastric polyps and gastric ulcers is well known for quite a long time, while the exact relationship between atrophic gastritis, intestinalization and cancerogenesis has not yet been clarified. Such a hypothesis may be supported by the high incidence of atrophic gastritis and intestinal metaplasia in countries with high gastric cancer mortality, and by the close topographical relation between gastric adenocarcinoma and the lesions mentioned above.

Since it would be rather difficult to take up mass biopsy studies in order to determine the correct ratio of gastric atrophy and intestinal metaplasia, we tried to invent other methods for detecting these lesions without the use of histology. After preliminary histochemical and cytochemical studies, the levels of some non-proteolytical enzymes were estimated in the gastric juice. The results of the enzyme-determinations were compared with the histological picture. The lactic acid de-hydrogenase (LDH) was asseyed in accordance with WROBLEWSKI's method modified by us. After the patient had fasted overnight, an intragastric tube was inserted and its position was monitored by fluoroscopy. After suction of the fasting secrets, the stomach was washed twice with 1,15 M, pH 7,5 Sörensen buffer. Samples contaminated with bile, saliva or blood were not exmined. The pyruvic acid / lactic acid reaction was measured on 366nm (WROBLEWSKI). The results of these tests are illustrated schematically in Fig. 2.

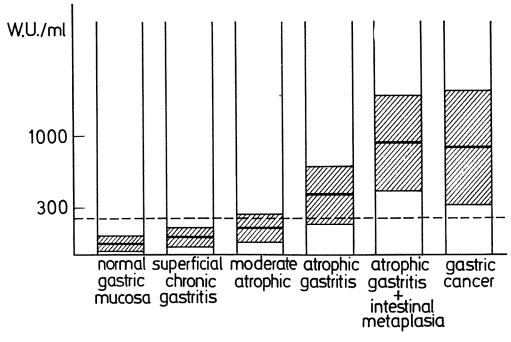


Fig. 2. Lactic acid dehydrogenase total activity of gastric juice in chronic gastritis and gastric cancer. (Mean ± SD)

It is obvious that, with exception of gastric cancer cases, the LDH total activity of gastric juice rises in parallel to the severity of gastric glandular atrophy. The increase is most marked in cases where histological examination has also revealed intestinal metaplasia. In our experience, atrophic gastritis and intestinal metaplasia could be taken as an indication for risk of gastric carcinoma. Patients with atrophic gastritis and intestinalization are screened out by the funtional method previously mentioned and - of course - by means of the so-called complex examinations", a combined clinical check-up. (Table 1.)

Table 1. The combined clinical check-up

1. X-ray examination
2. Gastroscopy
3. Gastric biopsy
4. Gastric cytology
5. LDH determination in the gastric juice
6. B-glucuronidase determination in the gastric juice
7. Complementary examinations

These clinical conditions - i.e. gastric polyp, gastric ulcer, atrophic gastritis and intestinal metaplasia - are considered to be the precursory stages of gastric carcinoma (Table 2), and patients with these lesions belong to the so-called "high risk" group.

Table 2. The possible precursory stages and diagnostic possibilities of gastric cancer

Precursory stages :	Diagnostic:
Chronic atrophic gastritis and/or intestinal metaplasia	Histology Functional diagnostics
Gastric polyp	X-ray
Gastric ulcer	Endoscopy Histology
Pernicious anemia	Hematology Histology
Others: Conditions after gastric surgery familial disease	Combined clinical check-up

The members of this group are kept under permanent surveillance and monitoring. In the course of this care, the clinical examinations mentioned above are completed by performing gastric cytology.

The different categories of diagnosis as found in the controlled population are shown in Table 3.

Table 3. The different categories of "high risk groups"

Causes	Male	Female	Total
Chronic atrophic gastritis + intestinal metaplasia	188	102	290
Group I and Pap. III-IV cytological findings	22	4	31
Pernicious anemia	2	2	4
Gastric polyp	11	8	19
Gastric polyp and Pap. III-IV cytological findings	1	0	1
Gastric ulcer	146	61	207
Pap. III-IV cytological findings without lesions that could be localised	39	32	71
Other causes	9	10	19
Total	418	224	642

In the last two years, six gastric cancer cases were detected in this group, five of which were in the early stages. The detailed data of these cases are illustrated in Table 4 (opposite page).

The possibilities of gastric cancer mass survey in Hungary

From a scientific point of view, the early detection of gastric cancer is one of the most important tasks to be faced by the medical profession as well as by the welfare organizations. Attempts have been made to solve this problem, but in Europe there is, as yet, no substantial advance in this field. The photofluorography and gastrocamera screening methods in systematic gastric mass surveys widely used in japan, are hardly conceivable under European conditions. Moreover, it has to be noted that (according to data of the Japanese National Society of Gastric Mass Survey) the percentage of subjects selected for closer examination after "direct" photofluorography screening, was 15, 2 to 18, 7 % of the material screened in 1969.

Our choice among the various methods of "direct" gastric cancer screening was for X-ray examination and exfoliative gastric cytology. Mass examinations with the help of roentgenology exclusively, seem to be less favourable with regard to financial considerations. In the course of our routine clinical examinations, six standard X-ray expositions are made by screening out-patients who are over 35. The classification published by the Japanese Endoscopical Society is used for evaluating and classifying the X-ray pictures.

Table 5 shows the diagnostic possibilities of gastric carcinoma in different stages. The value of X-ray examination should be emphasized in the stages II and III.

Table 4. Gastric cancer cases in the "high risk group" (1968-1971)

Case	age	sex	type of carcinoma	possible precancerosis	welfare cause	time	operation
1.	36	m	early, IIc	chron. gastrit.	chronic gastritis	1/2 y.	without metastases
2.	65	m	early, IIc	chron. gastrit.	chronic gastritis	3 years	without metastases
3.	65	f	early, IIb	chron. gastrit.	P. V, cytol. findings	1,5 yrs.	without metastases
4.	67	m	early, Ul. IIc + III	gastr. ulcer	gastric ulcer	7 years	without metastases
5.	62	m	early, IIa	chron. gastrit.	chron. gastrit. P. IV cyt. find.	2 years	without metastases
6.	56	m	small	gastr. ulcer	gastric ulcer	2 years	metastases in glands of lesser curvature

37 early gastric cancer cases were detected over the last few years. The results of different examination methods are presented on Fig. 3.

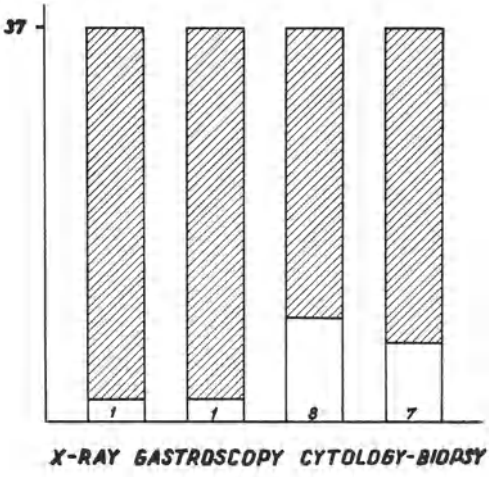


Fig. 3. ☐ negative; ▨ positive

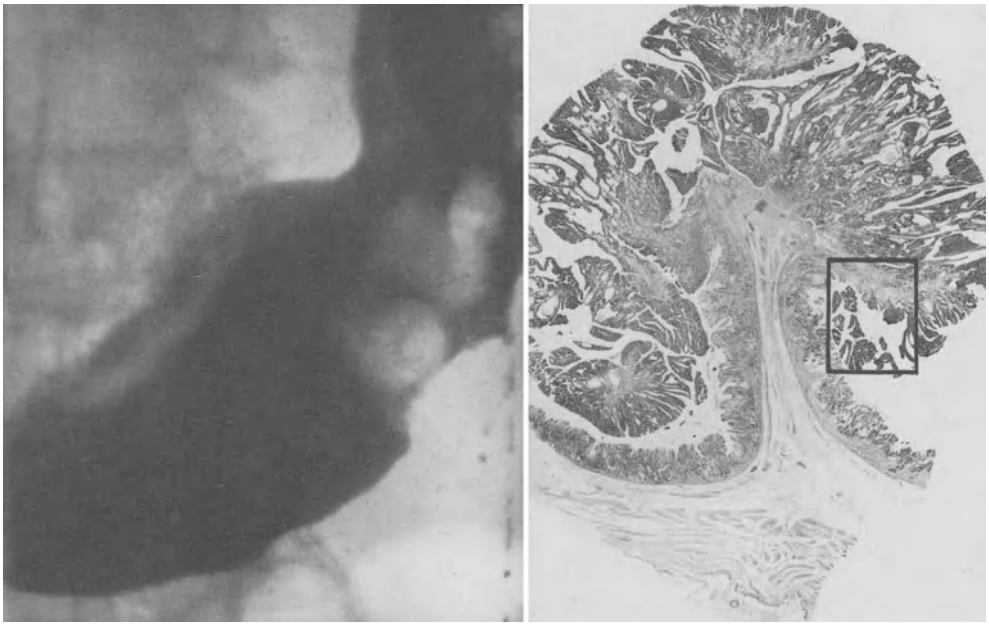


Fig. 4 a and b. Protruded type (I). Three gastric polyps are visible histological examination revealed early malignancy in one of them

The Figures 4 - 9 (following pages) demonstrate the specific X-ray findings of the five main types of early gastric carcinoma.

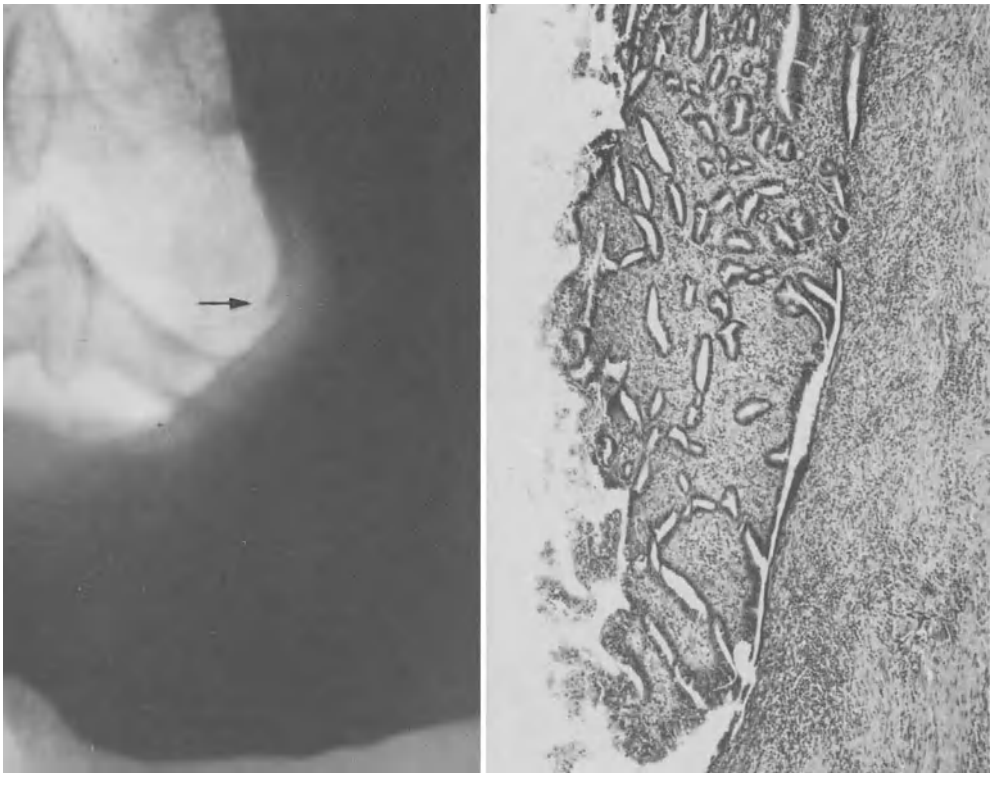
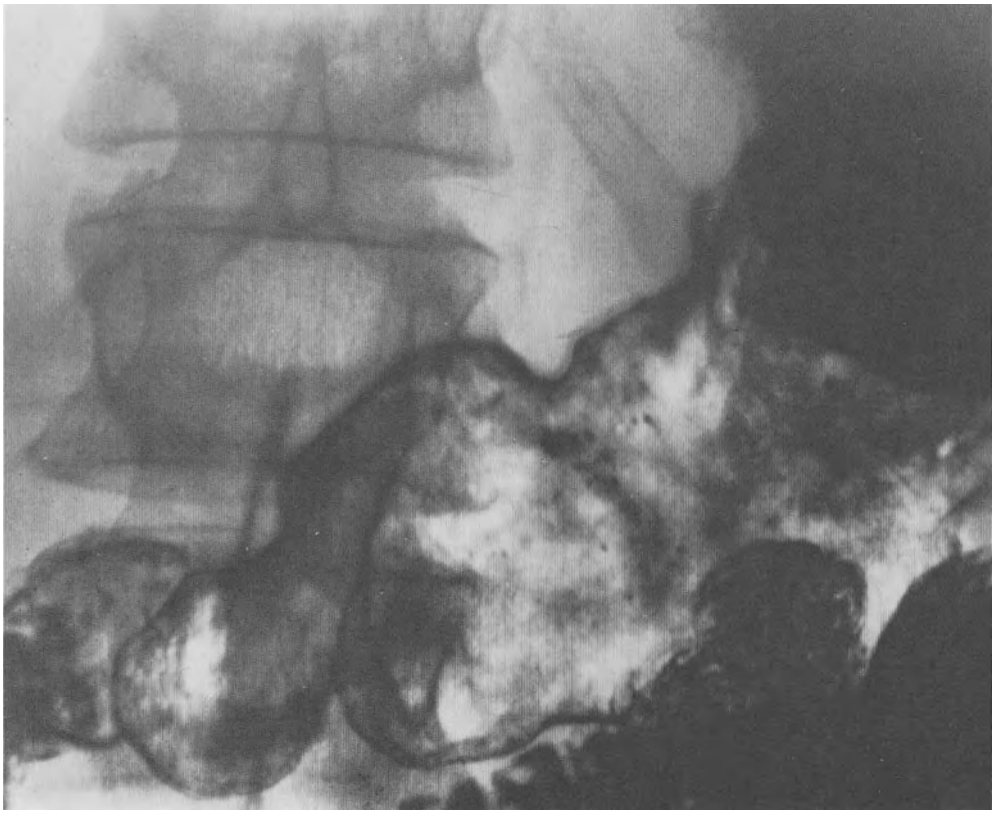


Fig. 5 a + b. Superficial "elevated" type (IIa). In the marked area a shallow depression can be seen plus a little filling. b=microscopic picture of early cancer

Table 5. Diagnostic possibilities of gastric carcinoma in different stages

Classification:	Diagnostic possibility:
First stage: microscopic cancer	Histology? functional methods?
Second stage: early cancer	X-ray)
I Protruded type	Endoscopy)
IIa Elevated type	Biopsy) Combined check-up
IIb Flat type	Cytology)
IIc Depressed type	Functional diagn.)
III Excavated types	)
Third stage: "Small cancer"	Combined check-up
1. 2 cm diameter 2. 2-4 cm diameter	Clinical symptoms
Fourth stage: Advanced ca. (Borrmann)	
Types I - IV	Clinical symptoms



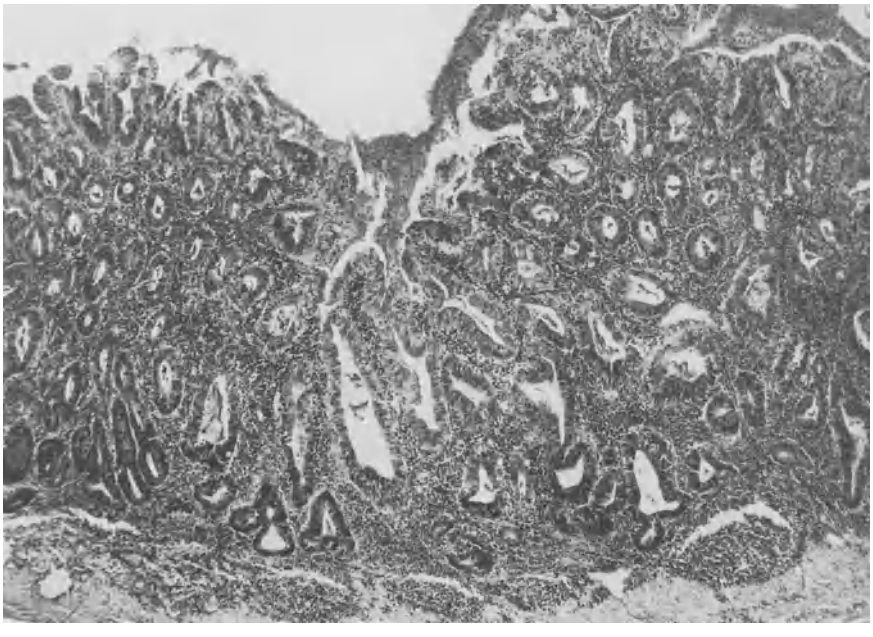


Fig. 6 a and b. "Flat" type (IIb). The patient was kept under observation for atrophic gastritis. On the lesser curvature of the antral canal a rigid area is visible, 0, 7 in diameter

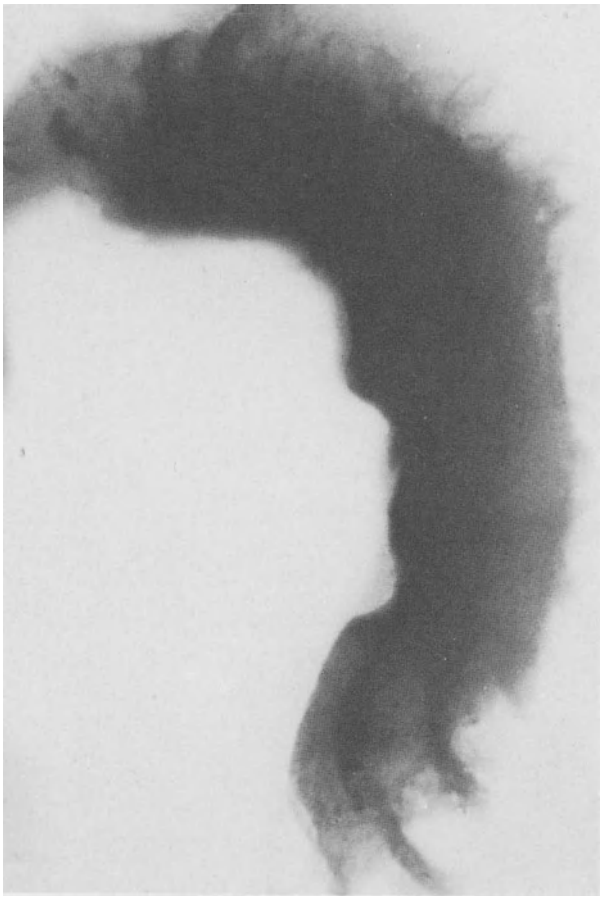


Fig. 7, a

Table 6. Age and sex of the population who reported for screening. No. of patients called: 2170, no of patients examined: 1534 (70, 6%)

	- 30	31-40	41-50	51-60	61-70	70+	missed exam.	total
Female	16	145	244	231	204	16	2	858
Male	10	117	188	176	164	18	3	676
Total	26	262	432	407	368	34	5 (o, 32%)	1534

SUMMARY

X-ray examination and gastric cytology are, in our opinion, very useful and valuable as first steps in selecting a "high risk group" of out-patients over 35 years. Under our present conditions, "indirect" screening methods seem more useful for the mass survey of a whole population. A characteristic of the method we call the "indirect" gastric cancer mass survey is that the tests are not made with the aim

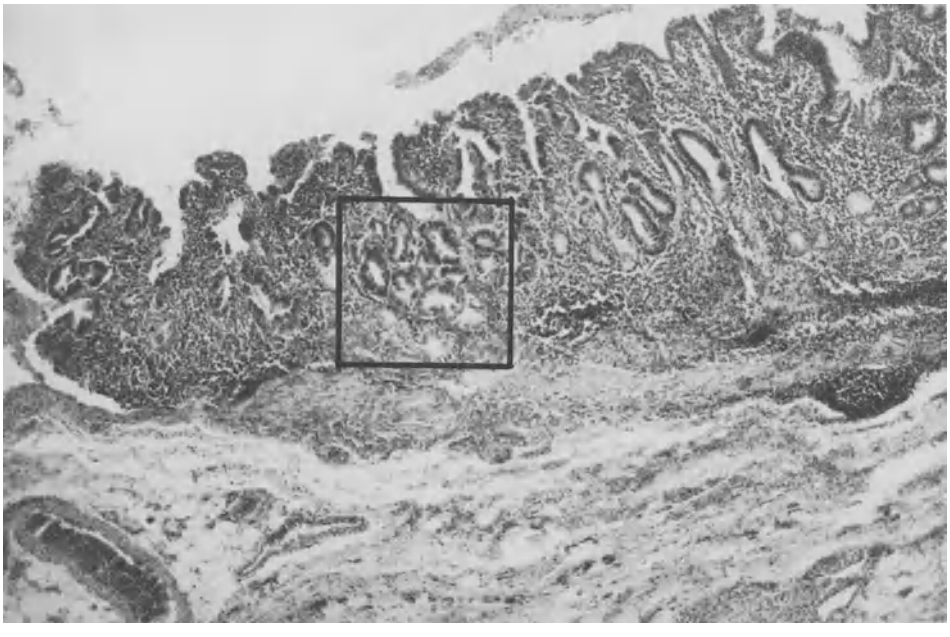


Fig. 7 a and b. Depressed type (IIc). Histologically verified type of early cancer

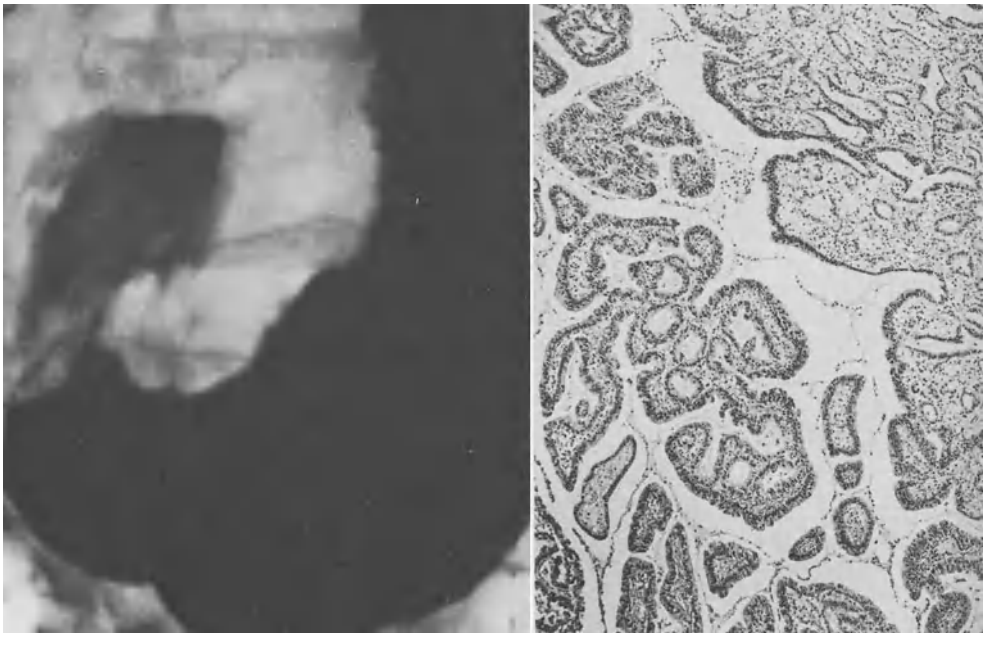


Fig. 8 a and b. "Excavated" type (III). Histologically verified type of early cancer

Table 7. Clinical diagnosis is established in 289 cases subjected to further study

Diagnosis	Male	Female	Total	% of screened people
Gastric cancer	4	3	7	0,456%
Gastric polyp	1	3	4	0,29 %
Gastric ulcer	13	9	22	1,43 %
Duodenal ulcer	17	14	31	2,02 %
Hiatal hernia	20	26	46	2,99 %
Chronic gastritis (histolog. proved)	61	93	154	10,03 %
Without gastr. disease	6	14	20	1,30 %
Total	122	162	284	18,40 %

of primarily detecting carcinomas of the stomach, but that a high risk group is selected containing patients with gastric cancer and individuals particularly prone to developing such carcinomas.

The laboratory method utilized in the selection has for the first time been employed for this purpose. At present, there is no method known that would screen out all conditions supposed to be possible precursors of gastric cancer. Other attempts for selecting high risk groups have been made by using, e.g., histamine gastric analysis, or the estimation of the uropepsine level. The results of our previous investigations indicated that when a high risk group is picked out by the determination of the lactate dehydrogenase (LDH) total activity of the gastric juice, this group would contain, besides cancer patients, also individuals with atrophic gastritis or intestinal metaplasia, prone to developing stomach carcinoma.

Of the 2.170 individuals summoned to the examination, 1.534 (70,6%) reported for the screening. These people were representative of the whole population. In five cases the intragastric tube could not be inserted because the subjects refused to co-operate.

On the basis of the criteria outlined above, 289 individuals (18,4% of the people examined) were called upon to report for a further examination.

The primary aim of the mass survey was considered to be the identification of patients with carcinoma of the stomach. The incidence of this disease was extremely high in our material: 7 cancer cases (= 4,56 0/oo of screened material), including 3 cases in the advanced stage. Early gastric cancer was detected in three patients.

The results of the examination of patients with gastric cancer are shown in Table 8. However, it has to be emphasized that, as shown by our first four cases, freedom from complaints or symptoms will not completely rule out the presence of carcinoma. The histological picture of one of our three early cancer cases is shown in Fig. 9.

On the other hand, a "high risk group" of patients with precancerous conditions was selected. The age distribution of this group is shown in Table 9. The determination of LDH total activity of gastric juice gives useful information not only about the secretory capacity of the gastric mucosa, but also about a possible presence of gastric atrophy, intestinalization and, in particular, of gastric carcinoma. Patients with gastric cancer are not identified directly by this method; consequently,

Table 8. Data of the cases of stomach cancer detected in the course of the screening study (7 patients = 4,56 0/oo)

Case	sex	age	anam-nesis	LDH /WU/	BAO	MAO	cytology	occult bleeding	histologic type of ca.	type of early ca.	possible precursor	metastases
1.	m	46	+	980	1,2	8,2	P.IV	+	adenocc.	Ul. III IIc + III	chronic gastritis	–
2.	w	54	–	1600	0,6´	4,3	P.III	+	adenocc.	IIb	chronic gastritis	–
3.	m	58	–	1950	0,0	0,0	P.IV	+	adenocc.	IIb	chronic gastritis	–
4.	m	69	–	1140	0,0	0,0	P.V	+	adenocc.	–	?	–
5.	m	70	+	840	0,0	0,0	P.V	+	adenocc.	–	?	+
6.	w	72	+	2200	0,0	0,0	P.V	+	adenocc.	–	?	+
7.	m	74	+	1400	0,0	0,2	P.V	+	adenocc.	–	?	+

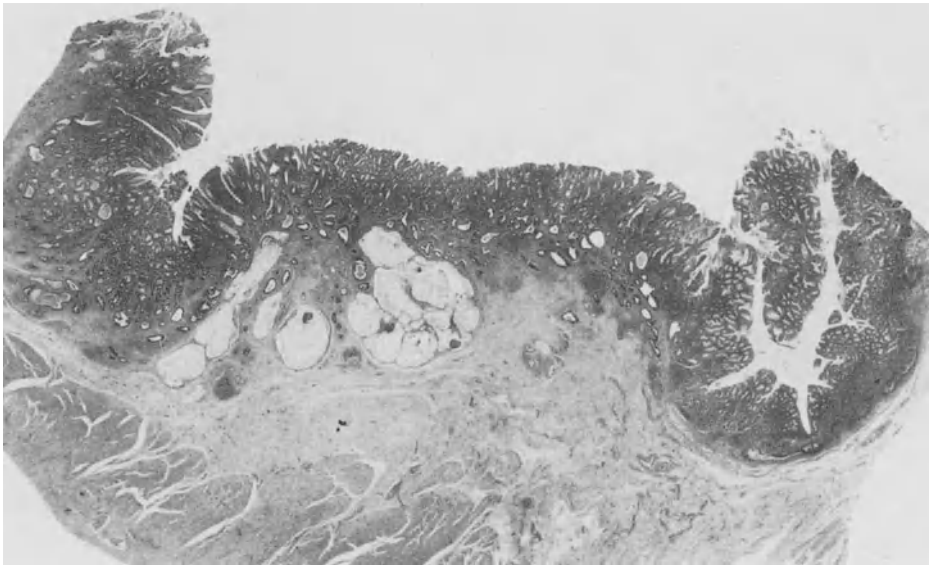


Fig. 9. Histological picture of early cancer

its efficiency seems to be much less than that of gastro-photofluorography or of gastroscopic mass survey. Nevertheless, we feel that it has a practical value in clinical gastroenterology : the actually positive cancer cases are more easily detected in this group of patients, and can be narrowed down by means of the LDH determination. On the other hand, the organization of prophylactic care can be based on the high risk group which is recognized simultaneously with the screening for cancer.

A gastrocamera mass survey (Olympus GTF-PF) shall be performed in the near future. In the course of this study we shall try to compare the effectiveness of the gastrocamera with that of our functional method for mass surveys.

Table 9. The results of histological examinations of gastric mucosal specimens in patients with increased LDH activity (229 cases, 14, 9%)

Histological diagnosis	Female	Male	Total
Gastric cancer	3	4	7
Gastric polyp with atrophic gastritis	3	1	4
Gastric ulcer with atrophic gastritis	9	13	22
Superficial chronic gastritis	1	3	4
Moderate atrophic gastritis	49	32	81
Atrophic gastritis and intestinal metaplasia	53	58	111
Total	118	111	229

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Problems Concerning Gastric Mass Surveys

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In Japan, gastric cancer has the highest mortality of all the malignant tumors, for both male and female patients. Early discovery and surgical treatment have been considered the most reliable ways of controlling such malignant tumors. The mass survey system has proved very valuable for detecting early gastric cancer in its asymptomatic stages, whereas symptomatic patients are generally diagnosed in outpatient clinics. In any case, gastric mass surveys must meet several requirements:

1. Safety, 2. inexpensiveness, 3. mobility, 4. low risk of false positives, 5. no false negatives in diagnosis.

With regard to these criteria the most promising method seems to be the indirect radiological examination which has been tested in Japan. Five X-ray films are usually taken during the screening (Table 1) and then analysed by three or more doctors. According to the films, one group of patients requiring only a normal examination is separated from the second group who needs a precise and detailed examination. Moreover, the gastric mass survey system itself is divided into two groups, one comprising the local residents of an area, the other a more limited occupational group.

Table 1. Order and positions for exposure in gastric mass survey

1.	Mucosal relief pattern in prone position
2.	Barium filled stomach in prone position
3.	Double contrast radiograph in supine position
4.	Barium filled stomach in standing front position
5.	Barium filled stomach in standing right oblique position

Implementation of gastric mass survey programs was successful; th proportion of early gastric cancer among the cancer cases detected was very high (over 40%) in both groups, field work as well as occupational work (Table 2). The persentage of early gastric cancer detected by gastric mass surveys, is much more encouraging than results obtained in hospital outpatient clinics (15 - 30%). Since the diagnostical techniques used in our surveys did not differ from those employed in outpatient clinics, the difference in early gastric cancer discovery rates is obviously due to the different types of patients participating in gastric mass surveys or in routine check-ups in outpatient clinics.

Table 2. Rates of early gastric cancer detected by gastric mass survey

	No.	Ca.	Early Ca.
Field work	14.049	47 (0,33%)	21 /47 (44,7%)
Occupational group	8.825	18 (0,20%)	9 /18 (50,0%)

In our survey of occupational groups, the incidence of early gastric cancer in proportion to advanced cancer is at its highest during the period of the first X-ray examination. It decreases continually in the course of our follow-up studies (Table 3 and Fig. 1)

Table 3. Detection of early gastric cancer by gastric mass survey

	Early Ca.	Adv. Ca.	Total
Detected by first examination	6	10	16
Detected by repeated examination	11	6	17
Total	17	16	33

Examinations of occupational groups have been carried out since 1962; up to the present, th mortality statistics for gastric cancer have been decreasing. Judging from this prototype mass surveys, we may say that the discovery of gastric cancer in its early stages (apart from infiltrating carcinoma) is possible if gastric mass surveys are carried out regularly.

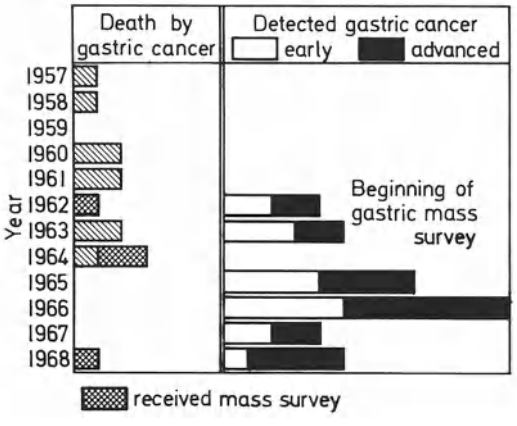

Fig. 1. Death by gastric cancer, and detection of gastric cancer by mass survey

Some problems, however, are yet to be solved: 1) In order to discover an early gastric cancer by means of the gastric mass survey, attention must be paid to very minute abnormal findings in X-rays; as a result of this difficulty 21% of the patients screened have to be re-examined (Fig. 2). 2) The detailed examination carried out after the check-up is very expensive and requires skilled doctors and nurses. The number of mass survey participants needing detailed and precise examination after the general check-up is rather high: approximately 90% of the occupational group,

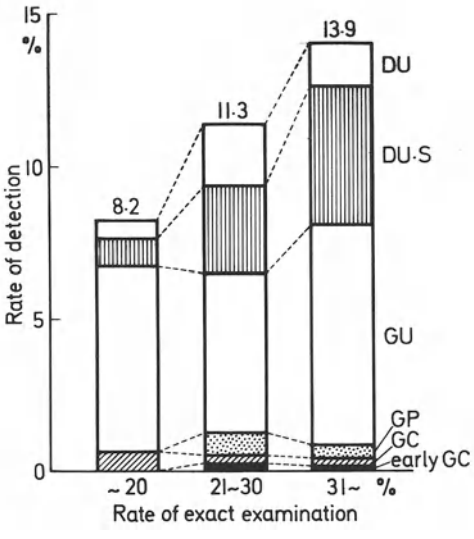

Fig. 2. Rate of exact examinations of lesions

somewhat less in the field work group (70%); in cities it is always lower than in the country. However, such precise intensive clinical examinations are most important for the success of gastric mass surveys; they are the backbone of the program. The consequence of this: the lower the number of precise follow-up examinations performed, the less significant the gastric mass survey itself.

Finally we have given some thought to the problem of making gastric mass surveys more effective. Close cooperation between doctors, administrative bodies and participants is highly important. If we do not impress the value of mass surveys upon the mind of prospective participants, they are apt to settle for just one examination in a lifetime and forget how important it is to have their regular check-ups.

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The Organisation of Mass Surveys for Gastric Carcinoma

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In a recently published book (PROLLA, KIRSNER, 1972), we discussed in detail the Japanese experience with mass surveys for gastric carcinoma. Our conclusions were somewhat negative, in the sense that we felt the emphasis made on photofluorography to be erroneous: the false-positive cases were too frequent, and the possible hazard of radiation, especially genetic, appears to be significant. We suggested a pilot study comparing exfoliative cytology by blind washings and the gastrocamera examination.

We also pointed out the need for careful study, and compared the so-called "Fourteen Step Project for Cervical Cancer Screening Projects", as analysed by WIED (1965). Step One is the most important because all the others depend on it. This step is concerned with the necessary planning involved in the development of a comprehensive program for the control of gastric carcinoma in a benificiary population. It involves the obtaining of information required for planning, the assessment of resources of personnel and facilities, and the establishment of objectives, including an outline of program operations. The greatest hazard in the preparation of such a plan is to omit those specialties or groups essential for the total process of controlling cancer of the stomach in a population.

Typical questions the planners should ask themselves are as follows:

a) What is known about the population as far as the incidence and the death rate of stomach carcinoma is concerned, as it occurred within the past several years or decades?
b) What has been done in the past about control of carcinoma of the stomach and how efficient were those programs?
c) Are those rates (incidence and death) high enough to justify such mass surveys?
d) Will the yield be large enough to keep the cost per case reasonably low?
e) Is cytology the best mass survey method? How does it compare with photofluorography and/or gastrocamera? What are the prospects of some immunological tests being developed? What would be the average cost per case of cytological surveys, of radiological surveys, or of endoscopic surveys? What is the ratio of "true positives/false positives" when applying these methods? How do they influence the t r u e cost in money and hospital time in the case finding?
f) Are public health nurses and social workers available for such a program?
g) Are sufficient well trained cytotechnologists, endoscopists or radiologists available in the community or the hospital, and how many are there?
h) If not, how can they be trained? Is there a school of cytotechnology in the community, in the state or province, in the country?

i) Are there hospital and clinic facilities for endoscopy, for X-rays, for surgery, for hospitalization?
j) What is known about the beneficiary population? What population was served by total facilities during the past year or years?
k) Who is responsible for informing the population?
l) Are there high risk target groups in the population?
m) What funds are needed and are available for this program?
n) Are there additional funds, such as insurance programs or social security benefits?
o) Is it a part of the objective to develop the program as a demonstration or training for the province or state, or the nation?

All these and certainly many other questions should be carefully studied by the planners of a mass survey. A beneficiary program can fail if, for example, the frequency of examinations exceeds the capacity of the other steps, and if low risk groups are examined too frequently or examined at all. It should also be kept in mind that a single cytological, or for that matter, any other kind of test, will provide only limited protection for a certain period of time if future routine checks are not carried out.

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Discussion by Invitation

Problems and Recommendations for Organizing Early Stomach Cancer Diagnosis in Hospitals, Out-Patient Clinics, Doctor's Offices and in Mass Screening

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In hospitals and outpatient clinics endoscopy with complementary aimed biopsy and cytology and better X-ray examinations including double contrast techniques, should be the routine practice today in the management of suspected cases. For mass screening in Western countries, however, we propose as a possibility, a model which was applied to our pilot study, that is the selection of a high risk group of individuals on the basis of:

a) Past family or personal history data indicating a higher susceptibility to gastric cancer;
b) suspicious symptoms or abnormal physical findings;
c) a degree of chronic gastritis.

Following our model (Fig. 2) this can be achieved by cheap and simple techniques (general physical examination, gastric secretion studies and abrasive blind gastric cytology). The expences for such an approach are quite acceptable (Fig. 1), especially if the whole procedure is carried out as part of a multiphasic health screening program.

Incidence of secretory deficiency in general population over 45	Incidence of cytologicyl grading 3-4 in general population over 45
22%	4%

Cost (material and personnel) per case

2 US Dollar

Incidence of severe atrophic gastritis in general population over 45

2%

Expected gastric cancer cases on the group of 12.500 examinations per year, for a ten year follow-up	Calculated cost for one case of gastric cancer detected by screening in a ten year follow-up
25 (= 200 cases per 100.000 pop.)	10.000 US Dollar

Fig. 1 Financial background and perspectives of the screening project on gastric cancer(maximum screening potentially: 12 500 persons/year)

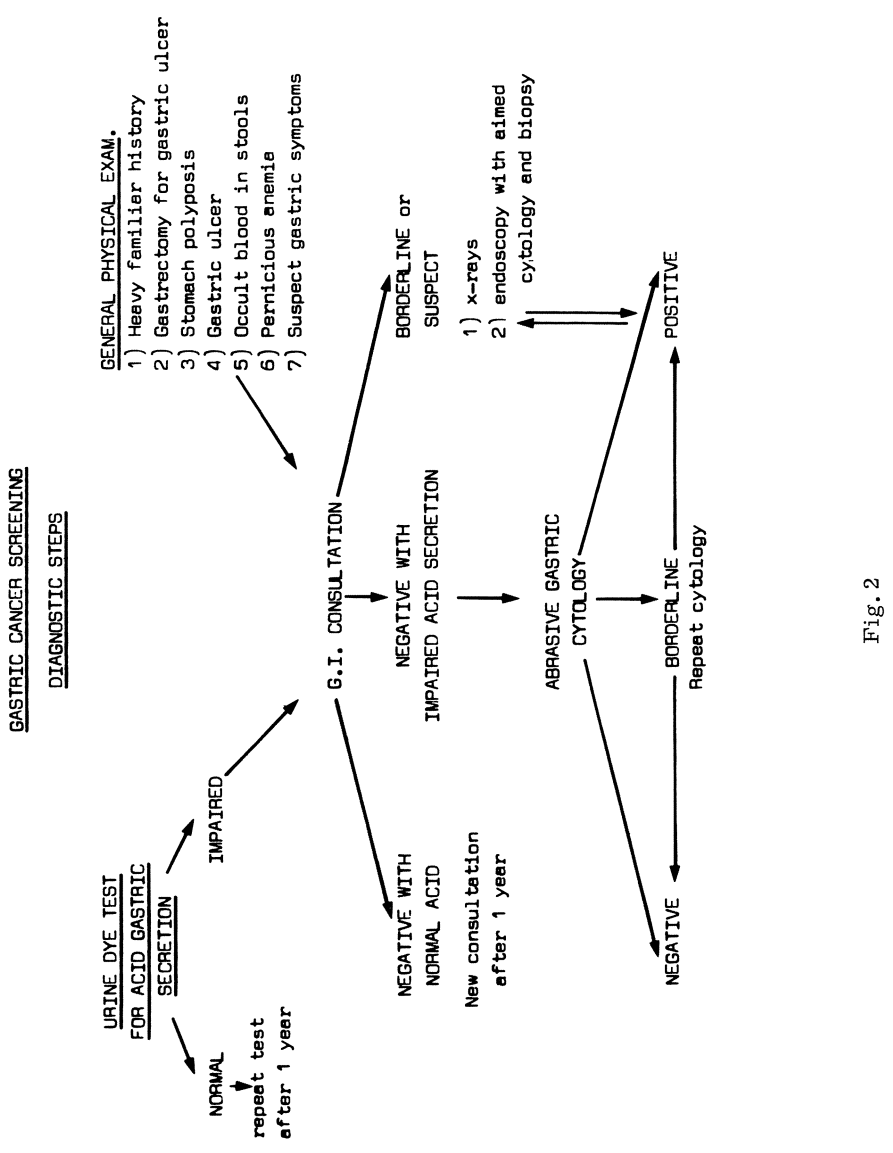

Fig. 2

To the specialized agencies of each country (leagues for fighting against cancer, etc.) must be delegated the task of informing medical practitioners of the facilities available for highly specialized diagnostic management, and of the results achievable by such methods with respect to a true diagnosis in the earliest phases of gastric malignancies.

Report on a Final Round Table Discussion of all Participants (Recommendations for Future Activities)

All participants were asked to discuss three main problems:

1. How to get a more systematic and effective diagnosis of stomach cancer?
2. How to promote earlier diagnosis of stomach cancer?
3. Which problems should be tackled first in order to ensure stomach cancer diagnosis early enough for therapy?

Concerning problem 1) there was a general feeling that steps should be taken for systematic improvement of clinical and patho-histological terminology. Recommendations should be given to all European endoscopy centres for adapting the Japanese scale of endoscopic diagnoses. Furthermore, European histo-pathologists should get together and work out clear definitions of early and advanced cancer. Prof. Gedigk, Bonn, was asked to organize such workshops as soon as possible and has agreed to do so. The participants agreed that pushing for a generally adopted terminology would be most beneficial for comparison of the results from different centres. In addition, attempts should be made to establish an equivalence scale between cytology and histology. This would be most helpful to the clinician and allow a better understanding of cytological results.

Concerning problems 2) and 3) it was agrred that the time has not yet come for organizing mass screening programs in Europe on a non-selected population (field work according to Kawai). However, encouragement should be given to any project investigating early gastric cancer diagnoses in high risk groups.

First attempts made at present in this direction may be evaluated in another symposium on the same subject to be held within 3 or 4 years, once more under the patronage of the "Gesellschaft zur Bekämpfung der Krebskrankheiten Nordrhein-Westfalen."

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