Reviews of

86 Physiology, Biochemistry and Pharmacology

With 44 Figures

Springer-Verlag
Berlin Heidelberg New York 1979

Reviews of Physiology, Biochemistry and Pharmacology

formerly
Ergebnisse der Physiologie, biologischen Chemie und experimentellen Pharmakologie

ISBN 3-540-09488-1 Springer-Verlag Berlin Heidelberg New York
ISBN 0-387-09488-1 Springer-Verlag New York Heidelberg Berlin

Library of Congress-Catalog-Card Number 74-3674

Offsetprinting and Binding: Konrad Triltsch, Würzburg
2121/3130-543210

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Rev. Physiol. Biochem. Pharmacol., Vol. 86

Role of Cardiac Vagal C-Fibers in Cardiovascular Control

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Contents

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I. Introduction

A. Objective of the Present Review

The main purpose of this review is to describe the functional characteristics, the reflex effects, and the pathophysiologic implications of the cardiac vagal C-fiber endings. A common view of Bezold-Jarisch reflex, as expressed by, e.g., *Mountcastle* (1974), is that it is a pharmacologic curiosity that takes no part in normal cardiovascular control. In contrast, evidence is presented in this review that the reflex effects elicited from cardiac C-fibers (i.e., the Bezold-Jarisch reflex) might be of importance both for normal cardiovascular control and for the cardiovascular control during several common pathophysiologic conditions such as fainting, aortic stenosis, myocardial infarction, and asphyxia.

The receptor characteristics and the possible reflex effects of cardiac receptors with medullated vagal afferents (*Linden,* 1975, 1976) and with sympathetic afferents (*Malliani* et al., 1975; *Mancia* et al., 1976a) have been discussed in several recent reviews and will not be discussed here at any length.

B. Historic Landmarks

1. Bezold-Jarisch Reflex. The presence in the heart of receptors affecting the circulatory system was suggested more than 100 years ago by *von Bezold* and *Hirt* (1867). They observed that injections of veratrum alkaloids caused a decrease in blood pressure and bradycardia, which could be prevented by sectioning the vagus nerves. *Von Bezold* explained the vasodepressor action of veratrum alkaloids as due to stimulation of the sensory nerve endings in the heart. *Jarisch* 70 years later began a long series of experiments on the cardiovascular effects of veratrum alkaloids (*Jarisch* and *Richter,* 1939a, b) which yielded the following conclusions. The receptor area for the reflex was in the heart and not in the greater vessels. The reflexogenic zone in the heart was predominantly in the ventricles. The afferent pathway was in the vagus, and the efferent pathways involved both inhibition of the sympathetic outflow to the peripheral vessels and an increased activity in the vagus nerve to the heart. *Jarisch* was also able to show that several other substances could activate the reflex (*Jarisch,* 1949), which was called the Bezold-Jarisch reflex (*Krayer,* 1961). According to studies by *Dawes* (1947) the area most sensitive to veratrum alkaloids was in the left ventricle. For reviews about the Bezold-Jarisch reflex see *Krayer* and *Acheson* (1946), *Dawes* and *Comroe* (1954), and *Benforada* (1965).

2. Depressor Reflex from Cardiac Distension. Depressor reflexes from the heart, triggered by increased pressure in the different heart chambers, have also been subjected to several studies. *Daly* and *Verney* (1927) were the first to provide evidence that mechanoreceptors existed in the left ventricle. In an innervated heart-lung preparation, in which the aortic pressure was kept constant, an increased pressure in the left side of the heart caused cardiac slowing. Later *Aviado* et al. (1951) showed that a rise in perfusion pressure in the right heart also caused bradycardia and hypotension. The receptors concerned seemed to be located mainly in the right atrium and not in the right ventricle. The different reflex effects produced by increased pressure in the different cardiac chambers have been the subject of several excellent reviews (*Aviado* and *Schmidt,* 1955; *Heymans* and *Neil,* 1958).

3. Electrophysiologic Recordings of Cardiac Receptors. The demonstration of receptors in the heart was greatly facilitated when adequate techniques became available for recording action potentials in afferent fibers of the heart. The first receptors to be examined in detail were the medullated receptors situated at the junction of the great veins and the right

and left atria (*Paintal,* 1953, 1973a). Ventricular medullated endings were described later (*Paintal,* 1955).

The existence of nonmedullated fibers in the heart was first described by *Jarisch* and *Zotterman* (1948), who recorded from thin fibers, which, thought to be C-fibers, responded to mechanical stimulation and injections of veratrum alkaloids. They concluded that these receptors were the most important for triggering the Bezold-Jarisch Reflex, a finding also suggested by *Dawes* and *Widdicombe* (1953). Later *Coleridge* et al. (1964) and *Sleight* and *Widdicombe* (1965) confirmed the existence of receptors in the heart ventricles with nonmedullated afferents and showed that the receptors responded not only to drugs, e.g., veratrum alkaloids, but also to mechanical stimulation, e.g., aortic occlusion. The characteristics of this receptor group have been described in detail by *Öberg* and *Thorén* (1972b) and *Thorén* (1977).

The existence of nonmedullated fibers from the atria was first shown by *Coleridge* et al. (1973), and the functional characteristics of this receptor group were later studied in detail by *Thorén* (1976a).

II. Morphologic Considerations

A. Cardiac Vagal Branches

Histologic examination of the cardiac vagal branches in cats reveals that the majority of afferent fibers are included in the C-fiber group (*Jarisch* and *Zotterman,* 1948; *Agostini* et al., 1957). *Agostini* et al. claimed at the cardiac vagal branches in the cat contain about 2000–2500 afferent fibers and that about 75% or 1500–2000 of them are C-fibers. Also the great majority of the afferent fibers from the lungs are C-fibers.

B. Intracardiac Route of Vagal C-Fibers

The intracardiac route of left ventricular C-fibers was recently studied by *Thorén* (1977) in the cat. The afferent fibers from endings in the posterior surface of the heart pass along the posterior descending coronary artery into the right atrium to join the right main cardiac nerve; those from the anterolateral region pass behind the aorta and the pulmonary trunk. Most of the C-fibers seem to exit from the heart at the junction of superior caval vein and the right atrium in the main cardiac branch of the right vagus, which passes underneath the azygos vein (*Thorén,* 1977). The depressor effects of veratrum alkaloids are also mediated via the same vagal branch in the cat (*Jones,* 1953).

The intracardiac route of the Bezold-Jarisch reflex has also been studied in the dog (*Frink* and *James*, 1971). The afferent pathways seem to converge toward the left main coronary artery and then into the left vagus (*Dawes* and *Widdicombe*, 1953). Some cardiac C-fiber afferents in the rabbit enter the aortic nerves (*Kulaev*, 1963; *Thorén* and *Jones*, 1977).

C. Histology of Cardiac Receptors

Several different types of nerve endings have been described in the heart. *Nonidez* (1937) described a complex noncapsulated atrial ending with a medullated afferent fiber. Less is known about cardiac endings with afferent vagal C-fibers. However, the myocardium has a rich innervation of thin nerve fibers both in the pericardial, epicardial, interstitial, and perivascular tissues (*Khabarova*, 1963; *Hirsch* et al., 1964; *Hirsch*, 1970). No description of any specific nerve ending in the heart, however, can be associated with vagal C-fibers, although these endings may very well be part of this fine network of fibers.

III. Characteristics of Cardiopulmonary C-Fiber Endings

A. Atrial C-Fiber Endings

1. Characteristics in Open-Thorax Cats. The existence of atrial receptors with nonmedullated vagal afferents was first described by *Coleridge* et al. (1973) in dogs. More recently the functional characteristics of these atrial C-fibers have been studied in the cat (*Thorén*, 1976a). In contrast to the "classic" atrial receptors, located mainly at the vein-atrial junctions, the atrial C-fiber endings are located throughout the atria also in the interatrial septum and atrial appendixes.

Figure 1 shows the site of 11 such atrial C-fiber endings located accurately by probing the open, nonbeating heart.

Atrial C-fibers show no or only a low-frequency discharge at rest (mean 1.4 impulses/s). The spontaneous discharge is normally irregular, but some receptors have a cardiac modulated rhythm either in phase with the atrial contraction (a-wave) or the atrial filling (v-wave). Figure 2a is an example of the progressive increase in discharge frequency of a right atrial C-fiber during stepwise infusions of dextran (Rheomacrodex, Pharmacia). In the control period there is no spontaneous activity. From a discharge frequency of 0.2 impulse/s at a pressure of 2 mm Hg (mean atrial pressure) the activity increases to 8 impulses at a pressure of 10.5 mm Hg.

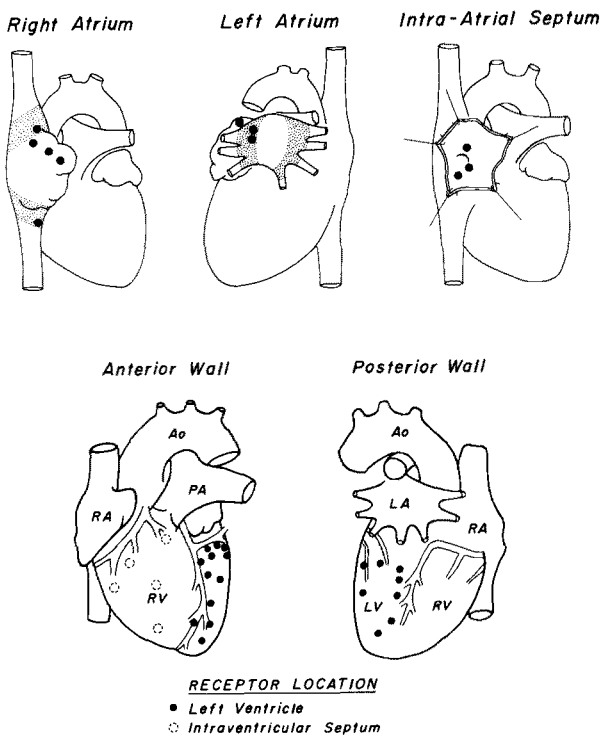

Fig. 1. Distribution of atrial and ventricular receptors with afferent C-fibers in cats. The location of 11 atrial and 25 left ventricular C-fiber endings. The receptors were distributed throughout the entire heart also in the intra-atrial and intraventricular septums. The receptors were located by probing the open, nonbeating heart

The relationship between the atrial pressure and the receptor discharge was examined in 11 receptors during occlusion of the outflow tract from the atria. Figure 3 shows the relationship between the mean pressures in right and left atria and the discharge frequency in atrial C-fibers. The curves for atrial medullated fibers are also shown for comparison. Note

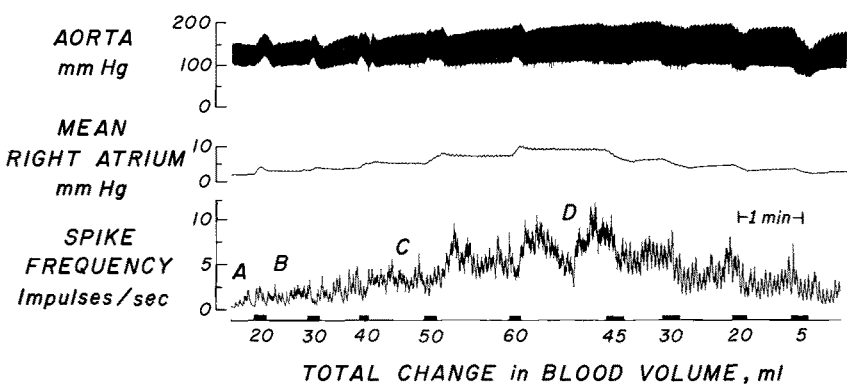

Fig. 2A. Arterial blood pressure, mean right atrial pressure, and spike frequency in a right atrial C-fiber in an anesthetized cat (3.2 kg). Upon transfusion with dextran increased activity in the receptor parallels with the changes in atrial pressure

that the atrial C-fiber endings have somewhat higher threshold and considerably lower discharge frequencies than the medullated endings. However, most of the atrial C-fibers seem to have thresholds within the normal pressure range in the atria. The thresholds for the right atrial C-fibers are 2–3 mm Hg and for the left atrial C-fibers, 4–12 mm Hg (mean atrial pressure), and the maximal discharge frequency ranges from 6 to 17 impulses.

The activity in the atrial C-fibers also during graded transfusion increased parallel with the rise in atrial pressure. The threshold for activation was 2–3 mm Hg in the right and 6–8 mm Hg in the left atria.

The firing pattern in relation to the cardiac cycle is shown in Figure 2B. In this experiment the total conduction time from the receptor site to the recording electrode is used to establish the correct position in the cardiac cycle of the receptor activation. The receptor is activated mainly during the v-wave even if occasional or sustained a-wave discharge can also be observed. This dominating v-wave discharge was typical for the atrial C-fibers. Thus, the atrial C-fiber endings seem to respond mainly to *atrial distension* and not so much to atrial contraction.

Recordings were also obtained from three inter-atrial septum endings. These receptors were activated both by pressure changes in the right and

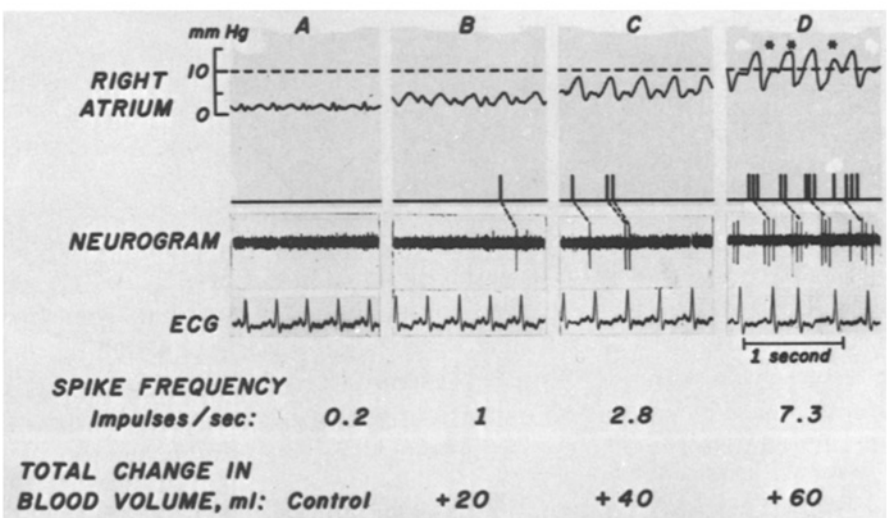

Fig. 2B. Increase in right atrial C-fiber discharge during stepwise increase in blood volume. From *top downward:* right atrial pressure, neurogram with corrected position *(above)* of spikes within the cardiac cycle, *ECG,* calculated spike frequency, and change in blood volume. Receptor fires with cardiac rhythmicity at v-waves (*C* and *D*), but a-wave firing can also occur (for example, when a-wave is markedly augmented as in postectopic beat, *D*); *, a-wave. Since the neurograms were obtained in the same experiment as Figure 2A the letters correspond. (From *Thorén,* 1976a, by permission of American Heart Association)

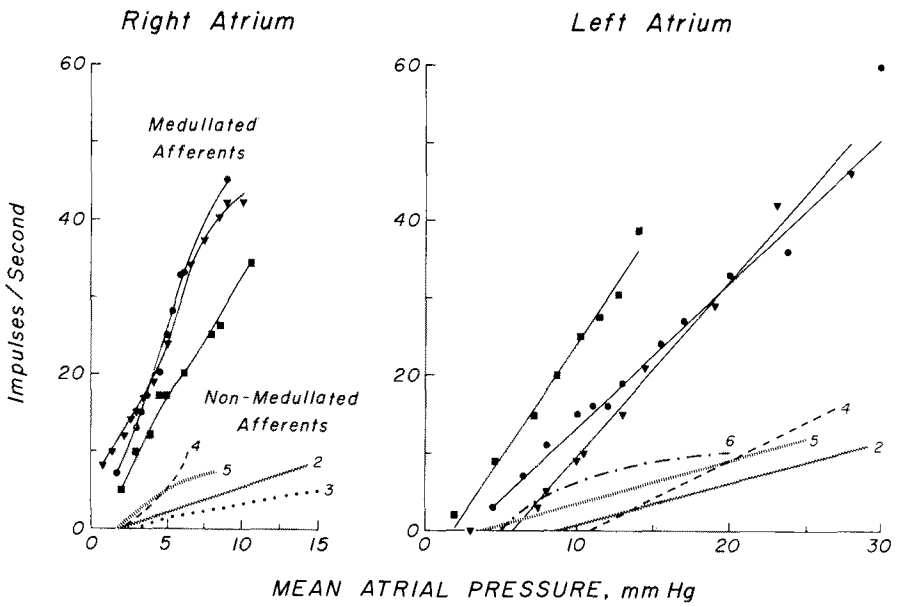

Fig. 3. Relationship between activity in medullated and nonmedullated vagal afferents from right and left atrium of cats during increases in atrial pressure caused by graded occlusion of the respective outflow tract. Each set of recordings is from a single fiber. (From *Thorén* et al., 1976, by permission of American Heart Association)

left atrium and seemed in part to respond to the pressure gradient between the atria.

2. Atrial C-Fibers in Spontaneous Breathing Cats. The characteristics of the atrial receptors with nonmedullated vagal afferents have recently been examined in spontaneously breathing cats (*Thames* et al., 1977). Five of eight left atrial C-fibers showed spontaneous activity with a mean discharge rate of 1 impulse/s. The receptor activity was modulated by the respiratory cycle with 1–3 impulses per cardiac cycle. Augmentation of respiration by CO_2 inhalation increased the average frequency of discharge markedly due to the increase in the transmural pressure of the atria.

3. Atrial C-Fibers in the Rat. The characteristics of the atrial receptors with vagal afferents in the rat were recently examined by *Thorén* et al. (1977c, 1979a). In anesthetized open-thorax rats 14 left atrial and 2 right atrial receptors were examined. All of the receptors had afferent fibers with conduction velocity less than 2 m/s, indicating that they were C-fibers. Interestingly enough, no receptors with medullated afferents were found in the rat heart. Moreover, it was not possible to identify any receptors with nonmedullated afferents in the left ventricle.

The thresholds for activation of left atrial C-fiber endings were between 2.0–8.0 mm Hg with a mean of 4.5 mm Hg. The pressure response curve was established for ten left atrial receptors as shown in Figure 4. Note the marked variation in the individual pressure-response curves. Some of the receptor afferents have surprisingly high firing rates for non-medullated fibers. These high frequency C-fiber endings also show a regular discharge with up to 8 impulses per cardiac cycle, in contrast to the atrial C-fibers in the cat, which normally do not show higher frequencies than 3–4 impulses per beat. Similar high frequency receptors with C-fiber afferents have also been seen in the aortic nerve of the rat (*Thorén* et al., 1977a).

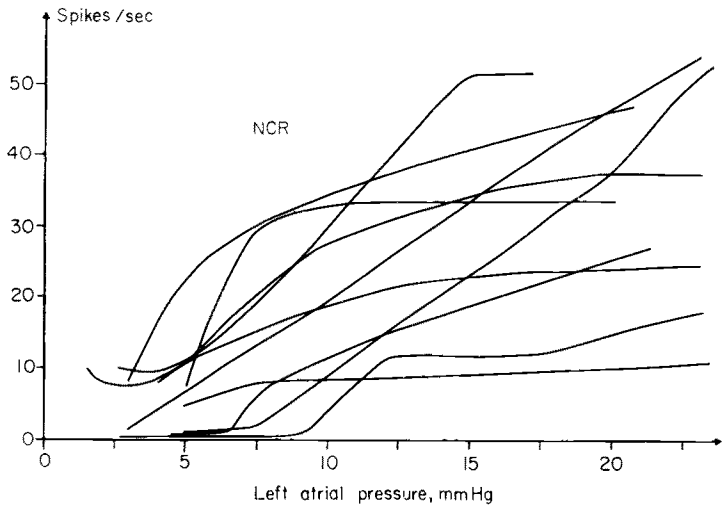

Fig. 4. Relation between the activity in the left atrial C-fiber endings in normotensive control rats *(NCR)* and the mean left atrial pressure. Note the marked variation in the pressure-response curves. Some receptors also show a surprisingly high discharge rate up to 55 Hz (data from *Thorén* et al., 1979a)

4. Atrial Receptors in the Bird. Atrial receptors with fine fiber afferents were recently described in the atria of the chicken (*Nye* et al., 1975). The receptors showed normally low and irregular tonic activity, and some could be activated by blood-volume expansion. Even if the conduction velocity was not measured, the fibers were probably C-fibers. No atrial medullated fibers were found.

B. Pulmonary Venous C-Fibers

It has been known for many years that it is possible to evoke vasodepressor reflexes from the pulmonary veins (*Daly* et al., 1937; *Heymans* and *Neil*, 1958). However, no receptor group has been identified as responsible for this reflex effect. Recent studies on this aspect by *Coleridge* and *Coleridge* (1977a, b) are therefore of great interest. These authors reported the existence of two types of vagal C-fibers in the lungs of the dog. One group was activated by Capsaicin injected in the pulmonary circulation. One-third of these receptors were also activated by elevation of the left atrial pressure to 5–10 mm Hg, and 75% were stimulated at pressures above 20 mm Hg. Thus, a population of afferent pulmonary vagal C-fibers responds to small left atrial pressure elevations, and these receptors are probably situated in or close to the pulmonary veins.

C. Characteristics of Ventricular C-Fibers

1. Left Ventricular C-Fibers. The existence of left ventricular C-fibers was first reported in the dog by *Coleridge* et al. (1964). The ventricular C-fibers normally showed a low firing rate with irregular rhythm, but were markedly activated by probing the epicardium or by injections of Capsaicin and Veratridine. The epimyocardial type of left ventricular receptors in the dog has also been studied by *Sleight* and *Widdicombe* (1965) and *Muers* and *Sleight* (1972b). These researchers examined the activity of the receptors during changes in ventricular pressure and contractility. After a brief aortic occlusion 60% of the endings were stimulated and their activity usually displayed cardiac rhythmicity during systole. Adrenaline injection induced a more powerful activation of the receptors than aortic occlusion. Carotid occlusion as well as electric stimulation of the sympathetic nerves to the heart could also activate these receptors, and several of these C-fiber endings were markedly activated when the coronary venous pressure was increased during a partial occlusion of the coronary sinus (*Muers* and *Sleight*, 1972a, b).

Recently, *Armour* (1973) described a large number of ventricular receptors with medullated and nonmedullated afferents in dogs. However, in the few animals studied, the method of locating the receptors was inadequate. Moreover the method of measuring conduction velocity was not described. Thus these data are difficult to evaluate.

The functional characteristics of left ventricular epimyocardial C-fibers have also been studied in the cat by *Öberg* and *Thorén* (1972b) and *Thorén* (1977). When recording from C-fibers, which normally have a low-fre-

quency activity, the method of selecting the receptors is of great importance. Since a silent C-fiber is impossible to find, every dissected filament must be manipulated to increase the receptor activity. Differences in results between different studies might very well be explained by the method of fiber selection. It is therefore important to point out that *Thorén* in his studies selected ventricular C-fibers, which showed a clear response to aortic occlusion.

Ventricular C-fibers in the cat normally showed low spontaneous activity (mean 1.4 impulses/s), either irregular or with cardiac modulated rhythm. The conduction velocity in the vagal nerve varied from 0.6 to 2.4 m/s, whereas the conduction velocity within the heart was significantly

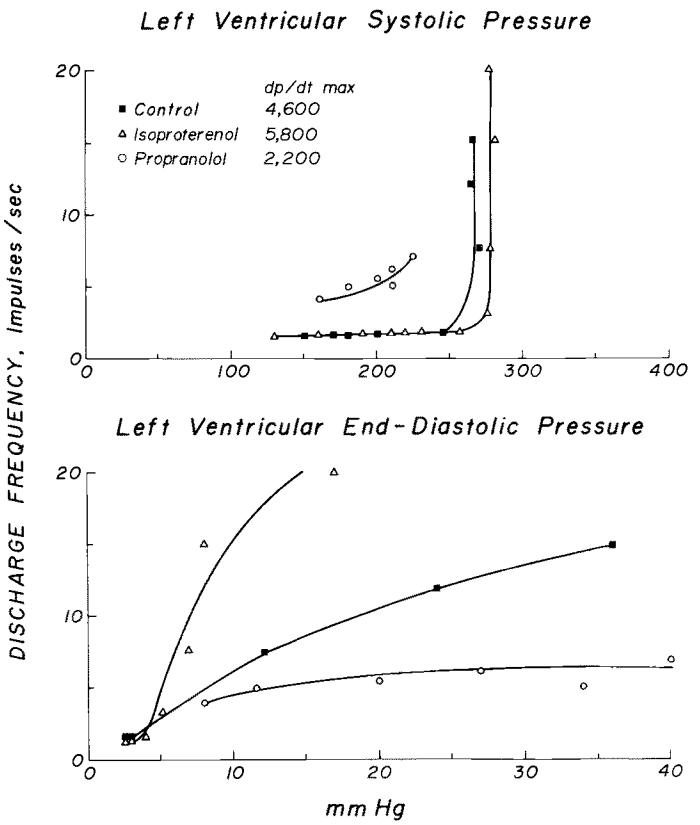

Fig. 5. Activity in one left ventricular C-fiber in a cat plotted against left ventricular systolic and enddiastolic pressure during graded aortic occlusion in the control situation by infusion of isoproterenol (Isuprel) (1.25–2.5 μg/min) and administration of propranolol (0.2–0.3 mg/kg). Values for maximal rate of increase in left ventricular pressure (dp/dt max) reflect changes in ventricular inotropism

lower. The location of 25 receptors was established in the open, nonbeating heart by probing. They were found throughout the entire left ventricle (Fig. 1) and also in the interventricular septum.

All the receptors responded to aortic occlusion with a maximal firing rate of 3–22 impulses/s. During a graded aortic occlusion the receptors did not normally respond to an isolated increase in ventricular systolic pressure. However, upon further occlusion and parallel with changes in left ventricular enddiastolic pressure (LVEDP) the receptors were markedly activated and displayed cardiac rhythmicity with 1–5 impulses/beat. The relationship between receptor activity and the left ventricular systolic and enddiastolic pressure in the ventricle is shown in Figure 5. The receptors could also be activated during a graded transfusion with dextran, and the activity then increased parallel with the change in LVEDP with a threshold of 2–12 mm Hg (Fig. 6).

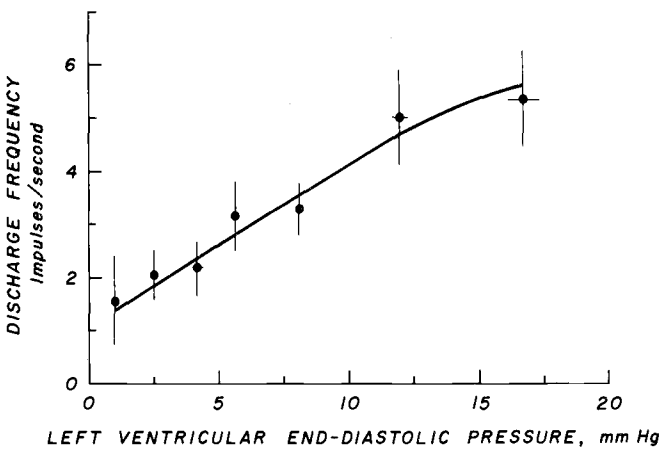

Fig. 6. Activity in nonmedullated vagal afferents from the left ventricular during increases in left ventricular enddiastolic pressure caused by transfusion with dextran (mean ± SE of recordings from 11 single fibers of eight cats, 81 observations. (From *Thorén* et al., 1976, by permission of American Heart Association)

An interesting characteristic of the left ventricular C-fibers is that changes in ventricular inotropism can markedly influence the receptor activity during aortic occlusion and transfusion. As illustrated in Figure 5 isoproterenol infusion increases the receptor response to aortic occlusion because the receptor discharge is higher at a certain change in LVEDP. The reverse is seen after a decrease in ventricular inotropism with propranolol.

In recent papers *Coleridge* and *Coleridge* (1977a, b) and *Coleridge* et al. (1979) have examined the characteristics of left ventricular C-fibers in

the dog. They also point out the importance of method for receptor selection. In an earlier study by this group (e.g., *Coleridge* et al., 1964) the left ventricular receptors were selected according to their response to injection of drugs (Capsaicin), and the examined receptors were then found to be rather nonresponsive to mechanical stimulation. In more recent studies receptors were selected with repeated aortic occlusions, and in this case the receptors responded to moderate changes in cardiac dynamics. These studies support the contention that the cardiac C-fiber group includes a large number of fibers with heterogeneous characteristics. There is much truth in the following statement on their research: "When picking C-fibers, you find what you are looking for."

In their later studies the *Coleridges* examined the characteristics of the left ventricular C-fibers in the dog during changes in intraventricular pressure. The results, in agreement with those found by *Thorén* (1977) in the cat, suggest that these endings do not respond to isolated changes in ventricular systolic pressure, but many receptors seem to be fairly sensitive to changes in enddiastolic pressure with thresholds below 10 mm Hg in LVEDP. After activation many of the receptors display cardiac rhythmicity, and after correction for total conduction time most receptors were found to be activated mainly in systole even if some receptors showed a distolic discharge. The different type of discharge was suggested to be due to different location in the ventricular wall.

Coleridge and co-workers have also examined the response of the receptors to different drugs, a wide range of responses being seen to chemical and mechanical stimulation. Most ventricular C-fibers were activated by veratridine as also reported by *Sleight* and *Widdicombe* (1965) and *Öberg* and *Thorén* (1972b). Endings markedly activated by Capsaicin and phenyldiguanidine showed either weak or no response to aortic occlusion. In contrast, receptors with a cardiac modulated discharge at aortic occlusion responded weakly to these drugs. Some receptors responded with irregular activity both to aortic occlusion and to drugs. These results provide further evidence that ventricular C-fibers are not a homogeneous group of fibers.

Coleridge and co-workers also studied the receptor response to hypoxia. In agreement with *Thorén* (1972a), they showed many endings to respond with cardiac rhythmicity, indicating progressive cardiac distension to be the cause of the increased firing. Some C-fiber endings localized in the dorsal wall of the left ventricle within 1 cm of the A-V ring responded to ventilation with 5% O_2 by quite irregular discharge in high-frequency bursts without relation to the cardiac cycle. The same type of endings were also described by *Armour* (1973), although the method for determining the exact location of the endings can be disputed (see Sect. III. C. 1).

2. Mechanism of Receptor Activation. The fact that the receptor activity shows a good correlation with changes in LVEDP both during aortic occlusion and transfusion may indicate that the receptors are functioning as distension receptors. An unexpected finding is that under these circumstances the receptors are activated mainly during systole (*Thorén,* 1977) (Fig. 7). However, the importance of ventricular systole for the receptor

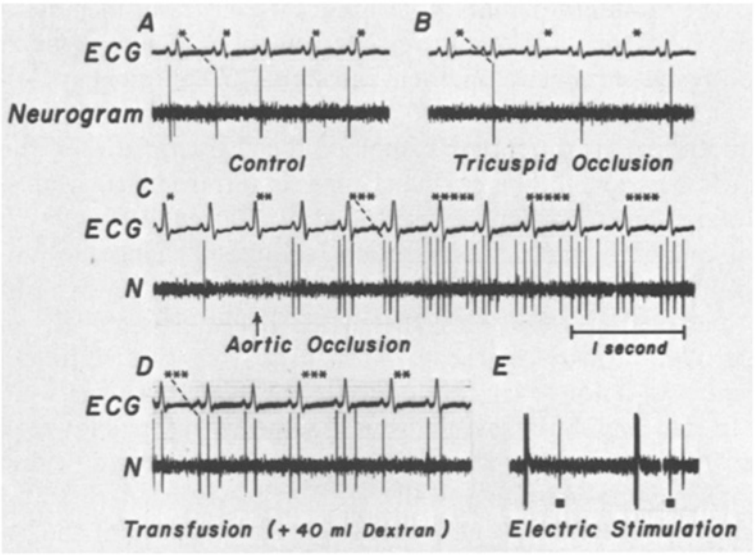

Fig. 7 A–E. Firing pattern in cardiac cycle of a left ventricular C-fiber in the cat. **A** control conditions; **B** after balloon occlusion of tricuspid valve; **C** during brief aortic occlusion; **D** after transfusion of 40 ml dextran; **E** total conduction time obtained by electric stimulation over receptor area. (■) indicates evoked potential. (*) indicates corrected position of receptor activation in cardiac cycle after total conduction time as measured in **E** is taken into account. Receptor fires spontaneously in early systole. During aortic occlusion and transfusion receptor discharges throughout systole. Occasional spikes in diastole are also seen (**C**). From *Thorén,* 1977, by permission of American Heart Association

activation is illustrated by several facts. First, during ventricular fibrillation the receptor discharge is not increased despite an increase in LVEDP, but it immediately increases after the cardiac contraction spontaneously is reestablished. Second, depression of contractility with propranolol or augmentation of contractility with isoproterenol will also markedly influence the activity at a certain enddiastolic pressure. Finally, a combination of an increase in enddiastolic pressure and an increased systolic pressure, e.g., during aortic occlusion, will induce a more marked rise in firing than during a more isolated change in enddiastolic pressure as during transfusion (*Thames* et al., 1977).

Thus we are left with the paradox that these left ventricular receptors are activated during systole, but the frequency of discharge appears related mainly to diastolic events. The explanation for this finding probably has to await more information about the morphology of the receptors and the relationship between the endings and the myocardial cells. Possibly the receptors are some type of branching nerve endings of nonmyelinated fibers, situated between the myocardial cells throughout the entire myocardium. Such a receptor system could respond to minor deformations of the receptor site. An increased end-diastolic pressure should markedly influence the following systole due to the Frank-Starling mechanism, and the increased stroke volume would in some way trigger the receptor to fire, perhaps due to a "microdeformation" of the receptor site. The actual firing would occur during systole. This theory cannot however, explain why pure systolic events, e.g., an isolated increase in systolic pressure or an isolated increase in inotropism, is a fairly weak receptor stimulus in comparison with change in LVEDP.

Another interesting feature of these receptors is their peculiar behavior under certain conditions. For instance, when the spontaneous activity of a left ventricular C-fiber is being recorded, a period of increased activity without concomitant changes in cardiac dynamics is not uncommon. Also commonly observed is the fact that the same receptor responds differently to the same stimulus at different times during an experiment. This is in contrast to the atrial medullated fibers, which generally behave in a very predictable manner. The mechanisms behind this odd behavior of the cardiac C-fibers remains to be elucidated.

3. Right Ventricular Receptors. A sparse population of receptor with C-fiber afferents also exists in the right ventricle in the dog (*Muers* and *Sleight,* 1972b) and the cat (*Thorén,* 1979a). These receptors also respond to moderate changes in right ventricular pressure. The receptor activity seems to correlate well both with the systolic and end-diastolic pressure in the right ventricle (*Thorén,* 1979a).

D. The Concept of Cardiopulmonary Receptors

When discussing reflex effects elicited from cardiopulmonary C-fibers it is important to keep in mind that this receptor group is distributed not only in the atria and ventricles but also in the lungs. Such a widespread innervation of the entire cardiopulmonary area makes reflex studies very difficult, because the only way to eliminate the reflex is to cut the vagus. Cardiac denervation will leave the afferent input from the lungs intact. Thus, the

whole group of cardiopulmonary C-fibers will be discussed as one group of fibers with similar reflex patterns. It is of course possible that C-fibers in the ventricles, atria, and lungs have different reflex patterns, although at present there is no evidence for such a concept.

IV. Reflex Effects of Cardiac Vagal C-Fibers

Reflex effects of cardiac vagal receptors have been studied extensively in the past. Several different methods of receptor activation have been used, e.g., electric stimulation of afferent vagal nerves from the heart, blockade of the tonic afferent traffic in the vagal nerves, increased pressure or inflation of balloons in the different chambers, and chemical agents. The different means of receptor activation will be discussed, emphasizing recent data on the role of cardiac C-fibers in the reflex responses. This topic has also been the subject of recent reviews (*Thorén*, 1972b, 1979b; *Thorén* et al., 1976; *Kidd* and *Linden*, 1975; *Paintal*, 1973a; *Sleight*, 1975).

A. Selective Electric Activation of Cardiac Vagal Afferents

Jarisch and *Zotterman* (1948) and *Öberg* and *White* (1970a) showed that afferent electric stimulation of the cardiac vagal branches in the cat can induce powerful depressor reflexes. More recently *Öberg* and *Thorén* (1973a) proved this depressor response entirely due to activation of nonmedullated afferents. In their experiments the central end of the right cardiac nerve of the cat was stimulated electrically at different intensities and durations. From the initial experiments, in which the strength duration curves for the different fiber groups in the cardiac nerve were determined, stimulation characteristics were selected such that the low-threshold medullated group was selectively and maximally activated. If the carotid and aortic baroreceptors were intact, the stimulation induced only small circulatory responses, consisting of slight increases in blood pressure, heart rate, and muscle- and renal-flow resistances. These effects were augmented when the buffering influences of the carotid sinus baroreceptors were minimized by clamping both carotid arteries and when the bulbar vasomotor center was inhibited by afferent electric stimulation of one aortic nerve. By contrast, high intensity stimulation, which activated both medullated and nonmedullated fibers, caused bradycardia, decrease in arterial blood pressure, and dilatation of the muscle and kidney vessels whether arterial baroreceptors were functioning normally or not (Fig. 8).

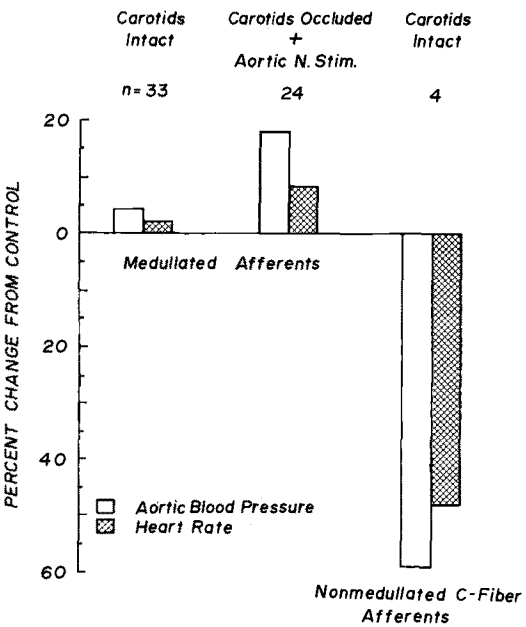

Fig. 8. Effect of selective electric stimulation of afferent fibers in the right cardiac vagal nerve in cats on aortic blood pressure and heart rate. In the first two pairs of bars, only the medullated fibers were stimulated; in the third both medullated and nonmedullated fibers were activated. The response to stimulation of the medullated fibers was markedly augmented if the carotid baroreceptors were eliminated; one aortic nerve was stimulated *(middle bars)* to decrease blood pressure according to control values. *n*, number of cats. (Data from *Öberg* and *Thorén*, 1973b; figure from *Thorén* et al., 1976, by permission of American Heart Association

The pattern of the reflex responses induced by electric stimulation of the afferent cardiac vagal C-fibers has been studied in detail in the cat by *Öberg* and *White* (1970a) and *Little* et al. (1975). The frequency-response characteristics of the reflex effects on aortic blood pressure, renal and muscular vascular bed, and heart rate showed that powerful reflex effects could be induced already at very low stimulation frequencies (less than 2 impulses/s). The kidney was especially responsive to low frequency stimulation of the right cardiac nerve. Thus, 1 impulse/s induced about 30% of maximal response in the kidney, the maximal renal response being obtained at 10 impulses/s. This powerful effect on the renal circulation at very low stimulation frequencies is of great interest because the spontaneous activity in cardiac C-fibers is normally very low ($\sim$ 1 impulse/s). If the *relation* between the renal and muscular vascular responses was compared over the whole range of stimulation frequencies, the cardiac receptors induced more powerful effects on the kidney than the arterial baroreceptors. However, the *maximal reflex response* of the renal vessels, obtained with right cardiac nerve stimulation, was equal to that from baroreceptor stimulation. In contrast, the maximal reflex response of skeletal muscle vessels to cardiac nerve stimulation averaged only 66% of that resulting from baroreceptor stimulation. Thus, the cardiac C-fibers (*Little* et al., 1975) seem to be unable to reach all the neurons in the vasomotor center controlling the sympathetic outflow to the muscle resistance vessels. In

comparison with the arterial baroreceptors, the cardiac C-fibers also elicited a more pronounced reflex bradycardia, which was mainly due to an increased vagal outflow to the heart (*Öberg* and *White*, 1970a). The relation between the precapillary resistance and postcapillary capacitance responses was the same during stimulation of arterial baroreceptors and cardiac C-fibers (*Öberg* and *White*, 1970a).

B. Tonic Vasomotor Inhibition via Vagal C-Fibers

Interruption of afferent vagal traffic from the cardiopulmonary region when the arterial baroreceptors were free to respond to changes in systemic arterial pressure generally evoked only a small response in arterial blood pressure and heart rate. However, when the influence of the arterial baroreceptors was eliminated, cooling of cervical vagus in the anesthetized cat, rabbit, and dog resulted in a rise in blood pressure, tachycardia, and constriction of the resistance vessel of the skeletal muscle, intestine, and kidney and of the splanchnic capacitance vessels (*Guazzi* et al., 1962; *Pillsbury* et al., 1969; *Öberg* and *White*, 1970a; *Mancia* et al., 1973). In addition liver volume (*Carneiro* and *Donald*, 1977) clearly decreased. The vasoconstriction, unaffected by atropine or section of the vagal nerves at the diaphragm, was due to an increased sympathetic adrenergic activity. Thus receptors in the cardiopulmonary region subserved by vagal afferents exert a tonic inhibition on the central vasomotor nerves controlling the sympathetic outflow to the resistance and capacitance vessels, with the exception of the cutaneous veins (*Mancia* et al., 1973)

1. The Receptor Stations. The important question whether the tonic inhibition of the central vasomotor neurons arises from the atria, the ventricles, or the lungs has been examined by *Mancia* and *Donald* (1975). In their experiments the venous return was oxygenated extracorporeally and returned to the aorta. The heart was removed, leaving the ventilated lungs in situ. In other experiments with the same extracorporeal circuit, the lungs and the ventricles were removed, leaving the beating atria perfused with the coronary arteries. In a third preparation lungs were removed and the atria denervated, leaving only the beating innervated ventricles in situ. In each situation vagal cooling resulted in an increase in aortic blood pressure. Thus, receptors in the lungs, the atria, and the ventricles each were responsible for the tonic inhibition of the vasomotor center.

Although the above experiments do not answer the question whether this tonic inhibition was due to nonmedullated or medullated vagal afferents, evidence from two other types of experiments indicate that non-

medullated vagal afferents are responsible for the tonic inhibition of the vasomotor center.

2. **Selective Vagal Cooling.** In anesthetized rabbits (*Thorén* et al., 1975) the sinus and aortic nerves were cut. The vagal nerves were cooled to 12°, 8°, 6°, and 0°C, causing progressive increase in aortic blood pressure. The activity in vagal medullated fibers in the same animal was blocked at 6°C. Thus the increase in pressure on vagal cooling from 6°C to 0°C (40% of the total increase in pressure) must be due to blockade of the spontaneous activity in nonmedullated fibers. Whether or not more of the vasomotor inhibition was due to tonic activity in vagal C-fibers could not be determined from these experiments.

3. **Anodal Block of Vagal Afferents.** Anodal block is a more selective way to block the medullated afferents (*Mendell* and *Wall*, 1964). This technique was used in cats by applying DC current to the cervical vagus, under circumstances of no evidence for simultaneous activation or blockade of nonmedullated fibers (*Thorén* et al., 1977b). The left vagosympathetic

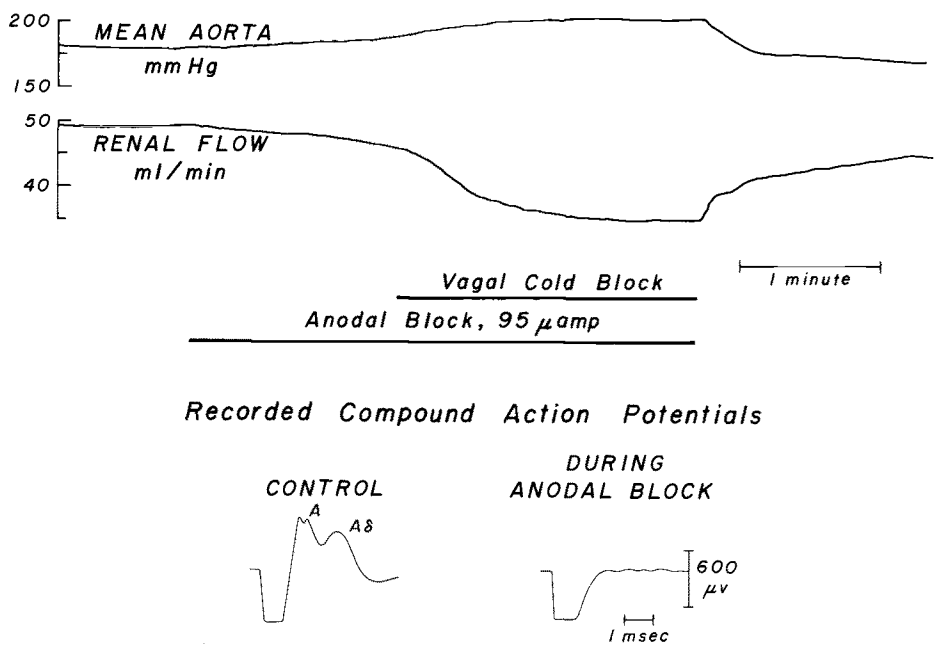

Fig. 9. Effects of anodal block medullated vagal fibers and subsequent vagal cold block on aortic blood pressure and renal blood flow in the cat. The compound action potentials were recorded before and during the anodal block. The disappearance of the *A* and *Aδ* potentials during block demonstrates that conduction in the medullated fibers has been prevented. The large downward deflection is the stimulus artifact. (From *Thorén* et al., 1976, by permission of American Heart Association)

trunk, the right aortic nerve, and both carotid sinus nerves were cut. Brief anodal block of vagal medullated fibers for ∿ 1 min induced a mean increase in pressure of 8 mm Hg. Interruption of all afferent vagal traffic by cooling to 0°C caused a mean increase in aortic blood pressure of 38 mm Hg. Thus at least 80% of the increase with cooling could be ascribed to interruption of traffic in nonmedullated fibers (Figure 9 shows renal blood flow measured simultaneously with aortic blood pressure). During anodal block of the medullated fibers renal blood flow was slightly decreased. However, when the nonmedullated fibers are also blocked by cooling, a marked decrease of flow occurred despite the increase in systemic blood pressure. Thus these two sets of experiments with selective cooling and anodal block proved that the tonic vagal inhibition from the cardiopulmonary area is principally or even totally mediated via nonmedullated fibers.

4. Interaction with Baroreceptor Reflexes. The effect on aortic blood pressure of interrupting afferent vagal traffic from the cardiopulmonary region at different sinus pressures was examined in cats and dogs. In the cat (*Öberg* and *White,* 1970a) interruption of the cardiopulmonary receptors by vagal cooling with intact baroreceptors induced fairly small increases in blood pressure and peripheral resistance. Vagal cooling after bilateral carotid occlusion resulted in higher blood pressure and a more pronounced vasoconstriction. The interaction between the baroreceptors and cardiopulmonary receptors has also been studied in detail in the dog by *Mancia* et al. (1973, 1975b, 1976b). High carotid sinus pressure (220 mm Hg) abolished the response to vagal cooling. When the sinus pressure was reduced to 200 mm Hg a small increase in pressure occurred with vagal cooling, becoming greater as the sinus pressure was further reduced and reaching a maximum at a sinus pressure between 100 and 50 mm Hg. After the activity of the cardiopulmonary receptors was increased by volume load, there was still no response to vagal cooling at the sinus pressure of 220 mm Hg, but at lower pressure the increase in blood pressure with vagal block was greater than during normovolemia. The inability of the cardiopulmonary receptors to affect the cardiovascular system when the arterial baroreceptors were maximally activated suggests that afferent fibers from the cardiopulmonary and carotid baroreceptors converge on the same neuron pools within the vasomotor center.

5. The Reflex Pattern. The pattern of reflex cardiovascular response to complete vagal block has been examined in several studies (*Öberg* and *White,* 1970; *Mancia* et al., 1973, 1975b, 1976b). As already discussed studies with differential blockade of the vagal nerves clearly indicate that

cardiac vagal C-fibers are to a great extent responsible for this tonic vagal vasomotor inhibition. Thus the pattern of reflex response to vagal block is likely to reflect the pattern of reflex response to blockade of the cardiopulmonary vagal C-fibers.

Several papers have examined to what extent the tonic inhibition from the cardiopulmonary region acts on vasomotor neurons controlling the sympathetic outflow both to the resistance and capacitance vessels and to the vascular bed in different organs. In anesthetized cats with sectioned aortic nerves *Öberg* and *White* (1970a) found that occlusion of the common carotid arteries decreased blood flow to a hindlimb and a kidney perfused at a constant pressure by 53% and 19%, respectively. When the vagal nerves were blocked during the carotid occlusion hindlimb and renal flow further decreased, especially the latter.

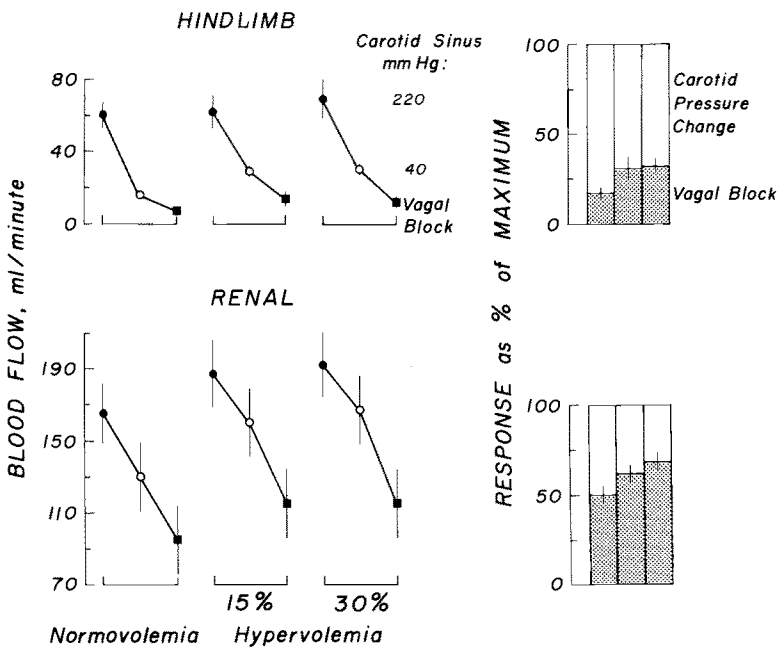

Fig. 10. Changes (mean ± SE) in hindlimb *(top)* and renal *(bottom)* blood flow in response to a decrease in carotid sinus pressure from 220 to 40 mm Hg and then to bilateral cervical vagal cold block at the sinus pressure of 40 mm Hg in 13 closed-chest dogs with aortic nerves cut, carotid sinuses vascularly isolated and maintained at desired constant nonpulsatile pressure, and their left hindlimb and left kidney perfused at a constant pressure of 120 mm Hg. The observations were made in sequence during normovolemia and during 15% and 30% increases in blood volume. The *bar graphs* show the mean decrease in blood flow with the decrease in carotid sinus pressure and with vagal block as a percent (± SE) of the mean decrease in blood flow caused by the combined procedures (maximum) during normovolemia and 15% and 30% hypervolemia. (From *Mancia* et al., 1975b, by permission of American Heart Association)

In experiments (*Mancia* et al., 1973, 1975b) conducted in anesthetized dogs with sectioned aortic nerves the carotid baroreceptor activity was abruptly changed from maximal to minimal by reducing the pressure within the isolated sinus from 220 to 40 mm Hg, and subsequently the vagi were blocked by cooling. Of the total decrease in hindlimb blood flow, 83% was due to withdrawal of carotid baroreceptor inhibition and 17% to withdrawal of the inhibition exerted by the cardiopulmonary receptors. Removal of the carotid and cardiopulmonary inhibition contributed equally to the total increase in blood flow in the kidney. After augmentation of the activity in cardiopulmonary receptors with volume expansion the relative role of these receptors for the control of renal and hindlimb flow was augmented (Fig. 10). Withdrawal of cardiopulmonary inhibition now made the greater contribution to the toal decrease in renal blood flow, but still the lesser contribution to the decrease in hindlimb blood flow. This relatively strong reflex effect on the kidney is probably due mainly to the cardiac C-fibers' ability to affect only a part of the neuron pool controlling the sympathetic outflow to the skeletal muscle (*Little* et al., 1975).

6. The Effect of Hypercapnia. In the dog (*Mancia* et al., 1975b) and the rabbit (*Ott* and *Shepherd*, 1973) the increase in renal vascular resistance upon reversible vagal cold block was two – four times greater during hypercapnia than during normocapnia. In contrast, changes in muscle vascular resistance were only moderately augmented. Further, hypercapnia also augmented the vasomotor inhibition on the renal and skeletal muscle resistance vessels exerted by aortic arch receptors, the effect of renal vascular being more pronounced. This increased reflex inhibition of the renal resistance vessels helps preserve the renal blood flow during respiratory acidosis and can then contribute to the control of acid base balance in respiratory acidosis. It is likely that the increased inhibition from the cardiopulmonary receptors during hypercapnia is due to a central effect (*Mancia* et al., 1975b, 1976a).

7. Summary. The cardiopulmonary mechanoreceptors with nonmedullated vagal afferents in dogs, cats, and rabbits exert an inhibitory influence on the resistance and capacitance vessels in the systemic circulation just as the arterial baroreceptors do. However, there is a quantitative difference between these reflex system: the muscle vasomotor fibers are less engaged by the cardiopulmonary receptors than by the arterial baroreceptors, i.e., the cardiopulmonary receptors have a relatively greater effect on the renal vessels than on the muscle vessels. As discussed later, man may differ somewhat in this respect, because cardiopulmonary receptors probably have a strong effect on muscle vascular resistance in man (Sect. VII).

C. Reflex Effects from Activation of Atrial Receptors

1. General Description. In 1915 *Bainbridge* observed that large infusion of saline or blood caused an increase in heart rate in the anesthetized dog. He ascribed this to stimulation of receptors by the increased pressure in the atria. In recent years *Linden* (1975, 1975) and his associates have stimulated interest in this field by showing in a long series of experiments that the Bainbridge reflex is mainly due to activation of atrial medullated endings (*Linden,* 1975). However, sympathetic afferents from the heart also seem to play a role in the reflex (*Bishop* et al., 1976; *Gupta,* 1975). Previously all the reflex effects from stimulation of vagal receptors in the atria had been ascribed to activation of the medullated afferents located at the vein-atrial junctions (*Paintal,* 1973). However, it is important to keep in mind that a substantial population of atrial receptors with nonmedullated afferents are located throughout the atria, and these atrial C-fiber endings can also respond to moderate changes in atrial pressures (*Thorén,* 1976a; *Thames* et al., 1977). Therefore, a detailed discussion of the earlier work on atrial reflexes is useful in distinguishing the reflex effects, which are likely to be triggered from the medullated and nonmedullated endings. Although many types of preparations have been used to study atrial reflexes, the receptors have usually been activated by one of three methods:

1) Inflation of balloons in the pulmonary vein-atrial junctions or the caval vein-atrial junctions (*Edis* et al., 1970; *Linden,* 1975, 1976) or distension of an isolated pouch of the left atrium (*Ledsome* and *Linden,* 1967). By this method the pressure and flow in the atria are not changed.

2) Inflation of balloons in the mitral valve to increase the pressure in the left atrium (*Mason* and *Ledsome,* 1974).

3) Partial hemodynamic isolation of the atria during extracorporeal circulation (*Aviado* et al., 1951; *Lloyd,* 1972, 1973, 1975).

2. Balloon Inflations at Vein-Atrial Junctions. Inflations of balloons at the vein-atrial junctions will stimulate atrial receptors with medullated afferents (*Linden,* 1975, 1976), but this procedure will also stimulate atrial C-fibers in that cat (*Thorén,* 1976a) and in the dog (*Coleridge* et al., 1973). Thus the reflex effects are likely to be the consequence of the combined effects of these two reflex mechanisms. In *Linden*'s experiments utilizing small balloons at areas with a dense population of medullated fibers (i.e., the vein-atrial junctions) activation of the medullated fibers will probably predominate. Reflex effects upon inflation of these small balloons consist of an increase in heart rate due to activation of the sympathetic fibers to the sinus node without any simultaneous change in the contractility of the ventricles (*Furnival* et al., 1971). The existence of a vagal component to

the increase in heart rate has been both suggested (*Burkhardt* and *Ledsome*, 1974) and denied (*Kappagoda* et al., 1975). The tachycardia observed with inflations of small balloons is accompanied by a transient vasodilatation in the perfused hindlimb (*Carswell* et al., 1970a; *Mason* and *Ledsome*, 1974). The sympathetic outflow to the kidney is also significantly inhibited (*Karim* et al., 1972) with small balloon inflation. When larger balloons were used to distend the pulmonary vein-left atrial junctions and the inhibitory influence from the aortic and carotid baroreceptors was eliminated, cardioacceleration was noted if the initial heart rate was below 140–150 beats/min. If the initial heart rate was faster, it slowed. Systemic vascular resistance (*Edis* et al., 1970) showed consistent and marked decrease.

3. Balloons in Mitral Valve or Extracorporeal Circulation. Inflation of balloons in the mitral valve has also been used to increase the pressure in the atria. However, this is accompanied by decrease in downstream pressures, and the contribution of atrial receptors in the reflex responses is thus difficult to assess. The experiments by *Kahl* et al. (1974) and *Mason* and *Ledsome* (1974) indicate, however, that increased pressure in the left atrium would induce vasomotor inhibition, especially in the kidney. Furthermore, increasing the left atrial pressure (with the animal on extracorporeal circulation) induced a general depressor reflex on the circulation (*Lloyd*, 1972, 1973). The threshold for the vasomotor inhibition was at left atrial pressure of $\sim$ 10 mm Hg.

Aviado et al. (1951) showed that increased pressure in the right atrium could induce depressor reflexes. However, *Ross* et al. (1961) denied the existence of depressor reflexes from the right heart.

4. Role of Different Fiber Groups. Thus two types of circulatory response seem to be elicited from the atria: an excitatory effect on heart rate when the junction between the veins and the atria was stimulated by small balloons (Linden technique) and a bidirectional effect on heart rate and a depressor reflex on the peripheral circulation if somewhat larger sections of the vein-atrial junctions or the whole atria were stimulated. Since tachycardia occurred on distension of these discrete sites in the atria where the complex nonencapsulated receptors with myelinated vagal afferents are numerous, it is reasonable to conclude that these receptors have a unique effect on the sympathetic nerve traffic to the sinus node. The change to a vasodepressor response as larger areas of the atrium were distended, might be attributed to activation of C-fibers, because these endings are much more widely distributed. Further support for this hypothesis comes from the study by *Öberg* and *Thorén* (1973a), which showed that electric stimu-

lation of the vagal afferents from the heart, with parameters such that only the medullated fibers were activated, induced an excitatory reflex response. In contrast, electric activation of the cardiac C-fibers induced powerful vasodepressor reflexes. In a preliminary study *Kappagoda* et al. (1977) have also shown that the atrial medullated afferents are likely to be responsible for the reflex tachycardia after small balloon inflation, in agreement with this hypothesis.

The finding by *Karim* et al. (1972) that small balloon inflation in the pulmonary vein-atrial junctions reflexly could induce not only tachycardia but also inhibition of the renal sympathetic traffic might be partly explained by simultaneous stimulation of both receptors with medullated and receptors with nonmedullated fibers.

Activation of the atrial C-fibers is likely to contribute to the renal sympathetic nerve withdrawal because of the pronounced inhibitory effect the latter receptors have on the sympathetic nerve traffic to the kidney even at very low level of activation (*Little* et al., 1975).

D. Reflex Effects from Activation of Ventricular Receptors

1. Reflexes from Ventricular Distension. Depressor reflexes elicited from left ventricular distension were first described by *Daly* and *Verney* (1927), and later papers (*Doutheil* and *Kramer,* 1959; *Aviado* and *Schmidt,* 1959; *Salisbury* et al., 1960; *Ross* et al., 1961; *Mark* et al., 1973a; *Öberg* and *Thorén,* 1973b; *Chevalier* et al., 1974; *Lloyd,* 1977; *Zelis* et al., 1977) have consistently confirmed these findings. The afferent pathway of this reflex is located in the vagal nerves. In contrast, distension of the right ventricle has very small or inconsistent reflex effects on the cardiovascular system (*Aviado* et al., 1951; *Barer* and *Kottagoda,* 1958; *Ross* et al., 1961).

Attempts have been made to estimate the sensitivity of the left ventricular receptor reflex in relation to changes in ventricular systolic and end-diastolic pressure. The experiments by *Ross* et al. (1961) indicate that isolated changes in the ventricular systolic pressure induce only moderate reflex effects, whereas a combined increase in systolic and end-diastolic pressure induces much more powerful reflex effects. These experiments were performed with a normally beating left atrial-ventricular preparation. In contrast, *Chevalier* et al. (1974) claimed that the threshold for left ventricular receptors was about 150 mm Hg in systolic pressure. In these experiments the blood was drained from the caval vein, and the dogs were placed on extracorporeal circulation. A balloon was placed in the left ventricle, and the pressure in the ventricle was increased by inflating the balloon

with saline. Thus the left ventricle was not allowed to contract in the normal manner, which probably alters the characteristics of the ventricular receptors. In another study *Zelis* et al. (1977) claimed that the threshold for the ventricular receptors was low. Their experiments were also performed on cardiopulmonary bypass with a balloon inside the left ventricle. Moreover the balloon was connected to a pressure bottle, ensuring constant pressure throughout the cardiac cycle. Thus it is very difficult to draw conclusions from these experiments as regards the normally beating heart.

Lloyd (1977) claimed that the threshold of the ventricular receptors during cardiac distension was unphysiologically high. These experiments were, however, performed during ventricular fibrillation, and a distending pressure of more than 20 mm Hg was needed to activate the receptors. As discussed previously (Sect. II), ventricular distension during fibrillation will not markedly increase the activity in the ventricular C-fibers. Instead the receptors were activated after defibrillation when the left ventricle contracted from an increased end-diastolic fiber length (*Thorén,* 1977).

Finally, *Öberg* and *Thorén* (1972b) also tried to estimate the sensitivity of the left ventricular receptors by graded aortic occlusion in the cat. They studied the reflex effects on heart rate and correlated them to the increase in ventricular end-diastolic volume. It was evident that the ventricular receptors do not respond to isolated changes in ventricular systolic pressure until the ventricular end-diastolic volume clearly changes. The same type of respone was also shown by *Doutheil* and *Kramer* (1959). It is of course possible to argue that the receptors responding to the increased end-diastolic pressure are not located in the left ventricle but rather in the left atrium or upstream the left atrium. However, the main afferent input for triggering vasodepressor reflexes during occlusion of the ascending aorta seems to be the left ventricle, as shown by the experiments by *Aviado* and *Schmidt* (1959) and *Mark* et al. (1973a). These authors showed that balloon occlusion of ascending aorta can trigger powerful depressor reflexes. The same reflex response was not seen when the left atrial pressure was increased in a similar way by mitral valve obstruction.

2. **The Receptors Involved.** No available data show whether the powerful reflex effects observed during left ventricular distension can be ascribed to activation of ventricular receptors with nonmedullated afferents or ventricular receptors with medullated afferents (*Paintal,* 1955, 1973; *Brown,* 1965). However, indirect evidence supports the view that the left ventricular C-fiber endings are the most important receptor group in this respect.

First, ventricular distension induces a reflex response pattern (see below), which is similar to the reflex response observed during electric activation of the afferent C-fibers from the heart (*Öberg* and *White,* 1970a; *Öberg* and *Thorén,* 1973a; *Little* et al., 1975).

Second, the ventricular C-fibers outnumber by far the medullated ventricular receptors, both in cats and dogs. Only 20% of the afferent vagal fibers from the heart are medullated fibers (*Agostini* et al., 1957), and probably less than 10% of these medullated fibers have their endings in the ventricles (*Coleridge* et al., 1964; *Paintal,* 1955; *Kolatat* et al., 1967). In contrast, the majority of the afferent C-fibers in the heart have their endings in the left ventricle (*Sleight* and *Widdicombe,* 1965; *Muers* and *Sleight,* 1972b; *Öberg* and *Thorén,* 1972b; *Thorén,* 1977). Consequently the medullated fibers constitute only a very small fraction of the total afferents from the left ventricle. This view is supported by the study of *Thorén* (1977), which found only two filaments with left ventricular medullated afferents despite the fact that these afferents have a much more favorable signal to noise ratio.

Third, right ventricular distension induced very weak or no reflex effects (see above) in contrast to the powerful depressor reflex that can be elicited from the left ventricle. As mentioned above, the ventricular C-fibers show a distribution with most of the endings in the left ventricle (*Sleight* and *Widdicombe,* 1965; *Thorén,* 1977) and only a few endings in the right ventricle (*Muers* and *Sleight,* 1972b; *Thorén,*1979a). In contrast, the medullated ventricular receptors were distributed equally in both ventricles (*Coleridge* et al., 1964; *Paintal,* 1973a). Thus indirect evidence shows that left ventricular C-fiber endings are probably the most important receptors responsible for the marked depressor reflex seen during ventricular distension.

3. **The Reflex Pattern.** The reflex effects of left ventricular distension on heart rate and kidney and hindlimb circulation were studied in a recent paper by *Öberg* and *Thorén* (1973b). The ventricular receptors were activated by graded occlusion of ascending aorta in baroreceptor denervated cats. A contribution of left atrial receptors to the aortic occlusion response was not ruled out, but as discussed above the left ventricle seems to be the main receptor station for eliciting depressor reflexes during aortic occlusion, even if a certain contribution of receptors further upstream could not be excluded. When the reflex effects from activating left ventricular receptors were compared with the reflex effects from activating carotid baroreceptors, the ventricular endings were seen to have especially marked effects on the vagal outflow to the heart and on the kidney circulation. The vasodilatation in the hindlimb was entirely due to withdrawal of sympathetic vasoconstrictor tone and not due to activation of vasodilator pathways. Thus the pattern of reflex response observed during activation of ventricular C-fiber endings was very similar to the pattern observed during electric activation of the afferent cardiac vagal C-fibers (*Öberg* and *White,* 1970a).

4. Other Ventricular Reflexes. Other depressor reflexes also originate in the left ventricle. Thus a vasodepressor response can be elicited by local coronary sinus distension (*Szentivanyi* and *Juhasz-Nagy*, 1962), increased pressure in the coronary venous system (*Szentivanyi* and *Juhasz-Nagy*, 1962; *Tiedt*, 1972), and increased pressure in the left coronary artery in the cat (*Brown*, 1966). However, the response to local coronary sinus distension is probably of local origin and not a reflex (*Muers* and *Sleight*, 1972c), and the response to increased pressure in the coronary venous system is due to activation of ventricular C-fiber endings distributed throughout the ventricle (*Muers* and *Sleight*, 1972a, b) and not due to receptors especially confined to the coronary venous system. The depressor reflex observed during increased pressure in the coronary arteries (*Brown*, 1966) can very well be due to activation of ventricular medullated fibers as claimed by *Brown* (1965), but participation of ventricular C-fibers in the response can not be ruled out at present.

E. Interaction Between Cardiac C-Fiber Reflexes and Other Cardiovascular Reflexes

1. Interaction with Baroreceptor Reflexes. The interaction between the carotid baroreceptor and cardiopulmonary C-fibers in cats and dogs has been discussed at length (see Sect. IV. B). In short, interruption of the cardiopulmonary C-fibers will tend to increase the gain of the carotid baroreceptor reflex (*Öberg* and *White*, 1970a; *Mancia* et al., 1973, 1975b; *Koike* et al., 1975), and increased activity in the cardiopulmonary receptors after volume load will tend to decrease the gain of the carotid baroreceptor reflex (*Mancia* et al., 1975b). These data together with the inability of the cardiopulmonary receptors to affect the cardiovascular system when the baroreceptors are activated maximally suggest that these two groups of receptor afferents converge on the same neuron pools within the vasomotor center. An important difference seems to be that the ventricular receptors do not affect all the neurons controlling the vasomotor outflow to the skeletal muscles (*Little* et al., 1975).

2. Effect of Volume Load. Acute volume loading in the conscious dog induced a marked increase in heart rate (*Horwitz* and *Bishop*, 1972; *Vatner* et al., 1975) in contrast to the anesthetized animal, in which volume load can induce both tachycardia and bradycardia depending on the initial heart rate (*Coleridge* and *Linden*, 1955). The increase in heart rate in the conscious animal during volume load was not only due to a reflex but also to direct mechanical stimulation of sinus node (*Horwitz* and *Bishop*, 1972). A possible explanation for these results might be that the afferent

traffic from the atrial medullated receptors and the sympathetic sensory endings will interact with simultaneous activated depressor reflexes from cardiac C-fibers and from arterial baroreceptors. As discussed before, the atrial medullated receptors seem to have a strong effect on the sympathetic outflow to the sinus node. Interestingly, volume load in man does not trigger reflex tachycardia (*Takeshita* et al., 1979).

3. Interaction with Arterial Chemoreceptor Reflexes. Left ventricular C-fibers are markedly activated upon acute severe asphyxia (see Sect. 7.7). The interaction between these reflexes and the arterial chemoreceptors is therefore of interest. *Koike* et al. (1975) showed that the response to carotid chemoreceptor activation by nicotine or perfusion of the carotid chemoreceptors with hypoxic blood was augmented if the vagal afferents were interrupted by cutting the vagal nerves in the neck. The interplay between the carotid sinus, cardiopulmonary, and carotid body reflexes has also been studied by *Mancia* et al. (1976b) in the dog. They showed that the carotid chemoreceptor reflex was markedly augmented during vagal cold block but only within an intermediate range of carotid sinus pressure ($\sim$ 140 mm Hg). At high carotid sinus pressure above 200 mm Hg vagal cold block and chemoreceptor activation were unable to induce any cardiovascular reflexes. At low levels of sinus pressure ($\sim$ 50 mm Hg) vagal cold block induced its maximal effect, and then the chemoreceptor reflex was ineffective. The reason for the discrepancy between these studies is not known.

The interaction between the carotid chemoreflex and cardiac C-fiber reflexes has also been studied in the cat by *Wennergren* et al. (1976a). These authors activated the cardiac C-fibers by electric stimulation of the right cardiac nerve, and the chemoreceptors, by perfusion of the carotid sinus with blood with low PO_2 and high PCO_2. The reflex vasodilator effects elicited by nonmedullated vagal cardiac afferents were much more effectively attenuated by a concomitant chemoreceptor stimulation than were the baroreceptor vasodilator effects. This phenomenon appeared only when a primary chemoreceptor response with initial bradycardia occurred. In contrast, the reflex bradycardia response induced from cardiac receptors was essentially not influenced by the prevailing chemoreceptor activity. Furthermore the reflex vasodilator effects on the kidney elicited via the nonmedullated vagal afferents were less effectively suppressed by the chemoreceptor stimulation than the vasodilator effects on the skeletal muscle.

4. Interaction with a Defense Area Stimulation. Left ventricular C-fiber endings are activated during the defense reaction as demonstrated by *Wennergren* et al. (1977). The interaction between the cardiovascular effects

induced by stimulation in the hypothalamic defense area and the cardiac C-fiber reflexes has been studied in the cat by *Wennergren* et al. (1976b). The powerful reflex vagal bradycardia upon cardiac nerve stimulation was found to be totally suppressed by the concomitant stimulation of the hypothalamic defense area. Furthermore the marked vasoconstriction seen in the kidney during defense area stimulation was also clearly attentuated by a simultaneous activation of the cardiac C-fibers. In the skeletal muscle the vasodilatation (cholinergic vasodilator fibers) was augmented due to the simultaneous sympathetic inhibition by the cardiac C-fibers. Thus the modifying influence from the ventricular receptors works in concert with the hypothalamic influences to produce maximal skeletal muscle perfusion without undue increases of pressure load on the heart during the defense reaction.

F. Reflex Activation of the Vomiting Center

Increased activity in cardiac C-fibers in the cat induced a marked relaxation of the stomach (*Abrahamsson* and *Thorén,* 1972) due to activation of the vagal noncholinergic relaxatory fibers to the stomach (*Abrahamsson* and *Thorén,* 1973; *Abrahamsson,* 1973). The relaxation could be elicited by electric stimulation of the cardiac afferent C-fibers (Fig. 11) by aortic

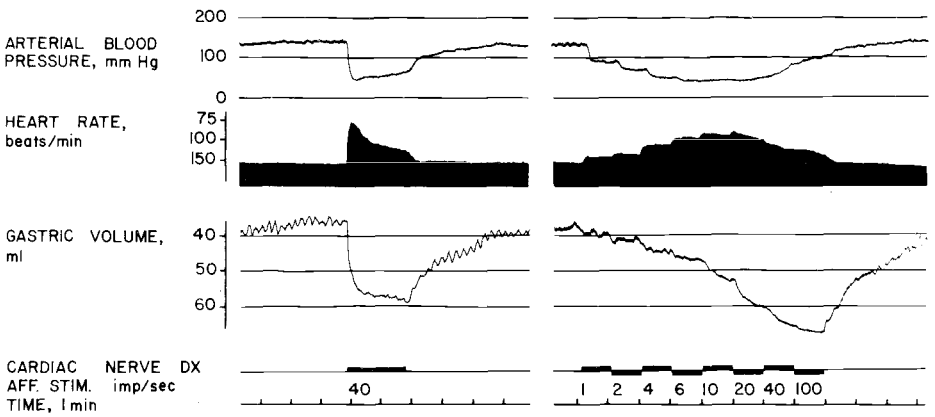

Fig. 11. *Left panel:* The effect of afferent stimulation of the right cardiac nerve (4 V, 1 ms) on arterial blood pressure, heart rate, and gastric volume. Note the "escape" of the heart and blood pressure responses during continued stimulation, whereas the gastric response is well maintained during the stimulation period. *Right panel:* Clear-cut circulatory and gastric responses are obtained already at stimulation frequencies as low as 1–2 impulses/s. Maximal circulatory effects are obtained at 10 impulses/s, whereas the gastric response shows a further increase with stimulation frequencies up to 40–100 impulses/s. (From *Abrahamsson* and *Thorén,* 1972, by permission of Acta Physiol. Scand.)

occlusion, by mechanical activation of the cardiac C-fibers, by coronary artery occlusion, and by chemical activation of the cardiac C-fibers with veratridine and nicotine (*Abrahamsson* and *Thorén*, 1972).

This reflex relaxation of the stomach is part of a more complex activation of the vomiting center (*Abrahamsson* and *Thorén*, 1973) since electric stimulation of the vagal cardiac afferent fibers elicited a typical vomiting response in nonanesthetized decerebrated cats. The reflex relaxation of the stomach observed in the anesthetized cat is therefore probably a manifestation of a more complex vomiting act, in which the somatomotor component is suppressed by the anesthesia.

The reflex relaxation of the stomach occurred first at considerably higher stimulation frequencies than did the reflex cardiovascular events. Low stimulation frequencies around 1 Hz induced marked reduction of blood pressure, but the concomitant change in gastric volume was slight or moderate. With stimulation frequencies above 5 Hz pronounced change in gastric volume occurred, but a full vomiting response was elicited only with higher frequencies around 10 Hz. Therefore alterations in the receptor activity in the lower frequency range will probably mainly affect the cardiovascular system, and an all-out activation of the vomiting center requires an intense afferent discharge of the receptors. Such an intense activation of the receptors can, for example, be observed during chemical activation, e.g., with veratridine, or by pathophysiologic activation, e.g., coronary artery occlusion. It is highly likely that the nausea and vomiting observed during these conditions are triggered at least in part by these reflex effects (Sect. VIII. F).

G. Reflex Cholinergic Coronary Vasodilatation

Feigl (1975) recently showed that activation of cardiac receptors with veratrum alkaloids injected into the coronary circulation could reflexly induce a marked vasodilatation in the coronary vasculature. In these experiments veratridine was injected into the anterior descending coronary artery, producing a 63% increase in circumflex coronary flow with a 88% increase in diastolic coronary conductance. This effect was entirely vagal, since it was abolished after vagotomy. It is highly likely that the ventricular C-fibers are the main receptor station responsible for this reflex effect (see Sect. IV. H). Such a reflex cholinergic vasodilatation of the coronary vasculature might very well be of importance under pathophysiologic conditions, e.g., myocardial infarction, because the cardiac C-fibers can be markedly activated during occlusion of a coronary artery (see VIII.F).

H. The Bezold-Jarisch Reflex

1. General Description. Extending old observations of *Bezold* (1867), *Jarisch* and *Richter* (1939a, b) showed that veratridine excited vagal receptors in the cardiopulmonary region and that this effect was accompanied by bradycardia and hypotension. Studies by *Dawes* (1947) indicated that the left ventricle was the main receptor station responsible for this reflex. However, it was also possible to elicit the Bezold-Jarisch reflex from the atria (*Mancia* and *Donald*, 1975).

Veratrum alkaloids were used for years as antihypertensive agents, but they have now been abandoned for other drugs with fewer side effects. Several excellent reviews have been published on the pharmacology of veratrum alkaloids (*Krayer* and *Acheson*, 1946; *Hoobler* and *Dontas*, 1953; *Dawes* and *Comroe*, 1954; *Benforado*, 1965; *Kupchan* and *Flacke*, 1967; *Ulbricht*, 1969).

2. The Receptors Involved. Various receptors with medullated and nonmedullated afferents in the lungs (*Paintal*, 1973a), ventricles (*Jarisch* and *Zotterman*, 1948; *Paintal*, 1955, 1973a; *Coleridge* et al., 1964; *Sleight* and *Widdicombe*, 1965; *Öberg* and *Thorén*, 1972b), and atria (*Paintal*, 1973a; *Coleridge* et al., 1973) are activated by veratridine. *Paintal* claims that at least in the cat the ventricular medullated receptors are the receptors of main importance for the Bezold-Jarisch reflex (*Paintal*, 1955, 1973a, b). This statement has been questioned by other investigators who claim that the ventricular C-fiber endings are the major receptor station responsible for the Bezold-Jarisch reflex (*Sleight* and *Widdicombe*, 1965; *Öberg* and *Thorén*, 1972b, 1973a; *Thorén*, 1972b, 1977, 1979b) for the following reasons:

1) The circulatory adjustment in the Bezold-Jarisch reflex can be mimicked by afferent stimulation of the cardiac nerves, but only when stimulation intensities are used which activate nonmedullated afferents (*Öberg* and *Thorén*, 1973a).

2) The left ventricular C-fibers outnumber by far the ventricular receptors with medullated afferent fibers (see Sect. IV.D.).

3) The ventricular C-fiber endings are mainly located in the left ventricle (*Coleridge* et al., 1964; *Sleight* and *Widdicombe*, 1965; *Muers* and *Sleight*, 1972b; *Öberg* and *Thorén*, 1972b; *Thorén*, 1977), i.e., in the part of the heart from which the Bezold-Jarisch reflex is said to be elicited (*Dawes*, 1947).

4) Finally, the ventricular C-fibers are activated by low doses of veratrum alkaloids both in dogs (*Dawes* and *Widdicombe*, 1953; *Sleight* and *Widdicombe*, 1965) and cats (*Öberg* and *Thorén*, 1972b). In contrast, the

ventricular medullated fibers are activated by veratrum alkaloids in the cat (*Paintal*, 1955, 1973a; *Brown*, 1965) but not in the dog (*Coleridge* et al., 1964). There is no reason to believe that the afferent mechanism for the Bezold-Jarisch reflex should be different in cats and dogs.

3. The Reflex Pattern. The efferent pattern of the Bezold-Jarisch reflex has been examined in cats and dogs. In the cat activation of the cardiac C-fibers with nicotine intrapericardially induced strong depressor reflexes with pronounced vagal bradycardia and vasodilatation (*Öberg* and *Thorén*, 1973b). The pattern was very similar to the pattern observed during electric activation of the cardiac C-fibers, i.e., a powerful vagal bradycardia and sympathetic inhibition, especially in the kidney. The vasodilatation in the skeletal muscle was entirely due to withdrawal of sympathetic tone and not to activation of the cholinergic vasodilator pathways. This finding was contradicted by earlier studies by *Bergel* and *Makin* (1967). The different results are probably due to the different pharmacologic approach. In the study by *Öberg* and *Thorén* nicotine did not induce vasodilatation in the isolated perfused skeletal muscle after local α-adrenergic blockade with guanethidine and phentolamine, despite the fact that electric activation of the cholinergic vasodilator pathways from the defense area induced marked vasodilatation. In the study by *Bergel* and *Makin* injection of 0.6–1 mg atropine in the femoral artery markedly reduced the reflex dilator response to nicotine administered intrapericardially. A similar degree of block was not achieved until a dose of 2 mg atropine/kg body wt. was injected intravenously. This dose seems high, since less than 0.05 mg atropine/kg body wt. is enough to block the cholinergic vasodilator pathways in the dog (*Mauskopf* et al., 1969), and these high doses of atropine may induce unspecified effects.

Voigts et al. (1975) have also studied the efferent pathways for the Bezold-Jarisch reflex in the dog. They confirmed the finding of *Öberg* and *Thorén* that the sympathetic cholinergic pathways to the skeletal muscles were not involved in the Bezold-Jarisch reflex.

4. Epicardial Chemoreflex. This reflex can be elicited by injections of nicotine or other drugs into the pericardial sac (*Kulaev*, 1963; *Sleight*, 1964) and can be ascribed to activation of ventricular C-fibers (*Sleight* and *Widdicombe*, 1965; *Öberg* and *Thorén*, 1972b) which involves the same reflex mechanism as the Bezold-Jarisch reflex. The word chemoreflex in the terms "coronary chemoreflex" and "epicardial chemoreflex" is not really adequate because these reflexes are mainly due to *chemical activation of mechanosensitive receptors*, even if there is evidence for the existence of mechanoinsensitive receptors in the heart which can respond to drugs

(*Coleridge* et al., 1979). However, the population of true chemoreceptors responding directly to changes in PO_2, PCO_2, or pH is probably small within the myocardium (*Mark* et al., 1974).

5. Detector Substances of the Bezold-Jarisch Reflex. The following drugs which *Jarisch* named detector substances for the Bezold-Jarisch reflex (*Jarisch*, 1949; *Krayer*, 1961) can also excite the cardiac C-fibers: Veratrum alkaloids intravenously or intrapericardially, nicotine intrapericardially, intravenous injections of aconitine, capsaicin, potassium ions, barium ions, rubidium ions, adenosine, citrates, phenyldiguanide, and nicotine (*Amann* and *Schaefer*, 1943; *Amann* and *Jarisch*, 1943; *Krayer* and *Acheson*, 1946; *Schaefer*, 1950; *Dawes* and *Comroe*, 1954; *Krayer*, 1961; *Zipf*, 1966; *Tokar* and *Gebber*, 1969; *Ginzel*, 1975). Calcium ions can antagonize the Bezold-Jarisch reflex (*Amann* and *Jarisch*, 1943).

The cardiovascular effects of several normally occurring substances are also partly mediated via activation of the Bezold-Jarisch reflex. Thus *Amann* et al. (1941) claimed that high doses of histamine was able to activate the Bezold-Jarisch reflex. However, *Öberg* and *Thorén* (1972b) observed no activation of left ventricular C-fibers in cats after moderate doses of histamine (100 μg). In a recent paper (*Neto* et al., 1974) bradykinin was shown to be able to activate the Bezold-Jarisch reflex. Thus 1 μg bradykinin into the left coronary artery in anesthetized dogs produced a vagally mediated decrease in blood pressure and heart rate.

Several papers have also discussed whether different prostaglandins can activate the Bezold-Jarisch reflex. Thus, *Koss* et al. (1973) and *Koss* and *Nakano* (1976) showed that intravenous injection of prostaglandin F_{2a} decreased systemic arterial blood pressure and produced bradycardia in the cat due to activation of left ventricular or left atrial receptors with vagal afferents. In contrast prostaglandin E_1 did not activate cardiac receptors. *Leach* et al. (1973) have also shown that intravenous injection of prostaglandin A_2 and E_2 caused a prolonged depression of the arterial blood pressure in the anesthetized, spontaneously hypertensive rat of the Okamoto strain but not in the normotensive control rat. Cutting both vagal nerves caused a prompt rise in pressure. Whether this effect originated centrally or peripherally was not demonstrated. Recent studies by *Coleridge* and *Coleridge* (1977a, b) and *Coleridge* et al. (1979) showed prostaglandin to have an effect on left ventricular C-fibers, i.e., left atrial injections of prostaglandin E_2 and prostaglandin F_2 could activate some left ventricular C-fibers in the dog. The receptors responding with cardiac rhythmicity to aortic occlusion were not at all or only weakly activated by prostaglandins. The more irregularly firing receptors with less response to mechanical stimulation were more markedly activated by the prostaglandins.

6. Vomiting and the Bezold-Jarisch Reflex. Administration of veratrum alkaloids to animals or to man induces nausea or vomiting in a high percentage of the subjects (*Hoobler* and *Dontas*, 1953; *Wang*, 1965). *Borison* and *Fairbanks* (1952) claimed that receptors near the nodose ganglion were responsible for the vomiting, and *Borison* and *Sampson* (1961) suggested later that the vagal body in the vicinity of the nodose ganglion was the receptor station involved. *Abrahamsson* and *Thorén* (1972, 1973) have also suggested that the reflex effects of the cardiac C-fibers on the vomiting center contribute to the nausea and vomiting. In their experiments intravenous injection of veratrum alkaloids to cats induced a marked depressor reflex and a gastric relaxation. As discussed earlier this gastric relaxation is part of a vomiting response. Injection of lidocaine in the pericardium abruptly abolished the gastric relaxation, indicating that cardiac afferents contribute to the nauseous effect of veratrum alkaloids.

I. Endoanesthesia of Cardiac C-Fibers

Intravenous injections of local anesthetic drugs have been known for many years to attenuate or block the Bezold-Jarisch reflex (*Fleckenstein* et al., 1950; *Zipf* and *Miestereck*, 1953; *Zipf*, 1966). This phenomena has been called "endoanesthesia" and has been reviewed by *Zipf* (1966). In addition to local anesthetic drugs, also certain antihistaminergic and anticholinergic drugs seemed to block the Bezold-Jarisch reflex (cf. *Fleckenstein* et al., 1950; *Hirsch* et al., 1954). The "endoanesthetic" effect of lidocaine (Xylocaine) has been studied by *Thorén* (1973b) and *Thorén* and *Öberg* (1979). A dose of 3–4 mg lidocaine/kg body wt. could markedly attenuate the reflex vasodepressor response to aortic occlusion and coronary artery occlusion. The plasma concentration of lidocaine needed to induce this "endoanesthetic" block was 2.5–4.7 μg lidocaine per ml plasma. These doses are in the upper range utilized during intravenous infusions of lidocaine in man. A study by *Thorén* and *Öberg* (1979) also showed that the attenuation of the left ventricular reflexes was really due to an effect at the receptor level, since the impulses in the afferents from the left ventricular C-fiber endings could be markedly attenuated or blocked by intravenous injections of local anesthetic drugs. This "endoanesthetic" effect of lidocaine can also likely be observed in patients with myocardial infarction, because infusion of lidocaine can increase heart rate in patients with myocardial infarction and bradycardia (*Ryden* et al., 1972; *Pantridge* et al., 1974). Whether this "endoanesthetic" effect of lidocaine can contribute to the antiarrhythmic effect of the drug is still a completely open question.

J. Central Connections of Cardiac Vagal C-Fibers

Juhasz-Nagy et al. (1965) claimed that the Bezold-Jarisch reflex could be markedly attenuated after sections at the pontobulbar junction thus indicating a suprabulbar component of the reflex arch. Later *Lee* et al. (1972) showed that the Bezold-Jarisch reflex was essentially integrated at medullar level, because midcollicular decerebration did not effect the bradycardic response to veratridine, and an additional transsection at the level of the lower pons did not significantly decrease the reflex actions of veratridine. Both the arterial baroreceptor reflex and the Bezold-Jarisch reflex were mediated via nucleus tractus solitorius. However, destruction of the ventral midline area in the medulla abolished the bradycardia induced by the baroreceptor reflex but not by the Bezold-Jarisch reflex. The conclusion was that most fibers involved in the Bezold-Jarisch reflex run from nucleus tractus solitarius directly to the dorsal vagal nucleus, whereas only a small part of the fibers pass through the midline areas. This is in contrast to the arterial baroreceptor where most fibers go to the ventral midline area. Also a preliminary report by *Donoghue* et al. (1977) shows that the cardiac vagal C-fibers in cats project to the medial portion of the nucleus tractus solitarius, between 3 mm rostral and 1 mm caudal to the obex. Further information about the central projections of the cardiac C-fiber reflex will be of great interest. These fibers and the arterial baroreceptors may likely have different central projections due to their different reflex patterns.

V. Role of Cardiac Vagal C-Fibers in the Control of Heart Rate and Peripheral Circulation

A. Blood Pressure Control

Cardiac C-fibers are probably not involved in the short-term regulation of blood pressure, because these receptors cannot register moderate changes in arterial blood pressure (*Sleight* and *Widdicombe*, 1965; *Muers* and *Sleight*, 1972b; *Öberg* and *Thorén*, 1972b; *Thorén*, 1976, 1977, 1978a). However, the receptors may be of importance in some situations of daily life, e.g., when blood pressure rises drastically to high values as a result of emotional influences such as fear and anger, and can then prevent the heart from acute pressure overloading by inducing strong vasodepressor reflexes. The activation of the receptors in such situations has recently been illustrated by *Wennergren* et al. (1977). In these experiments the activity in left ventricular C-fibers was recorded during electric stimulation of the

hypothalamic defense area in the anesthetized cat, and the stimulation induced a clear increase in receptor activity. The reason for the increased activity was probably the combination of the marked increase in left ventricular afterload and contractility. The marked poststimulatory bradycardia seen immediately upon release of defense area stimulation is probably triggered in part from these left ventricular C-fibers because bradycardia can be observed after complete baroreceptor denervation (*Lisander* et al., 1975). During the defense area stimulation the reflex bradycardia response is, however, centrally suppressed (*Wennergren* et al., 1976b) and can first be observed in the poststimulatory period.

Sinoaortic denervation in dogs will induce an acute and marked elevation of blood pressure. However, a few days later the arterial blood pressure returns to normal (*Cowley* et al., 1973). These animals show a marked lability in their blood pressure, with low blood pressure during sleep and transient, very marked rises under the influence of emotions. The return of blood pressure to normal might partly be due to the tonic inhibition from the cardiopulmonary afferents. Such a vagal inhibition will then explain the marked blood pressure lability, since the cardiopulmonary C-fibers are not able to sense moderate arterial blood pressure changes.

B. Exercise

The activity in left ventricular C-fibers is augmented when the contractility of the left ventricle is increased, e.g., during an isoproterenol infusion (*Muers* and *Sleight,* 1972b; *Thorén,* 1977) or stimulation of the sympathetic outflow to the heart. During exercise a marked increase in ventricular contractility occurs along with a rise in arterial blood pressure, and these factors together are likely to activate the left ventricular receptors. Accordingly, *Sleight* and *Widdicombe* (1965) have postulated that left ventricular C-fibers might play a role in the circulatory control during exercise and then act as a vagal break on the heart. During the period of exercise the reflex vagal bradycardia from the ventricular C-fibers will be blocked by central influencies (*Wennergren* et al., 1976b), but the sharp fall in heart rate after cessation of exercise might be a reflex effect via arterial baroreceptors and cardiac receptors.

C. Cardiac Receptors and the Diving Reflex

A large population of vagal nonmedullated endings (*Estavillo* and *Burger,* 1973) but no medullated endings is found in the left ventricle of birds. Furthermore intrapericardial administration of nicotine in the duck can

trigger the Bezold-Jarisch reflex with bradycardia and hypotension (*Blix* et al., 1976). These authors also showed that intrapericardial injections of low doses of lidocaine could block the afferent traffic from the heart, leaving the efferent control of the sinus node intact. Under these circumstances vagal bradycardia upon submersion was attenuated, indicating that the cardiac mechanoreceptors are of great importance for the establishment of the profound diving bradycardia in the conscious diving duck. The following reflex mechanism was suggested: after submersion a prompt but modest bradycardia and vasoconstriction is elicited, probably triggered from nasopharyngeal receptors. The arterial hypoxia following the respiratory arrest gradually stimulates the arterial chemoreceptors and gives rise to an intensive vasoconstriction and presumably to a modest bradycardia (a primary chemoreceptor reflex). The intense neurogenic vaso- and venoconstriciton induce a considerable displacement of blood to the heart with an increased central venous pressure and marked cardiac distension (*Aakhus* and *Johansen,* 1964). This cardiac distension activates cardiac mechanoreceptors, which help to trigger the powerful and prolonged vagal bradycardia. The reinforcement of bradycardia is of great importance for the performance of a prolonged dive. The generalized sympathetic inhibition normally seen during cardiac receptor activation is strongly suppressed by the concomitant chemoreceptor activation (*Wennergren* et al., 1976a). In contrast, bradycardia is not suppressed but rather reinforced. Thus it seems justified to assume that the cardiac receptors are of crucial importance for balancing the profound vasoconstriciton by inducing an intensified reflex bradycardia. The net effect would be that the cardiac output is greatly reduced, leaving only a heart-brain perfusion circuit. Moreover the arterial pressure remains largely unchanged when the ducks are under water.

VI. Role of Cardiac Vagal C-Fibers in the Control of Blood Volume

A. General Concepts

The role of cardiac receptors in blood volume control has been discussed extensively for many years, yet the field is still characterized by a great deal of controversy. Some experts in the field believe that the reflexes from cardiac receptors are of great importance for the neurohormonal control of plasma volume (*Gauer* and *Henry,* 1976); others claim that cardiac receptors are of little importance in the reflex regulation of the renal function (*Goetz* et al., 1975). In any case it is relevant to point out that the cardiac receptors with nonmedullated afferents have the potential to be involved in blood volume control, and the following points are important to consider.

1. A large number of receptors with nonmedullated vagal afferents are found in the cardiopulmonary area, and many of these endings both in the left ventricle and the atria are able to sense small or moderate changes in blood volume. Thus the threshold for activation of the left ventricular C-fiber endings upon volume load was 2.5–12 mm Hg in left ventricular end-diastolic pressure (*Thorén*, 1977). The corresponding thresholds (mean arterial pressures) for left and right atrial C-fiber endings were 2–3 mm Hg and 6–8 mm Hg, respectively. Even if the individual receptors have very low firing frequency ($\sim$ 1 Hz) the aggregated change in traffic in a large number of receptor afferents might mean an important change in tonic inhibition. Recent studies in the closed-chest cat indicate that the atrial C-fiber endings are more sensitive than left ventricular C-fiber endings to changes in central blood volume (*Thames* et al., 1977) and might thus be more important as a volume receptor station. This statement is, however, based on data from only a few receptors. It is also important to stress the diffuse localization of these volume-sensitive cardiopulmonary receptors. As discussed previously, the tonic vasomotor inhibition via vagal nerves derives from the atria, ventricles, and lungs. It is thus not enough to denervate the heart to completely exclude the receptor stations in the cardiopulmonary area. The only way to eliminate the tonic inhibitory effects of the cardiopulmonary receptors is to cut the vagal nerves; however, this procedure will cause at least the conscious animal such severe abdominal and lung problems that studies on the effect of vagotomy per se would be difficult to evaluate.

2. Cardiopulmonary C-fibers in dogs and cats seem to have an especially marked effect on sympathetic outflow to the kidney and less pronounced effects on the sympathetic outflow to the skeletal muscles. This fact will, of course, be of importance if these receptor stations are involved in blood volume regulation.

3. These endings are also located on the low pressure side in the circulation, which means that moderate changes in blood volume will markedly influence their activity. Even the left ventricle is part of the low pressure system in diastole, and the left ventricular endings are mainly affected by changes in diastolic filling. In dogs withdrawal or transfusion of 20% of the blood volume will only slightly influence the mean arterial blood pressure but will induce a clear change in the right and left atrial pressure (*Henry* et al., 1956; *Gauer* et al., 1970). Data from *Gupta* et al. (1966) indicate that receptors located in the heart, such as the atrial medullated receptors, change their activity much more than do the arterial baroreceptors in response to nonhypotensive hemorrhage. The fact that cardiopulmonary C-fiber endings in the atria, pulmonary veins, and the left ventricle can sense moderate changes in cardiac filling suggests that these receptors are of importance for the cardiovascular and renal effects of nonhypotensive hemorrhage or moderate volume load.

B. Cardiopulmonary C-Fibers and Water Diuresis

More than 20 years ago *Gauer* et al. (1954) suggested that stretch receptors in the cardiopulmonary circulation can induce water diuresis in the kidney due to an increased activity in atrial medullated receptors. The explanation was an inhibition of ADH release, an hypothesis now supported by additional experimental evidence (*Torrente* et al., 1975; *Gauer* and *Henry,* 1976; *Share,* 1976). However, this hypothesis has recently been questioned by *Linden* and co-workers (*Linden,* 1976). They were not able to find any change in plasma ADH in relation to the diuresis occurring upon distension of the left atrial-pulmonary venous junction, and the diuresis still occurred after ablation of the hypophysis (*Linden,* 1975, 1976).

The afferent mechanism for the diuresis (*Kappagoda* et al., 1979) was an activation of atrial medullated receptors, and the diuresis was due to an increased release of an unknown diuretic substance (*Kappagoda* et al., 1976).

The experiments by *Harris* and *Spyer* (1973) are also of interest in this respect. They examined the reflex changes in ADH release upon afferent stimulation of the right main cardiac vagal branches in the cat. They showed that the increased release of ADH induced by bilateral carotid artery occlusion was inhibited by electric stimulation of the cardiac nonmedullated afferents but not by stimulation of the cardiac medullated afferents. The right main cardiac branch joins the heart at the superior caval vein-atrial junction and contains a large number of atrial medullated afferents (*Jarisch* and *Zotterman,* 1948; *Thorén,* unpublished observations). It is also the major branch for the C-fiber afferents (*Jones,* 1953). However, pulmonary afferents also contribute, in most cats (*Thorén,* unpublished observations).

One possible explanation, although rather speculative at present, for these divergent results about atrial receptors and ADH might be the following: The water diuresis after cardiac receptor activation is not due to one mechanism but two different mechanisms. Increased activity in the atrial medullated receptors located at the vein-atrial junctions might *increase the plasma concentration of an unknown diuretic substance* not secreted by the hypophysis. The cardiac C-fibers located throughout the entire cardiopulmonary area can inhibit the release of ADH and can in that way also contribute to the water diuresis. Such a hypothesis would explain why *Kappagoda* and *Linden* could induce marked water diuresis in their experiments from distensions of the vein-atrial junctions despite no obvious change in plasma ADH or after ablation of the hypophysis. These authors used a technique with which the medullated atrial receptors were stimulated fairly selectively by very small balloons at the pulmonary vein-atrial junctions. The results of *Harris* and *Spyer* (1973), showing a reflex

inhibition of ADH from cardiac C-fibers, are also in accordance with these ideas. However, the proof for the existence of two different systems, a diuretic system controlled by atrial medullated endings and an antidiuretic system controlled by cardiac C-fiber, remains to be established.

C. Cardiopulmonary C-Fibers and Renal Sodium Excretion

The different mechanisms controlling the renal handling of sodium have been the subject of a great number of often very controversial studies. I intended to put forward the evidence here for the role of cardiac afferents in control of renal sodium excretion under normal and pathophysiologic conditions. I will first discuss the possible efferent systems and reflex pathways involved and finally present my arguments for the role of cardiac vagal C-fibers in these reflex mechanisms. I am not of the opinion that the cardiac afferents are in any way of critical importance for the renal sodium handling, but rather these reflex mechanisms might work in concert with other reflex mechanisms such as arterial baroreceptors and spinal afferents. It is also important to keep in mind that intrarenal mechanisms are able to control the sodium output in a kidney devoid of reflex influences.

1. Renal Sympathetic Nerves and Sodium Excretion. Renal sympathetic nerves are know to influence sodium output via the neural regulation of the renin-angiotensin system (see Sect. VII. E). It has recently been shown that low-frequency stimulation of renal sympathetic nerves can also markedly increase renal sodium absorption, independent of changes in plasma aldosterone concentration, total renal blood flow, or flow distribution in the kidney (*Di Bona,* 1977; *Bello-Reuss* et al., 1977). A functional role of renal nerves in sodium homeostasis is also indicated by other experiments. Thus acute renal denervation in dogs (*Bonjour* et al., 1969) and rats (*Bello-Reuss* et al., 1977) and chronic renal denervation in dogs increase the renal sodium output (*Bencsáth* and *Takács,* 1971; *Bencsáth* et al., 1972; *Zincke* et al., 1976). However, other data (*Berne,* 1952) indicate that sodium diuresis after chronic renal denervation could only be observed in the anesthetized dog and not in the conscious dog. *Bricker* et al. (1958) and *Carpenter* et al. (1961) also claimed that renal denervation or autotransplantation did not clearly influence renal function. The reasons for these divergent results are difficult to evaluate. However, so many different mechanisms are involved in renal sodium handling (*deWardener,* 1973) under normal conditions that the chronic elimination of renal nerve activity might be compensated by other mechanisms.

However, certain pathophysiologic conditions present clear evidence for the role of renal sympathetic nerves in control of sodium homeostasis.

Thus the sodium retention in heart failure in dogs (*Barger* et al., 1959) and man (*Brod,* 1972) is partly dependent on the renal nerves. Furthermore also the sodium retention in dogs with inferior caval obstruction is partly dependent on the renal nerves (*Gill* et al., 1967; *Azer* et al., 1972; *Slick* et al., 1974), and blocking of the renal sympathetic nerves in man will attenuate the renal sodium conservation during sodium depletion (*Gill* and *Bartter,* 1966). Sodium excretion during volume expansion is also augmented after adrenergic blockade in the dog (*Waugh,* 1970; *Bencsáth* et al., 1972) and man (*Gill* et al., 1964). This has, however, been denied by other authors (*Pearce,* 1968). Furthermore, there is evidence in the dog for a role of the renal sympathetic nerves for the conservation of sodium upon decreases in the intravascular blood volume (*Gill* and *Casper,* 1969; *Tanigawa* et al., 1974). Finally, patients with idiopathic orthostatic hypotension due to sympathetic insufficiency are not able to conserve sodium normally, indicating the role of the sympathetic nerve system in sodium handling in man (*Wilcox* et al., 1977).

2. Vagal Afferents and Renal Nerve Activity. *Clement* et al. (1972) showed that blood volume expansion in baroreceptor denervated rabbits induced a marked inhibition of the sympathetic outflow to the kidney via vagal afferents from the cardiopulmonary area. The same phenomenon was observed in anesthetized rats (*Ricksten* et al., 1978). Volume expansion markedly influence the renal sympathetic nerve traffic after moderate changes in blood volume in the intact animal. However, some preliminary data indicate that cardiac sympathetic afferents might also contribute to the control of the renal nerve activity (*Weaver,* 1976).

3. Mechanical Activation of Cardiac Receptors. Different types of experiments suggest that *activation of cardiac receptors* can influence renal sodium handling. Thus, increased pressure in the coronary venous system could markedly increase renal sodium output in the dog, despite the fact that the renal blood flow was unchanged or only slightly increased (*Lazzara* et al., 1970). The blood pressure was kept constant by compensation with a balloon catheter in the descending aorta, and the response was abolished by renal denervation. As discussed before, elevation of the pressure in the coronary venous system will markedly activate left ventricular C-fibers (*Muers* and *Sleight,* 1972a, b).

Gilmore (1964) showed that electric stimulation of the sympathetic nerves to the heart was associated with an increase in urine flow and electrolyte excretion. The effect was markedly attenuated by vagotomy, despite no changes in the hemodynamic response after vagotomy. The stellate stimulation decreased left atrial pressure, and thus *Gilmore* claimed

that atrial receptors were not involved. However, stellate stimulation will clearly increase the activity in the ventricular C-fiber (*Muers* and *Sleight,* 1972b), and it is thus likely that these receptors were responsible due to their strong reflex effect on the kidney.

Increased pressure in the left atrium induced by aortic snaring or balloon inflation reflexly augmented the renal sodium excretion both in anesthetized (*Arndt* et al., 1963; *Ledsome* and *Linden,* 1968) and the conscious dog (*Lydtin* and *Hamilton,* 1964; *Lydtin,* 1969; *Chapman,* 1971). This response was abolished after vagotomy (*Ledsome* and *Linden,* 1968). In the experiments by *Carswell* et al. (1970b) a natriuretic response was present also in the isolated perfused kidney, indicating involvement of *hormonal factors* (*Wardener,* 1977). However, *Chapman* et al. (1971) claimed that the renal response was absent in the denervated kidney, indicating that *neutral pathways* are also of major importance.

Kappagoda and *Linden* (see *Linden,* 1976), by inflating small balloons at the vein-atrial junctions in the dog, obtained a marked increase in urine flow with a concomitant, fairly small increase in sodium excretion, probably due to the inhibition of the renal sympathetic outflow (*Karim* et al., 1972). Both the diuretic and the sodium responses were abolished with vagotomy. Recent data from *Gillespie* et al. (1973) also indicate the role of cardiac receptors in sodium excretion. These authors showed that inflating the small balloon placed in the left atrial appendix induced an increase in urine flow due to reduction in ADH secretion. In addition, a clear-cut increase in sodium excretion was observed despite the absence of any change in renal blood flow. The threshold for the natriuretic response was $\sim$ 6 cm water in mean left atrial pressure.

Several other important papers on the effect of left atrial distension in conscious dogs on sodium excretion have recently been published. *Reinhardt* et al. (1977a) placed a nylon purse string around the mitral annulus in chronically prepared dogs on low sodium intake. After a recovery period the left atrial pressure was increased $\sim$ 10 cm H_2O by tightening the purse string. During the distension period the urine volume increased about three times, and the sodium excretion, about six times. Moreover this increased sodium response showed no correlation to the concomitant change in arterial blood pressure, indicating that receptors located in the cardiopulmonary area might be responsible for the sodium excretion and not receptors in the arterial circulation. The sodium response was not correlated to changes in total renal blood flow or insulin clearance (*Kaczmarczyk* et al., 1978). The same group had also demonstrated previously that intake of a sodium-rich meal (*Kaczmarczyk* et al., 1977) will increase left atrial pressure and that a clear correlation existed between the postprandial urine volume and the increase in left atrial pressure. These responses were

not dependent on adrenal cortex steroids, because they occurred after administration of DOCA or after adrenalectomy (*Reinhardt* et al., 1977b).

4. The Role of Cardiopulmonary C-Fibers in Renal Sodium Handling. Thus, there is clear evidence in literature that activation of cardiac receptors under different *experimental conditions* is able to reflexly increase the renal sodium excretion. The afferent activity is mediated at least partly via the vagal nerves, and the efferent mechanisms include neural and hormonal pathways (see above).

No experiments show whether or not these reflex mechanisms are triggered by any specific type of cardiac afferents. However, the following indirect evidence suggests that cardiac vagal C-fibers play a role in these response:

The cardiopulmonary C-fibers can respond to moderate changes in blood volume. Upon activation they do induce a marked reflex inhibitory effect on renal circulation (Sect. IV). Furthermore the tonic vagal vasomotor inhibition on both the renal (*Thorén* et al., 1976) and the peripheral circulation (*Thorén* et al., 1977b) is reflexly triggered by nonmedullated afferents (Sect. IV). The only direct evidence that cardiopulmonary vagal C-fibers can reflexly influence renal sodium excretion is seen in the experiments of *Wennergren* et al. (1976c) which show that electric stimulation of nonmedullated afferents from the heart induces a clear-cut increase in sodium excretion. Reflex activation of the arterial baroreceptors will also increase sodium output in a similar way.

On the basis of the experiments described above, two statements can be made about reflex control of sodium excretion. First, under experimental conditions increased activity in cardiac receptors with vagal afferents can augment the sodium output in the kidney via neural and hormonal mechanisms. Second, under certain pathophysiologic conditions reflex changes in sympathetic outflow to the kidney are probably of importance for renal sodium handling. However, these data do not allow a conclusion that cardiac vagal reflexes are important for renal sodium handling *under normal conditions.* Some data even indicate the opposite. *Knox* et al. (1967) and *Gilmore* (1968) claimed that the natriuretic response to plasma volume expansion could be attenuated after cardiac denervation but not after vagotomy (*Gilmore,* 1968; *Veress* and *Pearce,* 1972), suggesting an involvement of afferent cardiac sympathetic pathways. However, the involvement of afferent cardiac sympathetic pathways was denied by *McDonald* et al. (1970), who studied the renal sodium response to volume load after cardiac sympathectomy.

These findings, showing a clear-cut attenuation in the sodium response to volume load after complete cardiac denervation but not after cardiac

vagal denervation or cardiac sympathetic denervation per se, are obviously paradoxical. One explanation for these results might be related to the level of anesthesia, since anesthesia is known to depress renal sodium excretion (see *Reinhardt* et al., 1977a). Moreover vagal nerve sections eliminate not only vagal afferents but also a large number of afferents from other areas. Vagotomy in the conscious animal produces such severe disturbances in abdominal and pulmonary function as well as in the general condition of the animal that conclusions based on the experiments are difficult to evaluate.

Even if firm data is lacking at present, the evidence that increased activity in cardiac vagal afferents is able to influence sodium excretion under experimental conditions suggests that these receptors might be one receptor station for the normal control of sodium excretion. They are certainly not the only receptor station involved; also the arterial baroreceptors (*Di Bona,* 1977) can influence sodium output. Moreover under normal conditions the kidney can function well without any reflex influences (*deWardener,* 1973). The fact that several different mechanisms work together might explain why baroreceptor denervation alone or cardiac denervation alone do not markedly disturb blood volume regulation. However, in some pathophysiologic situations, e.g., congestive heart failure, when both the cardiac receptors and the arterial baroreceptors are affected, probably marked disturbances in the sympathetic control of kidney function (see Sect. VIII) can be triggered.

D. Cardiopulmonary Receptors and Control of the Avian Salt Gland

In birds with a marine habitat the nasal glands are modified into salt glands, which are able to excrete excess sodium chloride. The control of these salt glands is neurally mediated (*Fänge* et al., 1958). The normal stimulus for secretion is an increase in plasma salt concentration, but rapid injections of blood sufficient to raise the blood volume more than 10% failed to induce salt secretion. The secretion was, however, abolished by cutting the vagal nerves in the neck but not below the heart, and administering local anesthetic drugs into the pericardial sac immediately decreased the secretion (*Hanwell* et al., 1972). Thus receptors in the heart with vagal afferents seem to be responsible for the increased salt secretion. This interesting reflex mechanism was also studied recently by *Zucker* et al. (1977a), who showed that intravenous administration of 5% dextran in an amount equivalent to 30% of the estimated blood volume caused a transient, but significant increase in salt gland secretion independent of changes in plasma osmolarity or sodium concentrations. In contrast, intravenous 5%NaCl

caused a marked and sustained secretion. Interestingly, also veratridine caused an increase in salt glands secretion, but only when administered after prior volume expansion.

These reflex effects via vagal cardiac afferents are likely to be mediated through nerve endings with vagal nonmedullated afferents because medullated afferents with complex noncapsulated endings do not exist in the bird heart (*Estavillo* and *Burger*, 1973; *Nye* et al., 1975). These authors described some characteristics of thin vagal fibers from atrial and ventricular receptors. The endings normally have very low tonic activity with a sporadic discharge. Some of them could be activated by injection of epinephrine or veratridine and by increased central blood volume. These studies concluded that the avian atria and ventricles are exclusively innervated by thin fiber afferents probably belonging to the C-fiber category.

E. Cardiopulmonary Receptors and Control of Renin Release

1. Neural Control of Renin Release. The renin release in the kidney is controlled by several mechanisms (*Davis* and *Freeman*, 1976; *Haber*, 1976). During recent years the role of the renal sympathetic nerves in renin release has been the subject of a great number of studies. Direct electric stimulation of the renal nerves with low frequencies induces a marked increase in renin output (*La Grange* et al., 1973) despite no changes in renal blood flow or flow distribution. The reflex control of renin release via the sympathetic nerves has also been investigated in detail. There is now evidence that the renin response to nonhypotensive hemorrhage can be attenuated by neural blockade (*Bunag* et al., 1966; *Tanigawa* et al., 1974). Also the renin release during tilting, salt depletion, and administration of diuretic involves a significant neural component, since the denervated kidney has a much less pronounced renin release than the innervated kidney (*Zanchetti* et al., 1976). The increased plasma renin caused by a slow nonhypotensive hemorrhage in unanesthetized dogs and rabbits already occurs at moderate blood losses (*Claybaugh* and *Share*, 1973; *Weber* et al., 1973); this suggests a rather sensitive cardiovascular mechanism.

2. Arterial Baroreceptors and Renin. Which group of receptors can then influence the renin release through renal sympathetic pathways? The first receptor station examined was the arterial baroreceptors; opinions differ about the role of these receptors in renin release. *Bunag* et al. (1966) showed that occlusion of the common carotid arteries could cause release of renin. In contrast, *Hodge* et al. (1966) claimed that occlusion of the common carotid arteries in the dog did not alter the angiotensin concentration

unless long periods of occlusion were maintained. Later *Brennan* et al. (1974) found that changes in carotid sinus pressure do not influence renin release, a finding in contrast to a study by *McPhee* and *Lakey* (1971) showing that carotid occlusion could markedly increase the output of renin in sodium depleted anesthetized dogs. This controversy about the effect of the carotid baroreceptors on renin release can probably be explained by the results of *Jarecki* et al. (1978). In this study a reduction in carotid sinus pressure resulted in an increase in renin release in only three of ten dogs with intact vagal afferents. After section of the vagal nerves carotid sinus hypotension resulted in increased renin release in nine of the ten dogs. In contrast, vagal nerve section resulted in a significant increase in basal level of renin release in dogs with the carotid sinuses vascularly isolated, whereas intrasinusal pressure remained equal to the existing aortic pressure. The increase in renin release could be inhibited if the renal arterial pressure was allowed to increase during the carotid hypotension. The conclusion was that the carotid baroreceptor reflex is involved in the neural control of renin release. However, concomitant activation of cardiopulmonary receptors or a substantial rise in renal arterial pressure can suppress the reflex rise in renin release. These data may explain the earlier controversies since in a study by *Hodge* et al. (1966) and *Brennan* et al. (1974) the vagal nerves were intact, but in a study by *McPhee* and *Lakey* (1971) the vagal nerves were cut.

3. Cardiopulmonary Receptors and Renin. In recent years the role of the vagal afferents in the control of renin release has also been the subject of several studies. *Hodge* et al. (1969) were the first to suggest the role of vagal afferents in the reflex control of renin release and plasma angiotensin concentration. This problem has also been studied in detail by *Mancia* et al. (1975). In dogs with the aortic nerves cut and the sinuses vascularly isolated, bilateral vagal cold block caused an increase in aortic blood pressure, a decrease in renal blood flow, and a three–five fold increase in renin output. When the sinus pressure was maintained at the level of the existing arterial pressure, vagal cold block induced only a small increase in arterial pressure and a small decrease in renal blood flow, but a similarly marked increase in renin release. This phenomenon is shown in Figure 12. The release of renin was entirely due to increased activity in renal sympathetic nerves.

The role of the vagal nerves in the control of renin secretion has also been investigated in several very recent papers. Thus *Yun* et al. (1976) examined the effect of the carotid baroreceptors and the vagal afferents on renin release. These authors showed that vagotomy could increase the plasma renin activity in the dog as could carotid occlusion. Results along

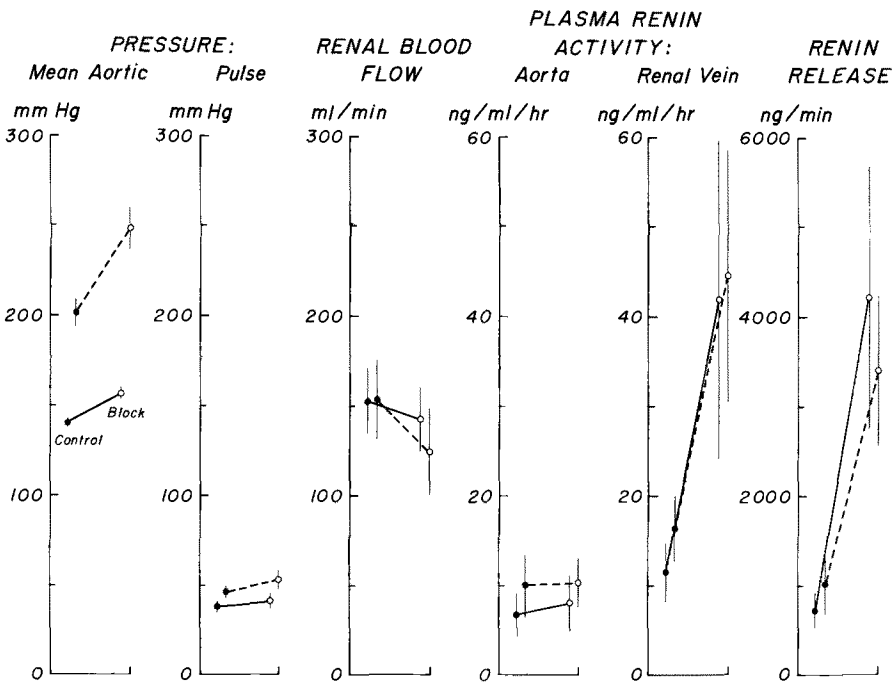

Fig. 12. Comparison of the effects of bilateral cervical vagal cold block at different carotid sinus pressures on aortic blood pressure, aortic pulse pressure, left renal blood flow, and plasma renin activity in the aorta and the left renal vein, and renin release, given as mean values ± SE for six dogs with severed aortic nerves. *Solid line,* sinus pressure maintained at the level of the mean aortic blood pressure before vagal block; *broken line,* sinus pressure maintained at 40 mm Hg; ●, control; ○, block. At low sinus pressure, vagal cold block caused a greater increase in aortic blood pressure and a greater decrease in renal blood flow, but the amount of renin released was not significantly different. (From *Mancia* et al., 1975a, by permission of American Heart Association)

the same line have also been presented by *Brosnihan* and *Travis* (1976). In their studies bilateral cervical vagotomy was followed by sustained increase in plasma renin concentration of anesthetized cats made hypervolemic by intravenous saline infusion. The increase in plasma renin concentration was attributed to vagotomy of the right side, which is the main afferent pathway for cardiac C-fibers in the cat (*Jones,* 1953). Bilateral carotid artery occlusion did not increase the concentration of plasma renin.

Results supporting a role of cardiopulmonary receptors in the control of renin release are also presented in two other reports. Thus *Brennan* et al. (1971) claimed that right but not left atrial distension inhibits renin release. *Zehr* et al. (1976) studied the effect of brief periods of left pulmonary vein distension on the rate of renin secretion in sodium-restricted anes-

thetized dogs. In their study renin secretion was depressed to 56% of the control during left atrial distension despite no change in arterial pressure, central venous pressure, or renal blood flow. This effect was mediated via the renal nerves, and cervical vagotomy totally abolished the response. A recent paper by *Thames* (1977), of interest in this respect, showed that intracoronary injections of veratrum alkaloids could markedly inhibit the renin release during nonhypotensive hemorrhage (10% of body wt.) despite a significant drop in blood pressure. The response was totally abolished after vagotomy. The role of vagal afferents in the control of renin release is further stressed by the Milan group in a recent study (*Stella* et al., 1978). These authors showed that vagotomy in cats could reflexly induce release of renin, however, the response was transient and disappeared within 30 min. The response was also inhibited by fluid expansion. Interestingly, the increase in renin obtained in anesthetized cats by tilting was also clearly attenuated after cervical vagotomy. They concluded that vagal fibers participate in the reflex control of renin release, but also additional reflex pathways might be involved. Finally, *Thames* et al. (1978a) showed that nonhypotensive hemorrhage could release renin from the kidney in the anesthetized dog; this release was abolished by vagotomy. The degree of hemorrhage used (4–6 ml/kg) did not lower the blood pressure or change carotid sinus baroreceptor discharge. *Thames* et al. concluded that cardiopulmonary receptors can respond to acute moderate decreases in blood volume which are not sufficient to change arterial blood pressure and so alter input from arterial baroreceptors. The reflex increase in renin secretion and hence activation of the renin-angiotensin-aldosterone system would imply a role for these receptors in the long-term regulation of blood volume.

Thus, the literature presents substantial evidence that cardiopulmonary receptors with vagal afferents can significantly influence renin release. These receptors are in fact probably the major receptor station for the neural control of renin. No direct evidence shows whether cardiac endings with medullated or nonmedullated afferents is the receptor group involved. However, the following experimental data suggest that cardiac C-fibers play a role in the response. First, it has been established that the cardiopulmonary C-fibers are mainly responsible for the tonic vasomotor inhibition on the renal vasculature (*Thorén* et al., 1976) and on the peripheral circulation (*Thorén* et al., 1977b) mediated via the vagal nerves. Second, other data clearly indicate that the cardiac C-fibers really have a strong effect on the sympathetic outflow to the kidney (see Sect. IV). Third, the strong inhibitory effect on renin release of small doses of veratrum alkaloid suggests that the cardiopulmonary C-fibers are able to strongly influence renin release. Fourth, the study by *Thames* et al. (1971) indicates

that vagal receptors other than the medullated afferents in the atria contribute to the regulation of renin release. These authors performed cardiac autotransplantation by a method that leaves the vein-atrial junctions intact. Thus the receptor areas for the medullated atrial afferents were not denervated. These animals showed subnormal increase in plasma renin in response to bleeding. Finally, *Oparil* et al. (1970) showed that the increased renin release in man upon tilting could be markedly attenuated during a fainting reaction. As discussed later (Sect. VIII) the vasovagal fainting reaction is probably triggered by an increased activity in left ventricular C-fibers. Thus even if firm evidence is lacking at present, these data suggest that cardiac receptors with vagal C-fiber afferents are an important receptor station for the neural control of renin release.

VII. The Role of Cardiopulmonary Afferents in Control of Human Circulation

Obviously only noninvasive methods can be used in the study of man, and that will markedly limit the experimental approaches. However, there are different methods by which one can alter the cardiopulmonary blood volume with small or no changes in arterial blood pressure, suggesting the role of cardiopulmonary afferents in the observed reflex responses. It is, of course, impossible in man to define by noninvasive method the specific receptors in the cardiopulmonary area, the type of afferent fibers, and the nerve pathways for the observed reflex responses. Thus, any suggestions concerning these points must be considered as speculative, since they are based on experimental evidence obtained in animals.

A. Bezold-Jarisch Reflex

As in cats and dogs, veratrum alkaloids can induce vasodepressor reflexes in man. However, not until recently has it been clearly established that vasodepressor reflex originating from the heart can be elicited. Thus it was shown by *Eckberg* et al. (1974) that injection of angiographic contrast medium in the coronary arteries in man induces a vasodepressor reflex with bradycardia and hypotension.

B. Increased Central Blood Volume

The first study on reflex effects in man elicited by stimulation of cardiopulmonary receptors was made by *Roddie* et al. (1957). These researchers

studied the effect of cardiopulmonary distension in man when passively raising the legs and lower trunk of a supine subject. This maneuver increased the central venous pressure without any changes in the arterial pressure and induced a marked increase in blood flow in the forearm due to reflex inhibition of vasocontrictor outflow.

The simple maneuver of seating a person on a chair in a thermally neutral bath with his head above the water (*Gauer* et al., 1970; *Epstein,* 1976) redistributes about 700 ml blood from the peripheral veins to the central circulation (*Arborelius* et al., 1972). The right atrial pressure increases from −2 to +16 mm Hg, and the arterial blood pressure increases ∿ 10 mm Hg. Thus even if cardiopulmonary receptors are likely to be one receptor station responsible for the reflex effects elicited during water immersion, they are certainly not the only receptors excited.

The effect of water immersion on kidney function has been studied in a large number of papers by *Epstein* and co-workers (see *Epstein,* 1976). Water immersion markedly increased the renal sodium output. Some humoral agent might be involved (e.g., a natriuretic factor), but inhibition of renal sympathetic outflow is also likely to be involved. Interstingly enough, water immersion in man can also decrease plasma renin activity by more than 60% and lower the plasma concentration of ADH. The mechanisms behind these marked changes in the renal handling of sodium and water in man are, of course, difficult to establish. They are not due to changes in composition of the blood, and it is not likely that the small change in arterial blood pressure is the main factor responsible. The marked cardiac distension during water immersion is likely to activate cardiopulmonary receptors, and it is possible that these receptors contribute to the responses.

C. Lower Body Negative Pressure

Other methods have also been used to study cardiac reflexes in man, e.g., local application of reduced pressure to the lower body (lower body negative pressure or LBNP). This method has been used extensively to stimulate potential cardiovascular changes during acceleration, e.g., during space flight, and has recently been reviewed by *Wolthuis* et al. (1974). Application of LBNP up to −10 mm Hg decreases central venous pressure without changing the arterial blood pressure or pulse pressure, hence implying a selectively decreased activity in cardiopulmonary receptors with no change in the arterial baroreceptor activity (*Zoller* et al., 1972). Higher degrees of LBNP also decrease the blood pressure and thus represent a combined effect of cardiopulmonary receptor and baroreceptor unloading. LBNP of

−10 mm Hg increases the skeletal muscle vascular conductance about 60% despite no change in the arterial blood pressure; this indicates that the cardiopulmonary receptors in man exert an important influence on muscle vascular tone in contrast to the situation in dogs and cats (see Sect. IV). Changes in venomotor tone have been both claimed (*Gilbert* and *Stevens*, 1966) and denied (*Mark* and *Abboud*, 1979; *Shepherd* and *Vanhoutte*, 1975) to participate in the reflex responses to LBNP. *Johnson* et al. (1974) also studied the effect of LBNP on forearm and splanchnic flow in man and showed that LBNP of −20 mm Hg did not change arterial blood pressure, but rather induced a vasoconstriction in forearm and splanchnic vascular beds. The forearm blood flow reached 67% of the control value, and the splanchnic blood flow, 89% of the control value. They concluded that unloading of cardiopulmonary receptors initiate splanchnic and forearm vasoconstriction with more pronounced vasoconstriction occurring in the forearm.

Recent data of *Mark* and *Abboud* (1979) support the above conclusion. These authors measured the clearance of indocyanine green dye by the same technique. Simultaneous application of neck suction (to activate carotid baroreceptors) did not alter the forearm constriction during LBNP, but decreased the splanchnic vasoconstriction. The data suggested that activation of carotid baroreceptors had little effect on adrenergic outflow to forearm vessels, but a marked effect on splanchnic vessels. Experiments performed with direct recordings of the sympathetic nerve traffic in man, however, indicate that carotid baroreceptors can influence the sympathetic outflow to the skeletal muscles (*Wallin* et al., 1975; *Sundlöf*, 1977). In contrast, the data by *Mark* and *Abboud* (1979) indicate that low pressure receptors have a profound effect on the forearm vessels, but a rather moderate effect on the splanchnic vessels. LBNP also has little effect on heart rate (*Zoller* et al., 1972), which normally seems to be mainly controlled by the arterial baroreceptors (*Takeshita* et al., 1979).

The effect of LBNP on renin release has been studied in several investigations. In a study by *Fasola* and *Martz* (1972) the effect of LBNP of −20 to −50 mm Hg was tested, and a significant increase in renin activity accompanied the LBNP. This effect was augmented at higher levels of lower body suction. The researchers concluded that cardiopulmonary receptors could influence renin release. *Bevegård* et al. (1977a) in a recent paper reached a similar conclusion. These authors showed that LBNP of −40 mm Hg induced a markedly increased renin release despite small changes in mean arterial blood pressure. The recent abstract by *Julius* and *Kiowski* (1977) also suggests that cardiopulmonary receptors play a role in the reflex control of renin release in man. They examined the changes in renin release during inflation of cuffs around the thighs and reported a clear-cut increase in renin release despite no change in arterial blood pressure.

In contrast, *Mark* et al. (1978) claimed that isolated changes in cardiopulmonary receptor activity during LBNP at −10 and −20 mm Hg did not release renin despite a clear-cut reflex increase in forearm vascular resistance. LBNP at −40 mm Hg decreased central venous and arterial pulse pressure and thus reduced both low and high pressure receptor inhibition, producing an increase in renin release. Isolated changes in arterial baroreceptor activity did not change renin release either (*Mark* et al., 1978). They concluded that reflex increase in renin release can be seen in man only when *both* arterial baroreceptors and the low pressure receptors were unloaded. Man should thus differ from dogs and cats, in which isolated changes in cardiopulmonary receptor activity can release renin (see above).

In dogs (*Claybaugh* and *Share,* 1973) and rabbits (*Weber* et al., 1973) a small nonhypotensive hemorrhage could reflexly release renin. Thus a hemorrhage of only 1.2 ml/kg in the conscious rabbit caused increased renin release. In contrast, a hemorrhage of about 10% of blood volume in man, corresponding to $\sim$ 7 ml/kg body wt. did not release renin (*Goetz* et al., 1974; *Hesse* et al., 1975). Consequently the sensitivity of the receptor mechanism releasing renin seemed to be considerably lower in man.

Changes in cardiopulmonary receptor activity in dogs can influence the gain of the arterial baroreceptor reflex (*Vatner* et al., 1975; *Mancia* et al., 1976b). *Bevegård* et al. (1977b, c) claimed that the same phenomenon can be observed in man during simultaneous application of LBNP and neck suction. This problem has also been studied by *Takeshita* et al. (1979), who examined the sensitivity of the arterial baroreceptor reflex during LBNP of −20 mm Hg or leg raising. No changes were found in the gain of the arterial baroreceptor reflex during variations in central blood volume. Volume load induced reflex tachycardia in the conscious dog (*Horwitz* and *Bishop,* 1972; *Vatner* et al., 1975) probably due to inhibition of the baroreceptor reflex and to activation of atrial medullated fibers and sympathetic afferents (Sect. IV. E). In man (see *Takeshita* et al., 1979) volume load does not increase heart rate. Hence, the interaction between high and low pressure reflexes is possibly different in dogs and in man.

In conclusion, the cardiopulmonary receptors in man as studied by LBNP seem to have a somewhat different reflex pattern than in dogs and cats. They seem to have a powerful effect on the vasomotor neurons controlling the muscle resistance vessels. In contrast, the arterial baroreceptors seem to have a rather weak reflex effect on the muscle vessels in man (*Bevegård* and *Shepherd,* 1966; *Abboud* et al., 1976; *Mark* and *Abboud,* 1979) but a strong effect on the splanchnic vessels. Moreover, the human heart rate seems to be controlled mainly from high pressure receptors. Finally, the cardiopulmonary receptors in man are probably one receptor station of importance for the neural control of renin release.

D. Cardiopulmonary Receptors and Weightlessness

Weightlessness during space flights also redistributes the blood with a marked increase in central blood volume (*Sandler,* 1976); probably ∿ 700 −1000 ml of blood are displaced from the lower body to the central circulation. Pilots during space missions show vasodilatation in the legs despite a slight reduction in the arterial blood pressure. During prolonged space flights marked changes in the blood volume and sodium balance are seen. Thus ADH and renin release is inhibited, the plasma volume is decreased about 10%, and a marked decrease in body fluid volume is seen. These changes in renal water and sodium hemostasis during prolonged space flight may be at least partly due to reflexes fom cardiopulmonary receptors (*Sandler,* 1976).

E. Cardiac Receptors and Respiratory Sinus Arrhythmias

There is a positive relationship between the depth of breathing and the degree of respiratory sinus arrhythmias (RSA) in man. *Freyschuss* and *Melcher* (1976) recently suggested that changes in activity in arterial baroreceptors alone cannot explain the RSA. Moreover they proposed that the increased heart rate in early inspiration was triggered from atrial medullated receptors (Bainbridge reflex) and that the bradycardia at later stages of inspiration was a reflex of ventricular receptors.

F. Physiologic Significance of Cardiopulmonary Receptors

The studies of the reflex effects of cardiopulmonary reflexes in man clearly indicate that these receptor stations are of major importance for the control of the skeletal muscle circulation and that the arterial baroreceptors are of importance for the control of the splanchnic circulation and the heart rate under physiologic conditions.

No data exist on the control of kidney circulation, but some data indicate that changes in renin release can be triggered from cardiopulmonary receptors or from combined change in arterial baroreceptor and cardiopulmonary receptor activity.

The fact that cardiopulmonary receptors in man have such a profound effect on the muscle circulation suggests that these receptors are of major significance for circulation control during standing when ∿ 500–700 ml of blood is distributed from the central circulation, the major part of which is pooled in the leg veins (*Gauer* and *Thron,* 1965). As discussed

above, it is a controversial issue whether or not cardiopulmonary receptors can trigger venomotor reflexes. Nevertheless, the control of the circulation in the legs is no doubt of major importance during standing since ganglion blocking agents normally trigger orthostasis.

Reflex adjustments of the precapillary resistance in the skeletal muscle are also of importance in diminishing the outward filtration of plasma during standing (*Mellander* et al., 1964), thus preventing decreases in plasma volume.

As discussed above, the vagally mediated vasomotor inhibition in cats is due to cardiopulmonary C-fibers. Whether man has C-fiber endings similar to those of dogs and cats is not known. There is, however, no reason to believe that the tonic vasomotor inhibition from the cardiopulmonary area in man should be dependent on other receptor stations.

VIII. Pathophysiologic Implications of Cardiac Vagal C-Fibers

A. Hemorrhage and Vasovagal Syncope

1. Reflex Adjustments to Hemorrhage. The ability of the cardiopulmonary as compared to the carotid sinus receptors to induce compensatory cardiovascular adjustments to blood loss has been examined by *Öberg* and *White* (1970b). In anesthetized cats with normally functioning arterial baroreceptor reflexes, the fall in arterial blood pressure upon hemorrhage of 10% of blood volume was the same whether or not the vagal cardiac receptors were intact. After arterial baroreceptor denervation hemorrhage of the same magnitude resulted in tachycardia and increased resistance, especially in the renal bed, whereas the response in the muscle was much smaller. The fall in blood pressure was considerably greater after baroreceptor denervation. These studies thus indicate that the afferent input from the cardiopulmonary area has a particularly strong engagement on the vasomotor neurons with a more marked effect on the skeletal muscle circulation.

In anesthetized dogs with the aortic nerves cut, hemorrhage of 10% of the blood volume decreases the blood pressure by 13%. With only the carotid baroreceptor reflex operative, only the vagal afferents operative, or neither of these reflexes operative, the decrease in arterial pressure was 18%, 24%, and 42%, respectively (*Pelletier* et al., 1971). With only the carotid or the vagal baroreceptors operative, hemorrhage caused a similar degree of renal and mesenteric vasoconstriction and splenic contraction. In contrast, the constriction in the hindlimb was less when only the vagal afferents were intact. The response of the different vascular beds to 10%

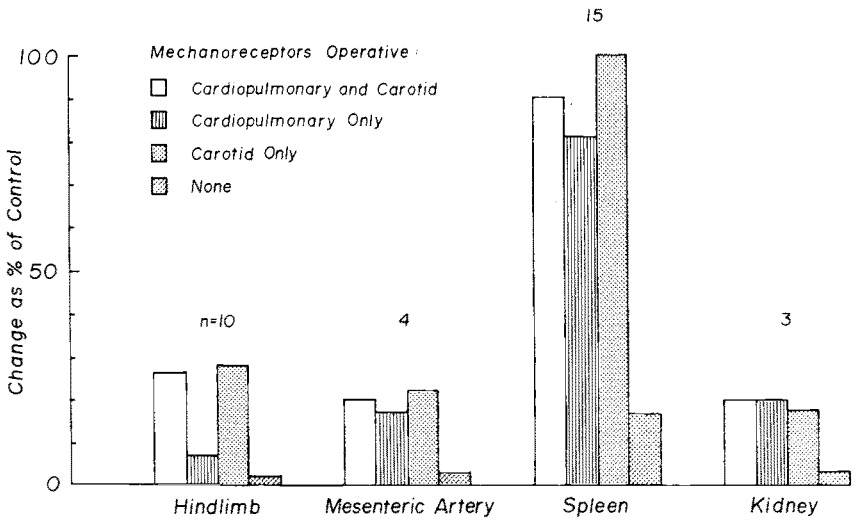

Fig. 13. Role of carotid baroreceptors and cardiopulmonary receptors in causing reflex constriction of resistance and capacitance vessels in response to 10% hemorrhage; studies in dogs with both aortic nerves cut. The number of dogs is given above each set of experiments. Hindlimb and mesenteric beds were perfused at constant flow, hence the percentage increase in perfusion pressure above control values reflects the degree of constriction of the resistance vessels in these beds. The percentage increase in pressure within the isolated spleen is an index of the constriction of the splanchnic capacitance vessels. The kidneys were perfused at constant pressure, and the percentage decrease in blood flow with hemorrhage is plotted. (Data from *Pelletier* et al., 1971. Figure from *Thorén* et al., 1976, by permission of American Heart Association)

hemorrhage in dogs with different intact afferent inputs is shown in Figure 13.

Reflex responses in the peripheral vascular beds after hemorrhage have also been studied by *Chalmers* et al. (1967). They used nonanesthetized rabbits and measured the blood flow in the portal, renal, muscle, and skin beds before and after baroreceptor denervation. Hemorrhage induced vasoconstriction in the kidney, the muscle, the portal bed, and the skin in the intact rabbit. However, in animals with baroreceptor denervation the constriction was absent in the portal, muscle, and skin beds, although a significant vasoconstriction was still evident in the renal bed but of smaller magnitude. The conclusion drawn was that the arterial baroreceptors were of major importance for reflex adjustments in the conscious rabbit after hemorrhage, but other afferent inputs presumably from the cardiopulmonary area were also of importance for the control of renal vascular resistance during hemorrhage. In this respect the study by *Vatner* (1974) is quite puzzling. *Vatner* showed that hemorrhage in the conscious dog induced vasoconstriction in the hindlimb and the gut, but a vasodilatation

in the kidney. The vasodilatation in the kidney is at variance with data from *Korner* et al. (1967) and *Gorfinkel* et al. (1972), who show a marked vasoconstriction in the *conscious* rabbit or dog. In the *anesthetized dog* hemorrhage normally induces vasoconstriction in the kidney (see *Chien*, 1967). However, the renal sympathetic activity in the anesthetized rabbit has been reported not to increase after hemorrhage (*Aars* and *Akre*, 1971). The reason for these different results is not known.

Thus, available data indicate that in the experimental animals cardiopulmonary receptors subserved by vagal afferents participate in the circulatory adjustment to hemorrhage. Their importance for maintenance of blood pressure seems less than that of the carotid baroreceptors due to the lesser influence of the vagal afferents on muscle vascular resistance. Evidence, however, indicates that the cardiopulmonary receptors are one receptor station of importance for the control of renal resistance during hemorrhage. As discussed earlier (see Sect. IV. B) the cardiopulmonary C-fibers are probably the fiber group responsible for the vagally mediated vasomotor changes during hemorrhage. However, the cardiopulmonary receptors may be of greater importance for the circulatory control during hemorrhage in man, because in man these receptors might have a more powerful effect on the muscular vascular resistance (Sect. VII) than in several other species.

2. **Vasovagal Syncope Reaction**. During severe hemorrhage in man a vasovagal syncope reaction can sometimes be evoked (*Barcroft* and *Edholm*, 1945) with a marked bradycardia, fall in blood pressure, and concomitant forearm vasodilatation. The vasodilatation has been explained as due to activation of the cholinergic outflow to the skeletal muscles (*Barcroft* and *Edholm*, 1945). However, data by *Murray* and *Shropshire* (1970) indicate that atropine injection does not influence the forearm vasodilatation during vasovagal syncope reaction triggered by lower body negative pressure. *Folkow* et al. (1965) have also suggested that the overshoot in muscle blood flow seen during the vasovagal reaction is purely of local nature and simply an example of reactive hyperemia due to withdrawal of sympathetic tone. Recently marked inhibition of the sympathetic outflow to the skeletal muscle has also been shown neurophysiologically to occur during orthostatically induced fainting in man (*Burke* et al., 1977).

The mechanism behind the vasovagal syncope reaction has been discussed for many years. Originally *Jarisch* (1941) suggested that activation of the Bezold-Jarisch reflex was the reason for the vasovagal syncope reaction. Later also *Konzett* and *Rothlin* (1951) showed that injection of 20 μg adrenaline in cats can induce a reflex vasodepressor reflex triggered by vagal receptors. They suggested that this was a Bezold-Jarisch reflex. The va-

sodepressor reflex from adrenaline injection can be augmented by previous injections of small doses of veratridine (*Cerletti* et al., 1948). The mechanisms behind the vasovagal syncope reaction have also been discussed by several other authors. Thus *Henry* (1950), *Pearce* and *Henry* (1955), and *Sharpey-Schafer* (1956, 1958) suggested that cardiac afferents play a role in the fainting reaction during hemorrhage: It was proposed that the left ventricular receptors were stimulated by the large transient intraventricular pressure rises developed during late systole, when all the blood has been ejected and the ventricle contracts around an empty chamber. Such large transient rises have been shown to occur during hemorrhage in animals (*Gauer* and *Henry,* 1964). *Scharpey-Schafer* also postulated that the vasovagal reaction elicited by fear and emotions could be triggered by activation of cardiac receptors. The mechanism should be an increased sympathetic outflow to the heart with a lowered cardiac filling possibly due to venodilatation. However, *Sharpey-Schafer* did not present any evidence for this hypothesis, and even if such an activation of the cardiac receptors can possibly occur during strong sympathetic drive (*Konzett* and *Rothlin,* 1951; *Sleight* and *Widdicombe,* 1965; *Thorén* 1977; *Wennergren* et al., 1977), activation (*Löfving,* 1961) of centers in the central nervous system are likely to be the dominating factor for emotional (but not posthemorrhagic) fainting. An equivalent in experimental animals could be the playing-dead reaction (see *Folkow* and *Neil,* 1971).

The cardiovascular responses to severe hemorrhage were originally examined by *Ebert* et al. (1962), who showed that hemorrhage in dogs could trigger a vagally mediated bradycardia of unknown origin. Definite proof for the role of cardiac receptors in the vasovagal bradycardia elicited by hemorrhage was provided by *Öberg* and *White* (1970b). Bleeding anesthetized cats rapidly, they observed in some animals a marked vasovagal reflex bradycardia due to activation of receptors located in the heart. *Öberg* and *Thorén* (1972a) recorded nerve traffic from left ventricular C-fibers and showed that these receptors could be markedly activated during severe hemorrhage or peripheral pooling of blood. The mechanism of receptor activation is probably the combined effect of an increased sympathetic outflow and a lowered ventricular filling. These two stimuli together induce a powerful contraction around an almost empty chamber, giving rise to deformation and squeezing of the myocardium, which activates the receptors.

B. Cardiac Receptors and Aortic Stenosis in Man

Fainting reactions sometimes with fatal outcome commonly occur in patients with severe aortic stenosis. The fainting reaction, often triggered by

exertion result in bradycardia and hypotension. The condition was originally suggested to be due to hyperreactive carotid sinus baroreceptor reflexes, but *Johnson* (1971) proposed that activation of left ventricular baroreceptors might be of importance for the fainting and sudden death in these patients, because the marked rise in ventricular pressure might initiate a depressor reflex producing bradycardia, peripheral vasodilatation, and venous dilatation. The diminished venous return together with a lowered systemic vascular resistance result in severe hypotension and syncope. Furthermore, the coronary blood flow is rapidly reduced in a phase of heavy left ventricular work, and the concomitant myocardial ischemia causes arrhythmias, which result in final failure of the circulation and death. This very interesting hypothesis was confirmed experimentally in man by *Mark* et al. (1973b) and *Daoud* and *Kelly* (1975). These authors recorded changes in forearm blood flow during exercise in patients with severe aortic stenosis, patients with mitral valve stenosis, and normal patients. In the control group and the group with mitral valve stenosis forearm vasoconstriction occurred during exercise. However, in sharp contrast, the patients with aortic stenosis showed forearm vasodilatation during leg exercise. The authors concluded that this inhibition of an expected vasoconstrictor response was probably triggered by activation of left ventricular receptors and that this depressor reflex is of importance for the fainting reaction and sudden death in patients with aortic stenosis. As discussed before, the left ventricular C-fiber receptors are most likely mainly responsible for these reflex effects.

C. Cardiac Receptors in Heart Failure

Patients with congestive heart failure show marked abnormalities in regional circulation. Part of these abnormalities is due to disturbed local control of the circulation with a limited ability to dilate the peripheral resistance vessels (*Zelis* et al., 1975).

However, there is also evidence for an increased sympathetic adrenergic tone to the kidney during heart failure. Thus, cardiac failure in dogs induces a marked vasoconstriction and redistribution of the flow in the kidney via sympathetic mechanisms (*Barger* et al., 1959; *Barger,* 1966; *Sparks* et al., 1972). The same type of redistribution of the kidney flow with a marked cortical vasoconstriction has also been observed in patients with congestive heart failure (*Kilcoyne* et al., 1973). The markedly decreased sodium output during heart failure in dogs (*Barger* et al., 1959) and man (*Brod,* 1979) is also partly due to the sympathetic discharge to the kidney. Furthermore the renal vasoconstrictor response to severe exercise is markedly augmented in dogs with experimental heart failure (*Millard* et al.,

1972). In normal dogs exercise induced small changes in renal flow; however, in dogs with experimental heart failure renal flow was decreased more than 60%, and this decrease was mainly due to increased sympathetic outflow.

Much speculation has centered on the afferent mechanism responsible for the abnormal sympathetic tone in heart failure. *Barger* et al. (1959) suggested an abnormal function in the carotid sinus mechanisms. This hypothesis has been tested experimentally by *Higgins* et al. (1972), who showed that dogs with experimental heart failure had a marked derangement in the baroreceptor mechanism. *Zelis* et al. (1975) suggest that increased activity in skeletal muscle afferents may contribute to the increased sympathetic outflow. A change in sensitivity of cardiac receptors has also been discussed. Thus *Greenberg* et al. (1973) showed that the atrial medullated receptors had much higher thresholds and lower sensitivity during experimental heart failure. The mechanism for the reduced sensitivity was a combination of a decreased left atrial compliance and a structural change in the receptor endings (*Zucker* et al., 1977b). No studies specifically dealing with changes in the sensitivity of the cardiac C-fibers during chronic heart failure have been made, but studies by *Thorén* et al. (1979b) are relevant for this problem. These studies showed that left atrial C-fiber endings had a higher threshold in the spontaneously hypertensive rat in comparison with the normotensive rat. The reason for this difference was probably a decrease in left atrial wall distensibility due to a chronic elevation of left atrial pressure (*Noresson* et al., 1979).

The response of left ventricular C-fiber endings in cats to aortic occlusion and volume expansion was also markedly attenuated by decreasing the ventricular contractility by propranolol (Fig. 5; *Thorén*, 1977). Decreased cardiac contractility is an early sign of cardiac failure, and therefore also the sensitivity of the left ventricular C-fiber endings are likely to be markedly decreased in heart failure.

Zehr et al. (1971) showed that dogs with chronic mitral stenosis have a much smaller increase in plasma ADH upon hemorrhage than normal dogs. Thus the altered distensibility of the atrial wall upon chronic pressure load markedly influences the gain of volume receptor reflexes.

Recently, however, evidence has been presented for a resetting of cardiopulmonary receptors during *chronic congestive heart failure in man*. *Harris* et al. (1977) examined the forearm vasodilator response to passive leg raising (*Roddie* et al., 1957) in normal patients and in patients with congestive heart failure. In the latter group no vasodilator response was seen despite evidence of left atrial distension, indicating a resetting of the cardiopulmonary receptors. There are no data on the renal effects of cardiopulmonary receptor activation in patients with chronic congestive heart failure. However, resetting of the cardiopulmonary receptors likely

also contributes to the impaired control of renal function during these circumstances.

Interestingly enough, patients with myocardial infarction and *acute congestive heart failure* show increased urine flow and glomerular filtration rate despite the fall in arterial blood pressure (*Efendigil* et al., 1975; *Bennet* et al., 1977). Several of these patients also showed an increased sodium output (*Bennet* et al., 1978). This increased renal function was most pronounced in patients with radiologic signs of elevated left atrial pressure (*Bennet* et al., 1977). A logical but of course speculative explanation for these findings is that an acute rise in left atrial pressure increases the activity in left atrial and ventricular C-fiber endings, and hence a reflex inhibition of renal sympathetic outflow occurs. Increased activity in left ventricular C-fibers within the ischemic zone is also triggered by the systolic bulging of the ischemic area.

In summary, there is evidence that atrial medullated receptors have markedly increased thresholds and lowered sensitivity upon chronic elevation of the atrial pressure, and even if experimental evidence is lacking, the same is probably true for the atrial C-fibers and also for ventricular C-fiber endings. Possibly this decreased sensitivity and higher threshold of the cardiac C-fiber group together with arterial baroreceptor reflexes contribute to the increased sympathetic discharge and to the altered renal function observed during congestive heart failure in man. However, such a suggestion must be considered speculative at present, and any definite conclusion will have to wait until more experimental work is carried out.

D. Cardiac C-Fibers and the Effect of Digitalis

The autonomic nervous system is of importance for the cardiovascular changes induced by digitalis glycosides such as acetylstrophanthidin (*Gillis* et al., 1975a).

The reflex vagal bradycardia induced by acetylstrophanthidin is partly due to activation of arterial baroreceptors (*Gillis* et al., 1975b; *McRitchie* and *Vatner*, 1976). There is also evidence that the bradycardia is partly due to increased activity in cardiopulmonary vagal afferents (*Gillis* et al., 1975a, b). *Gillis* et al. used anesthetized cats with the efferent vagal tone blocked by atropine. Injection of acetylstrophanthidin with only the carotid sinus baroreceptors intact, only the vagal afferents intact, or all the receptor stations intact induced bradycardia of about the same order of magnitude, thus indicating that the changes in heart rate were a combined effect of increased afferent input from baroreceptors and from vagal afferents. *Fukuda* (1950) and *Melville* (1952) have also shown that digitalis glycosides can activate the Bezold-Jarisch reflex.

The increased activity in tonic vagal inhibition following administration of digitalis is due to increased activity in cardiac vagal C-fibers; administration of small doses of acetylstrophanthidin into the epicardium of the left ventricle in dogs caused markedly increased activity in epimyocardial C-fibers (*Sleight* et al., 1969). *Öberg* and *Thorén* (1972b) have also shown that strophanthin can activate left ventricular C-fibers in the cat.

The fact that there is increased activity in baroreceptor afferents and in cardiac vagal C-fibers upon administration of digitalis glycosides raises the important question whether part of the renal effects of the alkaloids are due to reflex inhibition of the elevated sympathetic outflow to the kidney. Although there is no direct experimental evidence for such a mechanism, it is a very attractive hypothesis. The digitalis glycosides would increase the sensitivity of the cardiac receptors, and they would then respond to the increased filling pressure of the heart.

However, some indirect support for such a mechanism is forthcoming from the experiments of *Mason* and *Braunwald* (1964). These researchers studied the effect of intravenous injection of ouabain (a digitalis glycoside) on forearm blood flow in both normal patients and patients with congestive heart failure. The normal patients constricted their forearm vessels upon ouabain administration, probably due to a direct smooth muscle effect. In patients with congestive heart failure ouabain elevated forearm blood flow. The authors suggested a reflex withdrawal of sympathetic tone to explain this effect. Arterial baroreceptors are unlikely to be the major receptor stations responsible, because baroreceptor reflexes have rather small influence on forearm flow in man (*Abboud* et al., 1976). A more likely alternative is provided by the cardiopulmonary C-fibers. A reflex inhibition of the sympathetic outflow to the skeletal muscles is then probably accompanied by a similar sympathetic inhibition to the kidney.

Subjected to many studies, the emetic effect of digitalis seems partly due to reflexes from cardiopulmonary afferents (see *Wang*, 1965). If so, the cardiac C-fibers are probably the responsible afferents, because they seem to have a specific effect on the vomiting center (*Abrahamsson* and *Thorén*, 1972, 1973).

E. Cardiac Receptors and Hypertension

1. Resetting of Cardiac Receptors in Hypertensive Dogs and Rats. The development of different rat strains, which aquire spontaneous hypertension, has greatly stimulated research on control of the circulation in hypertension (*Hallbäck* and *Weiss*, 1977). One of these strains, the spontaneously hypertensive rat (SHR), was developed by *Okamoto* in Japan. The triggering factor for hypertension in this strain of rats seemed to be a central hy-

perreactivity in the sympathetic nervous system to external stimuli. Increased pressure load initiates structural adaptation (*Folkow* et al., 1973), both in the peripheral vasculature and in the heart. The structural adaptation in the vessel walls changes the sensitivity of the arterial baroreceptors (*McCubbin* et al., 1956; *Aars,* 1968). However, there is little data on the behavior of the volume receptors in the hypertensive animals. Recent studies by *Kezdi* (1976) indicate that left ventricular baroreceptors in the dog have somewhat higher thresholds during renal hypertension. *Kezdi* measured the change in perfusion pressure in the gracilis muscle upon increased pressure in the left ventricle. The relation between the inhibition of the vascular resistance in the gracilis muscle and the mean left ventricular pressure was changed in the hypertensive dog so that greater pressures were needed to induce vasodilatation. However, the significance of these data is difficult to evaluate because the vasodilator response was related to changes in mean left ventricular pressure and not to changes in afterload and preload.

In recent experiments *Thorén* et al. (1979a) have studied the characteristics of the cardiac C-fibers in the normotensive rat, which has a large population of C-fiber endings in the left atrium, but peculiarly enough no atrial medullated endings or ventricular C-fiber endings were identified. Some of these atrial C-fibers have low thresholds and high firing frequencies, and some receptors show a more low-frequency irregular discharge. The characteristics of these atrial C-fibers have also been studied in the spontaneously hypertensive rat (SHR) by *Thorén* et al. (1979b). These authors have shown a clear resetting of these cardiac C-fibers in hypertensive animals. The mean threshold for SHR was 10.2 ± 0.6 mm Hg (mean left atrial pressure) in relation to 5.4 ± 0.5 mm Hg in the normotensive rat. Figure 14A illustrates this with the pressure-response characteristics of left atrial C-fibers plotted in the normotensive and hypertensive rat.

The change in renal sympathetic nerve traffic in baroreceptor denervated rats upon volume loading was also examined by *Ricksten* et al. (1979). The sympathetic nerve activity decreased as the left atrial pressure increased, and the threshold of the reflex arc was higher, the sensitivity of the reflex arc, lower in SHR (Fig. 14 B). These reflex effects were mediated via the vagal nerves. These two studies together indicate that SHRhave a clear resetting of the left atrial C-fibers. The total venous distensibility in the hypertensive rats also decreased because transfusion with a given amount of plasma increased the left atrial pressure much more in comparison with NCR. This altered venous distensibility will then compensate for the resetting of the receptors. Hence the relation between the changes in plasma volume and renal nerve traffic was rather shifted to the left in SHR, signifying that a certain amount of plasma induced a more marked renal nerve inhibition (*Ricksten* et al., 1979).

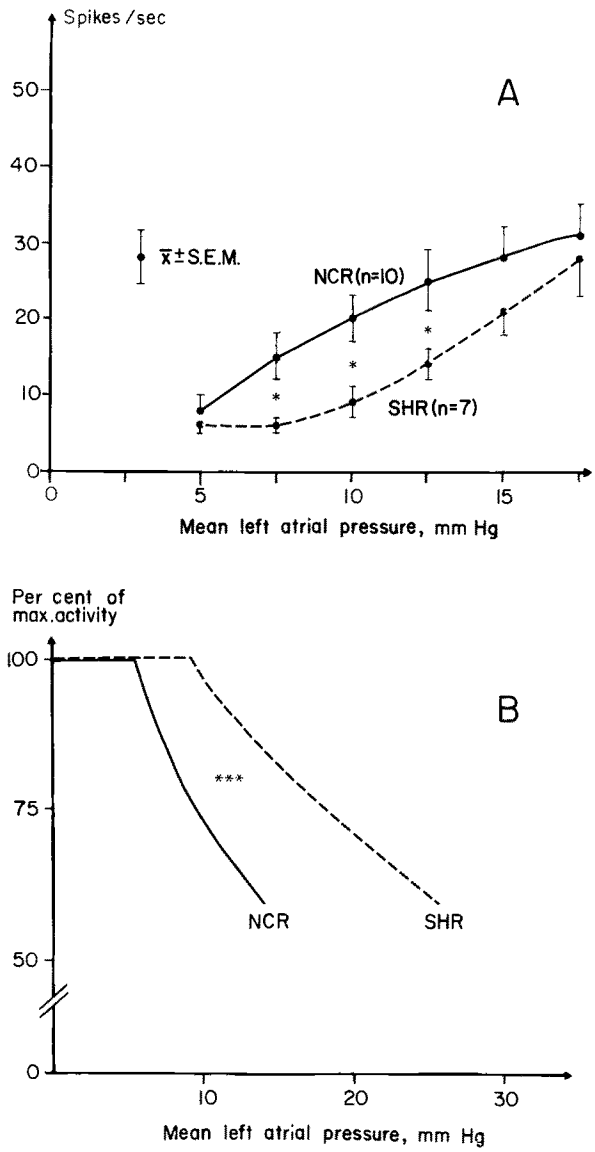

Fig. 14 A. The mean activity in left atrial C-fibers plotted against mean left atrial pressure for ten receptors in the normotensive rats (NCR) and seven receptors in hypertensive rats (SHR). Note that the thresholds for the C-fiber endings in the normotensive rats are ∿ 5 mm Hg, and the corresponding theshold for hypertensive rats is ∿ 9–10 mm Hg. In the range 5–12.5 mm Hg there is a significant difference between the two groups of animals. (*, $p < 0.05$). (Data from *Thorén* et al., 1979b). **B.** The relation between the mean left atrial pressure and the reflexly induced inhibition of the renal sympathetic outflow for six normotensive (NCR) and six hypertensive (SHR) sinoaortic denervated rats. Note that the activity in the renal nerves is inhibited at considerably higher pressure levels in the hypertensive animals. (***, $p < 0.001$). (Data from *Ricksten* et al., 1979)

The reason for the resetting is probably a changed distensibility of the left atrium, since it was shown by *Noresson* et al. (1979) that SHR have a considerably higher left atrial pressure. The mean value for the normotensive animals was 4.6 ± 0.3 mm Hg and for the hypertensive animal, 10.3 ± 0.4 mm Hg in left arterial pressure at end expiration. The increased left atrial pressure in these animals is probably due to an increased venous tone, induced by the elevated sympathetic outflow, which is triggered by central hyperreactivity. The increased venous tone then gives rise to a centralization of the blood volume.

Intesterestingly enough, the renin release in the spontaneously hypertensive rat seems to be inhibited (*Shiono* and *Sokabe,* 1976), probably due to an increased load on the cardiac receptors. This depression seemed more pronounced in the very young (5 weeks) hypertensive animals, when compared with the older animals with a more established hypertension, despite the marked increase in left atrial pressure in the older rats. A possible reason might be the resetting of the cardiac C-fibers in established hypertension.

The resetting of the left atrial C-fibers in the hypertensive animal is also of interest in another respect; the hypertensive animals show a marked hypertrophy of the left ventricle with a shift of the Frank-Starling curve to the right. This shift means that the hypertensive heart needs considerably higher filling pressure to obtain the same stroke volume (*Hallbäck* et al., 1975). It is thus of vital importance for SHR that the left atrial receptors are reset in order to keep up the filling pressure of the left ventricle.

2. Resetting of Cardiac Receptors in Hypertensive Man. Does this resetting of the cardiac receptors in established hypertension in rats have any significance for the pathophysiology of essential hypertension in man? Some recent studies may indicate the significance. Patients with mild essential hypertension (*Julius,* 1977) and low renin values have a 30% mean increase in central blood volume (*Julius* and *Esler,* 1976) with no change in the total blood volume. The increased central blood volume is likely to activate the cardiac receptors, which will reflexly inhibit renin release. In contrast, patients with mild high renin essential hypertension mainly have a marked increase in the sympathetic outflow to the peripheral vessels (*Esler* et al., 1977) but no centralization of the blood volume. These studies by the group in Ann Arbor were performed on patients with mild essential (borderline) hypertension. Interestingly enough, patients with established and more severe hypertension do not show this inverse relationship between the central blood volume and renin level (*London* et al., 1977). One reason might be resetting of cardiac receptors in established hypertension in man.

The importance of plasma renin activity in established human hypertension has been discussed extensively for many years (*Haber*, 1976). The balance between the central drive on the renal sympathetic nerves and the degree of inhibition from the cardiopulmonary receptor and arterial baroreceptors is probably one factor determining renin release in man. The degree of inhibition from the cardiopulmonary receptors is thus determined by three factors: the central blood volume, the degree of structural resetting of the pulmonary capacitance vessels, and the degree of resetting of the cardiopulmonary receptors. As the hypertension advances, pathologic changes in the kidney are of increasing importance for determining the level of renin release.

F. Cardiac C-Fibers and Myocardial Infarction

1. Experimental Evidence for Cardiac C-Fiber Activation. Vagal depressor reflexes elicited from cardiac receptors during myocardial ischemia were first shown by *Costantin* (1963) and *Dokukin* (1964). Since then a great number of papers have confirmed this original observation (*Ascanio* et al., 1965; *Toubes* and *Brody*, 1970; *Uchida* and *Sakamoto*, 1970; *Gillis*, 1971; *Hanley* et al., 1971, 1972; *Gorfinkel* et al., 1972; *Thorén*, 1973b; *Corr* and *Gillis*, 1974; *Kezdi* et al., 1974; *Peterson* and *Bishop*, 1974; *Franciosa* et al., 1974; *Maximov* and *Brody*, 1976; *Corr* and *Gillis*, 1974).

Different types of vagal receptors in the heart can be activated during coronary artery occlusion. Ventricular pressure receptors with medullated afferents (*Kolatat* et al., 1967), atrial receptors with medullated afferents (*Recordati* et al., 1971; *Zucker* and *Gilmore*, 1974), and ventricular nonmedullated endings (*Thorén*, 1972a; 1976b, 1978) are activated within 1 min after onset of an experimental coronary artery occlusion. However, the left ventricular receptors with nonmedullated afferents are likely to be the receptor station responsible, for the same reasons as discussed earlier in connection with the receptor group responsible for the reflex response to aortic occlusion.

2. Mechanisms of Receptor Activation. The typical response of the left ventricular C-fibers to occlusion of a coronary artery is shown in Figure 15 (*Thorén*, 1976b). The receptor was located in the inferior wall of the left ventricle and is tested with a brief occlusion of the right coronary artery. The basal discharge is low ($\sim$ 1 Hz), and the receptor is markedly activated within 30 s after onset of the occlusion and in phase with the systolic bulging of the ischemia area. During the coronary occlusion the receptor is initially activated in systole, but later the firing becomes continuous with a peak discharge of 15 Hz.

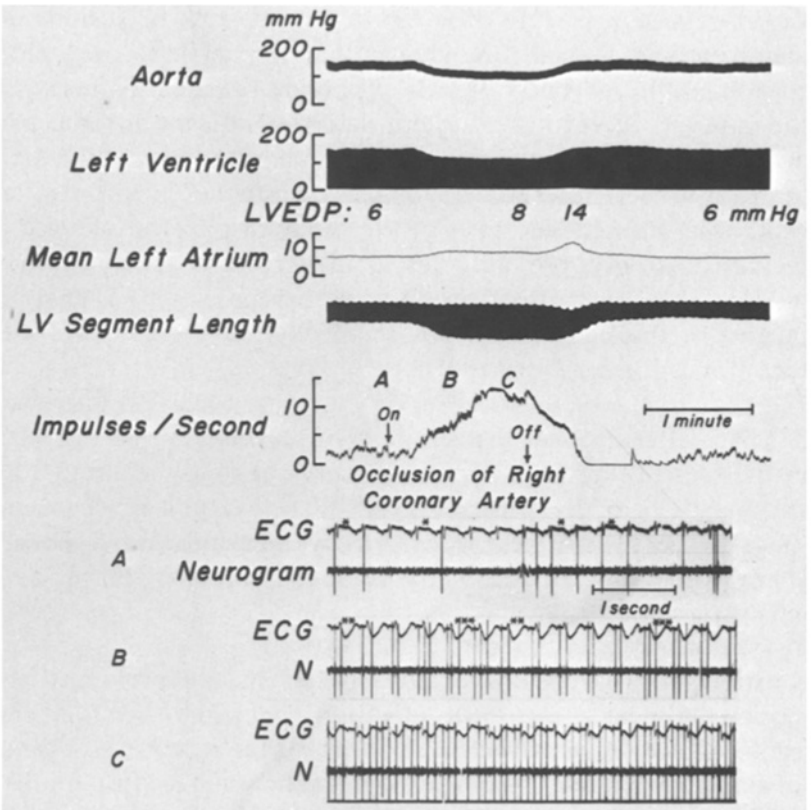

Fig. 15. Left ventricular C-fiber activity during occlusion of right coronary artery in the cat. Aortic, left ventricular, left ventricular enddiastolic *(LVEDP)*, mean left atrial pressure, left ventricular *(LV)* segment length (downward deflection means increased length), and discharge frequency in a left ventricular receptor are shown before and during occlusion. The electrocardiogram *(ECG)* and neurograms were recorded at times *A*, *B*, and *C*. The receptor initially *(A)* has a low rate of discharge which is greatly increased $\sim$ 20 s after onset of the coronary occlusion. At time *B* the receptor discharge has a cardiac modulated rhythmicity with two or three impulses every cycle. From the total conduction time (220 ms) the receptor is calculated to be activated in systole (*asterisks* indicate the corrected position in the cardiac cycle of receptor activation, which occurs 220 ms before the recorded spike). At time *C* the receptor is firing continuously. The reciprocal S-T segment depression in the electrocardiogram is already obvious at time *B*. During occlusion, the increased firing occurs together with the bulging of the ischemic area. The time lag between the release of occlusion and the decrease in systole bulging was probably due to an observed spasm of the coronary artery, which relaxed slowly on release of the ligature. Disappearance of the dyskinesia was accompanied by a rapid decrease in discharge frequency. (From *Thorén*, 1976b, by permission of Amer. J. Cardiol.)

When receptors were observed during separate occlusions of the three major coronary vessels, the greatest increase in firing occurred during occlusion of the coronary vessels supplying the area of the heart in which the receptors were located. There was no significant difference in the maximal frequency obtained from receptors located in vascular areas supplied by the right, left anterior descending, and circumflex coronary arteries. Receptors in nonischemic parts of the left ventricle often showed a modestly increased activity, probably due to an increase in end-diastolic pressure attending the coronary occlusion. Another possibility is that the systolic bulging of the ischemic area mechanically triggers receptors within the intact myocardium around the area.

Is the increased activity during coronary occlusion due to chemical or mechanical changes in the receptor area? The fact that the initial increase in the receptor activity during coronary occlusion occurred during systole and parallel with the systolic bulging of the ischemic myocardium indicates that the receptors were activated by mechanical and not "chemical" changes in the ischemic zone. It is unlikely that "chemical" activation occurs with cardiac rhythmicity.

3. Effect of Prolonged Myocardial Ischemia. In a prolonged coronary occlusion the peak firing occurred within 1 min, and then the firing declined again. Figure 16 illustrates the pattern of the receptor discharge for seven different receptors. Note that the maximum receptor discharge occurs very early after onset of the occlusion, and in three of four receptors discharge markedly increases after the release of the occlusion persisting for 2–3 min after restoration of coronary flow.

The rapid decrease in discharge rate of the receptors after the initial peak is a very interesting phenomenon with potential clinical application. The reason is probably the diminished oxygen supply of the receptors, which is suggested by the fact that restoration of coronary flow markedly increases the discharge. The receptors can then begin to respond to the systolic bulging of the ischemic area, which persists up to 1.5 min after release of the occlusion. Other factors such as mechanical adaptation, release of intracellular substances or altered extracellular ionic concentrations, can of course also contribute to this attenuation of receptor response in a prolonged occlusion.

4. Changes in Peripheral Vasculature in Experimental Myocardial Ischemia. Experimental occlusion of a coronary artery can induce depressor reflexes via the vagal nerves (for references see above). The left ventricular C-fibers are probably responsible for this vagal depressor reflex, as discussed above. The changes in peripheral vasculature and heart rate in coronary artery occlusion are the result of several cardiovascular reflexes, both pressor and

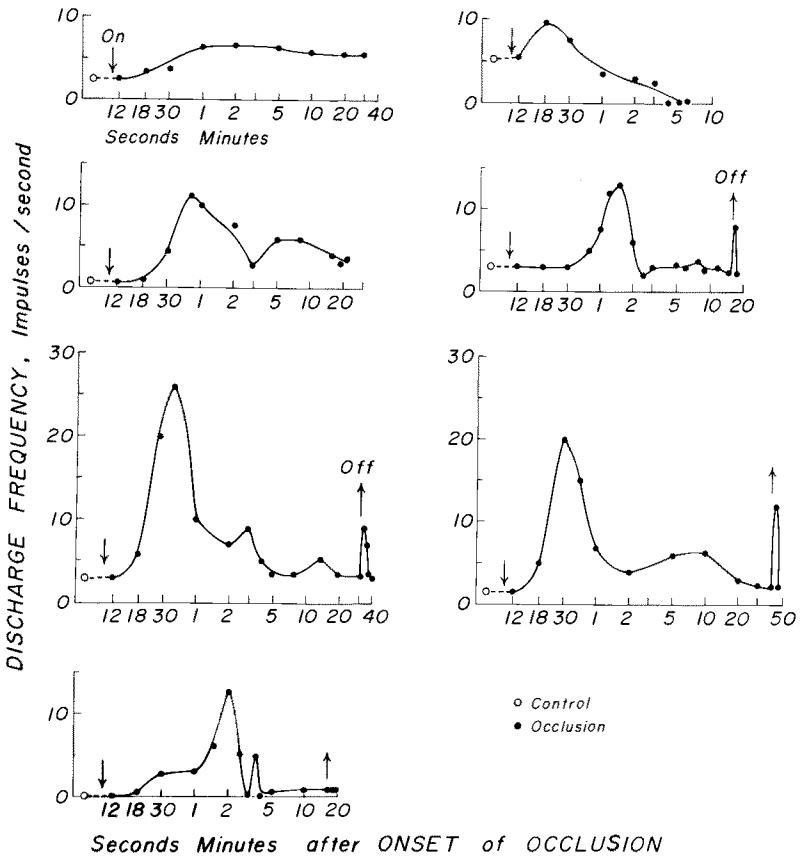

Fig. 16. The discharge frequency of seven left ventricular receptors from seven cats plotted against time after onset of occlusion of the coronary artery supplying the receptor area (the time scale is logarithmic). The activity in four receptors was observed also after release of the occlusion, and in three of the four endings a rebound phenomenon occurred during the first 2–3 min after release. (From *Thorén,* 1976b, by permission of Amer. J. Cardiol.)

depressor operating at the same time (illustrated in Figure 17). In these experiments (*Thorén,* 1973b) the response in a perfused skeletal muscle was small. Upon carotid artery occlusion but with vagal afferents intact, the coronary ischemia induced vasodilatation. After vagal cooling but with arterial baroreceptors intact, the coronary artery occlusion instead induced vasoconstriction. Thus during occlusion of a coronary artery in the experimental animal the vagal afferents tended to induce vasodilatation, and unloading of the arterial baroreceptors tended to induce vasoconstriction. With both reflexes operative, some animals showed a vasodilator response, and some, vasoconstrictor response, hence the mean response was small. Thus the vagal afferents can prevent the expected vasoconstriction triggered from the unloading of the baroreceptors.

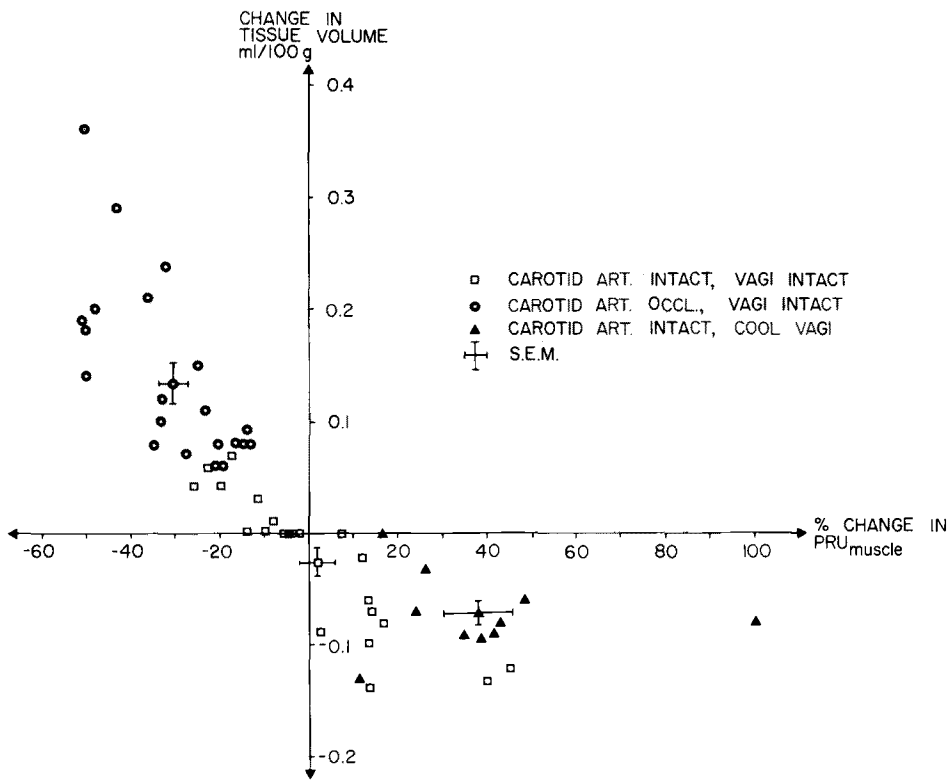

Fig. 17. The changes in calf muscle flow resistance (PRU) and tissue volume during occlusion of one coronary artery under different experimental conditions. The results of a total of 55 occlusions in 8 cats (40 left anterior descendent and 15 right coronary artery) are shown in the diagram as well as the mean response ± SE for each of the three groups of data. The vascular responses to coronary occlusion are small when the carotid arteries were left intact (22 observations). After bilateral carotid occlusion (23 observations) a clear-cut vasodilatation is observed. When the cervical vagi were cooled, coronary artery occlusion induced a clear-cut vasoconstriction. (From *Thorén*, 1973b, by permission of Acta physiol. Scand.)

The reflex change in renal circulation during myocardial infarction has been studied in several papers (*Gorfinkel* et al., 1972; *Hanley* et al., 1972; *Falicov* et al., 1975; *Maximov* and *Brody*, 1976). Interestingly enough, the renal vascular bed in the dog showed no or only moderate decrease in blood flow during experimental myocardial infarction with shock. This contrasts with the situation during hemorrhagic shock, when marked renal vasoconstriction was observed. The efferent pattern of the vagal depressor reflex during myocardial infarction is very logical; the left ventricular C-fibers are known to have an especially strong effect on the renal circulation (Sect. IV).

Coronary artery occlusion can also reflexly induce a marked release of adrenaline from the adrenal medulla (*Staszewska-Barczak* and *Ceremuzyski,* 1968). This effect on the adrenal medulla was not an unspecific effect upon the fall in blood pressure, but was mainly due to a reflex via vagal afferents (*Staszewska-Barczak,* 1971). However, it is not known, whether this reflex effect upon the adrenal medulla is triggered from the cardiac C-fibers or from any other afferents within the vagus.

A reflex activation of the vomiting center can also be seen during experimental myocardial ischemia in cats. *Abrahamsson* and *Thorén* (1972) showed that coronary occlusion in cats induced marked relaxation of the stomach, which is a part of an activation of the vomiting center (see Sect. IV). This will probably explain why nausea and vomiting are so common during myocardial infarction in man.

5. Vagal Depressor Reflexes and Arrhythmias in the Early Stage of Myocardial Infarction in Man. Bradyarrhythmias and hypotension are common during the initial stage of myocardial infarction in man (*Pantridge* et al., 1974). This depressor response is probably triggered from ventricular C-fibers (see above). Recent years have witnessed much discussion on whether this early depressor reflex can trigger severe arrythmias and contribute to sudden death during myocardial infarction in man. Much experimental work has been performed in cats and dogs to answer this important question. In cats the bradycardic reflex observed during myocardial ischemia can decrease the incidence of arrhythmia during occlusion of the left anterior descendent coronary artery (*Corr* and *Gillis,* 1974) but not of the right coronary artery (*Corr* et al., 1976). In dogs the results are even more confusing. Some authors (*Epstein* et al., 1973; *Kent* et al., 1973; *Myers* et al., 1974) claim that bradycardia produced by low-frequency cardiac pacing or vagal efferent stimulation diminished the incidence of severe arrythmias in myocardial infarction, but others claim that bradycardia increases the tendency for arrhythmias (*Han* et al., 1966; *Han,* 1969). Another investigation showed that the incidence of arrhythmias was lowest within a medium heart rate range and higher at high and low heart rates (*Chadda* et al., 1974).

It is of course difficult to apply conclusions from the above-mentioned animal experiments to the situation during human myocardial infarction, because the only way to induce severe bradycardia in these experiments was to pace the heart or to stimulate efferent fibers in the vagal nerves. Spontaneously induced bradycardia was only weak or moderate. In contrast, spontaneous bradycardia (less than 45 beats/min) frequently occurs in man during the early phase of myocardial infarction (*Pantridge* et al., 1974). The marked spontaneous bradycardia observed in man might be more important for triggering arrhythmias than the electrically induced bradycar-

dia in the experimental animal, since several other reflexes are likely to be activated during myocardial infarction, and the balance between these reflexes is probably of greater importance than the individual reflexes per se. Thus, activation of vagal nonmedullated afferents induces marked bradycardia, due mainly to a powerful activation of the vagal outflow to the heart but also to a small inhibition of the sympathetic outflow (*Öberg* and *Thorén,* 1973b; Sect. IV). The unloading of the arterial baroreceptors induces a generalized sympathetic activation. Finally, activation of the atrial medullated afferents (*Recordati* et al., 1971; *Linden* et al., 1975) and the cardiac sympathetic afferents (*Malliani* et al., 1975) reflexly increases the sympathetic outflow to the heart. Therefore these different reflexes can probably increase both the cardiac vagal and the cardiac sympathetic outflow due to their different efferent patterns. Such an increase in vagal outflow and sympathetic outflow to the heart during myocardial ischemia has also been shown experimentally (*Gillis,* 1971), and an imbalance between vagal and sympathetic efferents is likely to trigger severe arrhythmias in the ischemic myocardium. Such an imbalance of vagal and sympathetic efferents has been shown by *Pantridge* et al. (1974) to likely occur in the early phase of myocardial infarction in man.

Bradycardia has been noted within 1–2 min after onset of cardiac pain (*Mogensen* and *Orinius,* 1973). The incidence of bradyarrhythmias in man rapidly declines in direct relation to the time from onset of the myocardial infarction (*Pantridge* et al., 1974). The fact that the initial high activity is not usually sustained in cats is in keeping with the higher incidence of bradycardia in the early phase of myocardial infarction in man. Since receptors in the cat heart usually reach their maximal activity within 1–2 min after onset of an experimental coronary occlusion, the incidence of bradycardia in man is probably higher within the first 1–2 min after onset of myocardial infarction than the incidence for the first 30 min might indicate. The neurophysiologic studies on cardiac C-fiber endings in cats and dogs provide no explanation for the higher incidence of bradycardia in patients with posterior myocardial infarction (*Pantridge* et al., 1974). This phenomenon has been ascribed to an especially dense innervation by vagal afferents of the posterior part of the heart around the venous sinus (*Szentivanyi* and *Juhasz-Nagy,* 1969). However, this explanation has been questioned by other investigators (*Muers* and *Sleight,* 1972a, b, c). Results in cats (*Thorén,* 1977) and dogs (*Coleridge* et al., 1964; *Sleight* and *Widdicombe,* 1965; *Muers* and *Sleight,* 1972b) indicate that the receptors in cats and dogs are distributed throughout the left ventricle. This statement is based on neurophysiologic evidence on the distribution of the endings, but it is difficult to obtain quantitative data with such techniques. A recent study in man gives some evidence for a more dense population of left ventricular receptors in the posterior surface of the human heart (*Perez-*

Gomez and *Garcia-Aguado*, 1977). These researchers examined the bradycardic response in man to injection of angiographic contrast medium and correlated the decrease in heart rate with the anatomic distribution and integrity of the coronary tree. The degree of bradycardia was not influenced by the origin of the sinus node or AV-node arteries, but showed good correlation with the injection of contrast medium in the artery, which supplied the inferior wall of the left ventricle. Recent data from *Thames* et al. (1978) also indicates the same thing in the dog. The latter authors reported a more pronounced depressor reflex upon injection of nicotine in the circumflex coronary artery than was the case in the anterior descending coronary artery. Occlusion of the circumflex artery also triggered a more marked depressor response.

Atropine is commonly used to treat patients with bradyarrhythmias during myocardial infarction (see *Pantridge* et al., 1974). Treatment with atropine in most cases corrects the bradycardia, but it may instead trigger sympathetic overactivity by blocking the vagal efferents. In addition, atropine does not correct the changes in peripheral vasculature. A drug that can block the vagal afferents might be a more suitable treatment, because such a drug will only abolish the depressor reflex, leaving the baroreceptor reflexes intact to control the circulation. Interestingly enough, lidocaine i in a dosage of $\sim$ 3–4 mg/kg can partly block the vagal cardiac afferents in the cat (*Thorén*, 1973b), and thus diminish the hypotension and bradycardia observed during myocardial ischemia. This phenomenon has been called endoanesthesia (*Zipf*, 1966) (see Sect. IV). The blocking effect is localized at the receptor level (*Thorén* and *Öberg*, 1979), and lidocaine in this dosage will not significantly influence baroreceptor reflexes. Whether or not the endoanesthetic effect of lidocaine on cardiac receptors is of importance for the pharmacologic effect of the drug is very much an open question. However, the fact that lidocaine injections in man decrease the spontaneously developed bradycardia during myocardial infarction indicates that this effect contributes to the pharmacologic action of the drug (*Ryden* et al., 1979; *Pantridge* et al., 1974).

Lidocaine is not an ideal endoanesthetic drug, because dosage of $\sim$ 3–4 mg/kg has to be administered in the cat to get a clear endoanesthetic effect, and this dosage is two – three times higher than the antiarrhythmic dosage. A drug with a more specific endoanesthetic action in relation to its antiarrhythmic properties might be of clinical value in treating patients with myocardial infarction and vagally mediated depressor reflexes.

6. Vagal Depressor Reflexes and Cardiogenic Shock in Man. Cardiogenic shock is a severe complication of acute myocardial infarction in man. The main reason for the shock in most patients is of course the ischemic destruction of a major part of the myocardium with severe derangement of

the heart as a pump. However, in some patients the shock is partly due to an inadequate reflex vasoconstriction or even a vasodilatation (*Gunnar* and *Loeb,* 1972). Such inhibition of an expected vasoconstriction is likely to be triggered by vagal nonmedullated afferents. Another important question is whether early, severe hypotension of reflex origin will tend to increase the size of the infarction and hence trigger the cardiogenic shock (*Pantridge* et al., 1974).

The strong effect of the cardiac vagal C-fibers on renal circulation is also of interest for the pathophysiology of myocardial infarction in man. Thus, as discussed by *Hanley* et al. (1972), hypotension during acute myocardial infarction in man appears to be a very uncommon cause of acute renal failure. A review of 785 collected cases of acute renal failure from six different unselected series (see *Falicove* et al., 1975) reveals that in only 18 instancies (2%) was postmyocardial infarction shock the cause of acute renal failure. Although it can be argued that shock after myocardial infarction carries such a high and early mortality as to prevent development of acute renal failure, it is still significant that such a common medical condition as hypotension following acute myocardial infarction should be diagnosed so rarely as the cause of acute renal failure. In contrast, hemorrhagic shock induces a marked vasoconstriction in the kidney (*Gorfinkel* et al., 1972), and the vasoconstriction contributes to the development of acute renal failure. Studies by *Bennet* et al. (1977, 1978) are also of great interest in this respect. These authors examined the renal function in patients with acute myocardial infarction and moderate left ventricular failure as showed by radiologic measurement of the heart size. The patients had both increased creatinine clearance and sodium excretion in comparison with patients with myocardial infarction and no evidence of heart failure. The acute elevation of the cardiac filling pressure was suggested to activate ventricular and atrial receptors, producing reflex renal vasodilatation and elevated renal function.

G. Cardiac Receptors and Asphyxia

Acute, severe asphyxia in the experimental animal and man triggers a marked bradycardia. The bradycardic response is mainly due to an increased vagal outflow to the heart (*Litwin* and *Skolasinska,* 1966; *Thoren,* 1973a). The increased vagal tone can be triggered from different mechanisms. Thus activation of chemoreceptor afferents are known to elicit bradycardia, but only if the ventilation is controlled (*Daly* and *Scott,* 1962). No doubt also central mechanisms can trigger bradycardia during asphyxia (*Austen* et al., 1963; *Cross* et al., 1963) and local myocardial factors are also likely to contribute. *Skolasinska* et al. (1971) suggested that activa-

tion of the Bezold-Jarisch reflex might be involved, and *Thorén* (1973a) showed that reflex effects from left ventricular receptors are of major importance for triggering pronounced bradycardia during severe asphyxia in the opened-chest anesthetized cat. In *Thorén*'s experiments ventilation with 3% oxygen decreased the heart rate by an average reduction of 83 beats/min within 2 min. After bilateral vagal cooling the decrease in heart rate was reduced to 18 beats/min. Blockade of the vagal afferents from the heart by administration of procaine solution around the ventricular epicardial surface did not influence the vagal efferents, as indicated by intact response to vagal efferent stimulation. During the blockade the heart rate response to severe hypoxia was reduced to about 1/3 of control, indicating that reflexes from ventricular receptors were of importance for triggering bradycardia during acute, severe hypoxia.

Thorén's observations were also confirmed by *Wennergren* et al. (1976 a), who showed the reflex bradycardia seen during severe hypoxia to be almost completely abolished after blocking the cardiac vagal afferents in a preparation, in which at least a considerable part of the efferent vagal supply to the heart was intact. They also showed that the vascular response to hypoxia was unaffected by elimination of the influence from the cardiac receptors. This observation agrees with the idea that chemoreceptor activation is able to block the vasodilator effects of ventricular receptor stimulation, but not the bradycardic response. The authors suggested that this blockade of the vasodilator influence from ventricular endings by the concomitant chemoreceptor activation together with an enhancement of the bradycardic response, provides an effective way of saving oxygen, e.g., in the diving animal during prolonged submersion.

The increased inhibitory input from the heart during asphyxia is due to activation of left ventricular C-fibers (*Thorén,* 1972a; *Coleridge* et al., 1979). The activation is probably secondary to the marked distension of the ventricle because the ventricle is then forced to contract from an increased end-diastolic length, which will activate the receptors. *Coleridge* and co-workers also showed increased activity in chemosensitive C-fiber endings in the left ventricle during asphyxia. The discharge in these fibers was quite irregular and showed no obvious relationship to the cardiac cycle. These endings were located in the dorsal wall of the left ventricle near the atrio-ventricular ring. Release of prostaglandins was suggested to contribute to the activation of the ventricular C-fibers during asphyxia (*Coleridge* and *Coleridge,* 1977a, b).

These findings in anesthetized cats and dogs raise the important question whether left ventricular reflexes also contribute to the bradycardic response observed in the fetus or the newborn at birth. Studies by *Rosen* and *Kjellmer* (1975) indicated that vagal reflexes were of no importance for the control of heart rate in the anesthetized cat or sheep fetus. How-

ever, *Nuwayhid* et al. (1975) showed that IV injections of veratrum alkaloids or rapid injections of 4–5 ml blood induced clear bradycardia in the nonanesthetized mature sheep fetus but not in the anesthetized fetus. Thus the question whether cardiac reflexes are of importance for the circulatory control during severe asphyxia in the neonatal period remains unanswered.

H. Other Pathophysiologic Implications of Cardiac C-Fibers

1. Ventricular Receptors and Cardiac Tamponade. Acute cardiac tamponade due to cardiac rupture in patients with acute myocardial infarction triggers an immediate and pronounced bradycardia (*Mogensen* et al., 1972). The bradycardia is due to an increased activity in vagal afferents, as shown during experimental tamponade in the anesthetized dog (*Friedman* et al., 1974, 1977). Left ventricular C-fiber endings are likely to be activated by the deformation of the myocardium seen during the tamponade and are probably responsible for this depressor response during tamponade.

2. Bezold-Jarisch Reflexes During Coronary Angiography. Activation of cardiac receptors during coronary angiography in man was first shown by *Eckberg* et al. (1974) and later confirmed by *Frink* et al. (1975), *Zelis* et al. (1976), and *Perez-Gomez* and *Garcia-Aguado* (1977). Mainly of reflex origin, the bradycardia is also partly due to a direct effect on the sinus node. There is also evidence for a peripheral vasodilatation during the injection. The degree of bradycardia does not seem markedly influenced by the origin of the sinus or the AV-node arteries, whereas injection of contrast medium in the artery supplying the inferior wall of the left ventricle induced the most pronounced response. This suggests that the receptors responsible are located preferentially in the inferior wall of the left ventricle in man (*Perez-Gomez* and *Garcia-Aguado*, 1977) and provide an explanation for the bradycardic syndrome being more common during acute inferior myocardial infarction in man than during acute anterior infarction (*Pantridge* et al., 1974). These data in man have also been confirmed in the experimental animal. *Carson* and *Lazzara* (1970) showed that hyperosmotic solutions injected in the coronary vasculature of the anesthetized dog induced bradycardia due to an increased vagal tone. Bradycardia can also be induced by a direct effect on the sinus node (*James* and *Nadeau*, 1963), but this bradycardic response was not influenced by atropine administration, which during angiography in man can markedly attenuate bradycardia.

The mechanism behind the activation of the ventricular receptors during coronary angiography seems to be the hyperosmolarity of the injected

medium, since *Abe* et al. (1976) showed that reflex bradycardia could be elicited not only by angiographic media but also by hyperosmotic solutions such as 20% glucose and mannitol. Left ventricular C-fiber endings are likely to be responsible for these depressor responses. Recently *Coleridge* et al. (1979) showed that angiographic contrast media can activate these endings in the dog.

IX. Concluding Remarks

In this section I will present my own concept about the characteristics and the physiologic importance of the cardiac vagal receptors.

A. Atrial Receptors with Medullated Afferents

These receptors are mainly located in specific areas of the heart at the vein-atrial junctions. Convincing evidence shows that the receptors can induce a reflex tachycardia due to an increased sympathetic outflow to the sinus node without affecting the ventricular contractility. Also these receptors can induce a diuretic response with a marked increase in free water clearance. The concomitant changes in sodium output are small. The receptors are at least partly responsible for the reflex tachycardia (Bainbridge reflex) which is triggered by volume load, an effect especially pronounced in the conscious dog. The function of the reflex is probably to speed up the heart in situations with an increased filling. In addition, the receptors are involved in the regulation of blood volume. Whether the efferent mechanism for the water diuresis is due to an inhibition of ADH secretion or increased release of an unknown diuretic factor is controversial.

B. Ventricular Receptors with Medullated Afferents

These receptors, extremely rare both in cats and dogs, consist only of a very small fraction of the total receptor population in the ventricles. Their function is largely unknown, but they possibly contribute to arterial blood pressure regulation by inducing vasodepressor reflexes upon increased pressure in the coronary arteries and the left ventricle.

C. Cardiopulmonary C-Fiber Endings

This receptor group located throughout the entire cardiopulmonary region constitutes the major part of the afferent vagal input to the vasomotor center. These receptors respond mainly to increased volume of the heart, but ventricular C-fibers can also increase their activity upon an increased ventricular contractility. They are not involved in the short-term regulation of blood pressure since they cannot register blood pressure. However, they respond to moderate changes in blood volume and are probably involved in the blood volume regulation. The fact that the receptors seem to have a strong reflex effect on the sympathetic outflow to the kidney further supports such a possibility. Evidence is accumulating that these receptors may be of major importance for the neural control of renin release under physiologic conditions. Their role in regulating ADH secretion and renal sodium handling is more speculative at present. In contrast to the situation in cats and dogs, cardiopulmonary receptors in man may be of major importance for controlling the skeletal muscle blood flow.

These receptors may also be of major importance in man for the pathophysiology of several common clinical conditions such as the syncope in aortic stenosis, the bradyarrhythmias and hypotension during myocardial infarction, severe asphyxia, and the vasovagal syncope reaction. A resetting of these receptors is possibly one important factor in the pathophysiology of cardiac failure and essential hypertension. However, further studies are needed to draw definite conclusions about their role in these latter conditions.

Finally, the cardiac C-fibers can be activated by several different drugs such as veratridine, digitalis, and nicotine. They are the major receptor station for eliciting the Bezold-Jarisch reflex. Thus, it is my opinion that the Bezold-Jarisch reflex is not a pharmacologic curiosity, but rather a reflex of major importance for the cardiovascular control both under normal and pathophysiologic conditions.

Acknowledgments. The author's studies in this field were supported by grants from the Swedish Medical Research Council, No. 14X–0644, 14X–04764, and 14X–00016. The author also had the great privilege of spending 1 1/2 years of rewarding research at the Mayo Clinic together with Drs. D.E. Donald and J.T. Shepherd with the support of US Public Health Service Grants HC 05883 and HC 06143 from the National Heart and Lung Institute.

The author thanks Drs. T. Svensson, G. Wennergren, and Professor B. Folkow for commenting upon the manuscript and Mrs. E.-C. Einarsson, G. Jidesten, and K. Lundgren for typing it. Submitted for publication 30. Jan. 1978.

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Rev. Physiol. Biochem. Pharmacol., Vol. 86

Renal Countercurrent Multiplication System

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Contents

I. Introduction

The mechanism by which urine is concentrated has intrigued numerous investigators for the past century. As early as 1883 *Ribbert* noted that a kidney could not generate maximally concentrated urine if its medulla had been destroyed. Soon thereafter it was shown by *Filehue* and *Biberfeld* (1902) and *Hirokawa* (1908) that the medulla was hypertonic to plasma. The demonstration that the papillary concentration of various solutes is higher than plasma was confirmed by a number of later studies (*Glimstedt*, 1942; *Ljungberg*, 1947). The importance of these findings was not appreciated until 1951 when the countercurrent multiplication model was first conceived for the kidney (*Hargitay* and *Kuhn*, 1951; *Wirtz* et al., 1951).

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Initially the countercurrent multiplication model was not readily accepted, and was thought to be unnecessarily extravagant and physiologically complicated (*Smith*, 1959). However, the subsequent experimental, conceptual, and morphological advances have all been consistent with a medullary countercurrent multiplication system. The earlier history and data are nicely reviewed by *Smith* (1959) and *Ullrich* et al. (1961). The present review concerns itself with more recent advances in our knowledge of the countercurrent multiplication system with special emphasis being put on data put forth since 1970. This review is divided into four main subsections: (a) an overview of the countercurrent multiplication system; (b) a morphological description of the medulla and of the epithelial characteristics of nephron segments involved with the countercurrent system; (c) a discussion of the physiologic characteristics of these segments; and (d) a description of the later modifications of the countercurrent system.

II. Overview of the Countercurrent Multiplication System

The purpose of this section is to provide the reader with a review of the general features of the countercurrent multiplication system, and will be limited to a discussion of generally accepted facts. Controversial aspects of the mechanism and operation of the countercurrent system will not be discussed until later in the chapter. The overview will be followed by a more detailed account of the anatomy and physiology of the individual nephron segments that are involved in the concentrating process. In the final section we will return to a consideration of the mechanism of the renal concentrating process, incorporating more recent experimental data and theories.

Figure 1 shows the general architectural features of the urinary concentrating mechanism. When tubular fluid issues from the straight proximal tubule and enters the descending limb of the loop of Henle it is isosmotic to its surroundings. As the tubular fluid courses down the descending limb through the outer and inner medulla it comes into contact with areas of increasing osmolality. Osmotic equilibration occurs between the tubular fluid and surrounding interstitium, resulting in increasing osmolality of the tubular fluid as well. This increase in osmolality may occur either as a result of water abstraction or of solute addition, and the extent to which each occurs is probably species dependent. Regardless of which mechanism predominates, the tubular fluid that reaches the hairpin bend of the loop of Henle has a higher concentration of sodium chloride than occurs in adjacent vasa recta.

As the tubular fluid ascends along the thin ascending limb, it becomes more dilute as a result of the transport of salt out of the tubular fluid with-

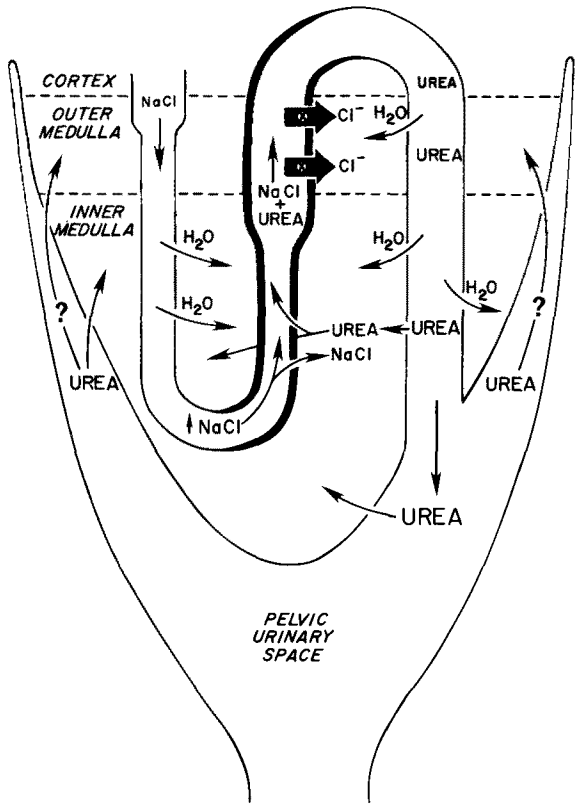

Fig. 1. General features of the countercurrent multiplication system

out movement of water. Whether all of the salt efflux occurs by passive diffusion down its concnetration gradient, or whether some of the salt is transported by active processes has not been completely agreed upon, but the important point is that the tubular fluid becomes more dilute. It is also pertinent to note the occurrence of urea entry into the loop of Henle. The major site of this urea entry is also a controversial subject; however, the only direct measurements suggest that the thin ascending limb is by far the most permeable segment to urea.

When the tubular fluid enters the thick ascending limb in the outer medulla of the kidney further salt removal occurs as a result of active outward pumping of chloride. This results in the tubular fluid becoming even more hypotonic. However, urea that is accumulated within the loop of Henle is not removed from the thick ascending limb as this segment is relatively impermeable to this solute. The tubular fluid that leaves the thick ascending limb therefore has a low osmolality, a large percentage of which is made up of urea.

The final stage of the concentrating process takes place in the collecting duct system. The epithelial wall of the collecting ducts in the cortex and

outer medulla is impermeable to urea but permeable to water in the presence of antidiuretic hormone (ADH). As tubular fluid courses down the collecting tubule it enters areas of increasing osmolality. Osmotic equilibration of the tubular fluid occurs in antidiuretic states and this results in tubular fluid becoming more concentrated, with the major solute being urea (which is impermeant in this segment of the collecting duct system). The epithelial wall of the collecting duct in the inner medulla has a much greater urea permeability than that occurring more proximally, resulting in urea reabsorption in this area. Back diffusion of urea into the papillary interstitium and sodium chloride reabsorption from the ascending limb of the loop of Henle generate and maintain the high interstitial osmolality that occurs in the inner medulla. Hence, the stage is set for abstraction of water and/or addition of solute and the cycle is repeated.

It will be noted that Figure 1 incorporates a schematic drawing of a nephron within an outline of the renal pelvis. This is intended to highlight the fact that recent evidence has provided new insight into the role of the renal pelvic urine in the concentrating mechanism and has stimulated many investigators, including ourselves, to combine this important structure into our consideration of the concentrating mechanism. As can be seen from the figure, we have depicted urea entry from the pelvic urine into the inner and outer medulla of the kidney. This process will be discussed in greater detail later.

Having provided the reader with a general outline of the concentrating mechanism we will now proceed to describe the anatomic and physiologic properties of individual nephron segments involved in the concentrating mechanism

III. Morphology

When considering the morphology of structures involved in the renal concentrating mechanism, it is important to note that considerable interspecies heterogeneity exists. Careful examination of interspecies variations has lead to the conclusion that there probably exists some species differences with respect to the quantiative aspects of the countercurrent multiplication system. In this section we will review the following areas of importance:

1) The structural organization of the renal medulla.

2) The ultrastructure of the epithelium of the thin limbs of the loop of Henle.

3) The vascular bundles and tubulovascular relationships.

4) The structural complexity and epithelial lining of the pelvic space.

5) The importance of compartmentalization of the inner medulla.

A. Structural Organization of Renal Medulla

Most mammalian species share the same overall design of medullary structure, which consists of an outer and an inner medulla. The outer medulla is usually subdivided into outer and inner stripes, as depicted diagrammatically in Figure 2. The outer stripe of the outer medulla contains the "straight" proximal tubule (pars recta) and the thick ascending limb, of both superficial and juxtamedullary nephrons. Also found in this segment are collecting ducts and ascending and descending vasa recta, the later arising from efferent arterioles of juxtamedullary glomeruli.

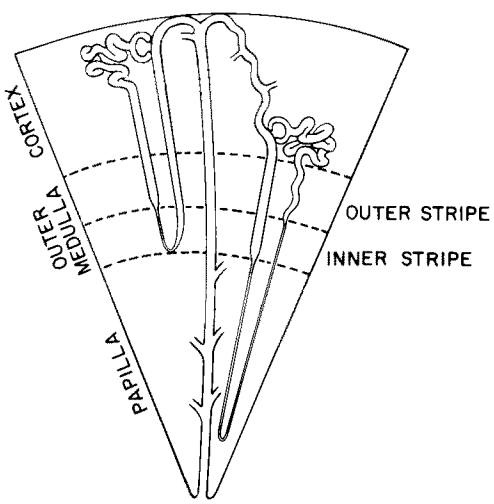

Fig. 2. Representation of the nephron segments that occupy renal zones

The inner stripe of the outer medulla contains collecting ducts, the thin descending limbs and the thick ascending limbs, associated with ascending and descending vasa recta.

The inner medulla consists of collecting ducts, vasa recta, and the descending and ascending thin limbs of juxtamedullary nephrons. The superficial nephrons do not enter the inner medulla as their thin descending limbs drain into thick ascending limbs at or before the junction of the inner and outer medulla. The transition from thin descending to thick ascending epithelium in these superficial nephrons usually occurs just proximal to the hairpin bend, but may also occur at or just beyond the bend. The descending limbs of juxtamedullary nephrons penetrate the inner medulla to a variable extent before the hairpin bend. The type of epithelium covering the thin descending limb usually changes its appearance to one that is characteristic of thin ascending limb epithelium a few hundred microns before the bend.

This general outline of the structural organization of the medulla applies to most mammalian kidneys. There are, however, some animals which possess a very poorly developed inner medulla. They are unable to conserve urea efficiently when placed on a low protein diet and do not improve their maximal urinary concentrating ability when urea or protein loading is then superimposed. Species with such poorly developed inner medullae include the mountain beaver, pig, beaver, and certain species of monkey (*Schmidt-Nielsen* et al., 1961; *Tisher* et al., 1972)

B. Ultrastructure of Thin Limbs of Loop of Henle

Many investigators have studied the histology of the thin limbs of Henle's loop (*Bulger* and *Trump*, 1966; *Osvaldo* and *Latta*, 1966). However, the major problem in interpreting these early studies concerns the inability to define accurately the nephron segments whose histologic characteristics were described. This problem is exemplified by the ultrastructural study of ascending and descending thin limbs in the rabbit kidney carried out by *Darnton* (1969). This study suffers from a serious drawback since the two limbs were identified on the basis of previous studies in the rat, whereas it is now apparent that the rat descending thin limb differs in many aspects from the corresponding segment in the rabbit. Attempts to define fully the epithelial lining along Henle's loop in superficial and juxtamedullary nephrons were therefore only partially successful prior to the studies of *Schwartz* and *Venkatachalam* (1974) and *Kriz* (1976). These two sets of investigators were able to delineate the fine cellular detail of accurately localized segments of the superficial and juxtamedullary nephrons in the rat. *Kriz* et al. (1978) have also carried out extensive comparative animal studies. It would of course be impossible to provide a detailed review of the work of *Kriz* or *Venkatachalam* in the space available in this section. However, we will attempt to highlight the major findings, particularly where these structural findings may have functional implications.

Accurate localization of the segments to be described was achieved by tracing the paths of individual nephrons following the microinjection of silicone rubber. Two types of epithelium were differentiated by *Schwartz* and *Venkatachalam* (1974), in terms of the following features: (a) the complexity of the projections arising from the cell membranes (i.e., surface microvilli and cellular interdigitations), and (b) the depth of the intercellular zonae occludentia (tight junctions). These features are depicted in Figure 3 (DLH/OM and tALH, type I; DLH/IM, type II).

Type I epithelium is characterized by complex cell membrane projections and very shallow tight junctions. This type I epithelium was further divided by *Schwartz* into two subgroups based on the complexity of the

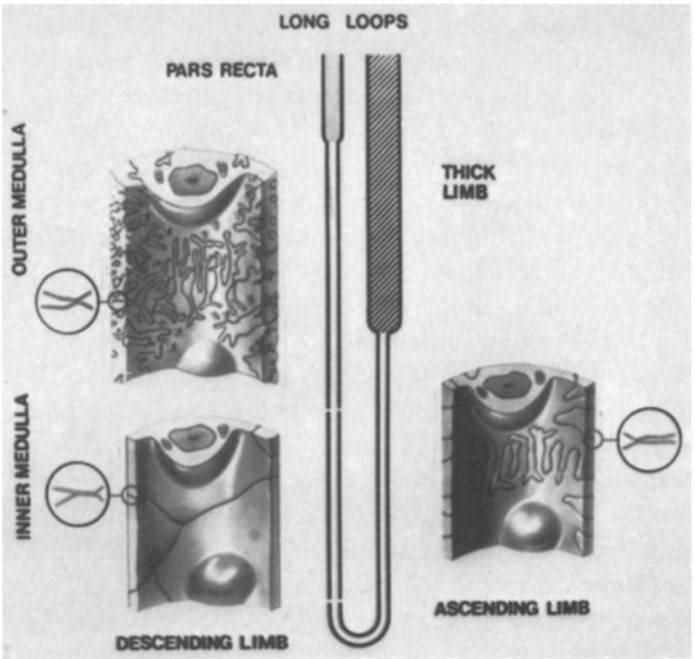

Fig. 3. Representation of the two types of epithelium seen in the thin limbs of the loop of Henle. (From *Schwartz* and *Venkatachalam*, 1974)

cellular interdigitations. *Kriz* has disagreed with this approach and has taken the view that the differences between these "subgroups" are sufficient to regard the two epithelia as being completely different.

The second type of epithelium described by *Schwartz* and *Venkatachalam* (1974) (type II) displays completely different features. It is an extremely simple epithelium with few if any surface microvilli and no true cellular interdigitations. The tight junctions to be found in this epithelium are much deeper than those found in type I epithelium (Fig. 3).

This histologic typing of the epithelium lining the loop of Henle thin limb in the rat has been extended to the mouse, Psammomys, and rabbit by *Kriz* et al. (1978). Although disagreement exists between *Schwartz* and *Kriz* as to whether two or four types of epithelium exist in the thin limbs of rodent nephrons the actual description of the histologic features agree closely. Both investigators have also noted some heterogeneity with regard to the type of epithelium lining different populations of nephrons. The epithelium lining the thin descending limbs of superficial nephrons is relatively uniform in all species studied. In general this simple epithelium conforms to the criteria set by *Schwartz* and *Venkatachalam* (1974) for type II thin limb epithelium, i.e., very few cellular interdigitations and long tight junctions.

Contrasting with this situation is the finding that both intra and interspecies differences may be found when the descending limbs of juxtamedullary nephrons are examined in different species. In the rabbit, the thin descending limbs of long-looped nephrons show some differences along their length but the overall appearance is that of type II epithelium. Hence, in the rabbit, the superficial and juxtamedullary descending thin limb epithelia show considerable homogeneity. Whether the demonstration by *Kriz*, of minor differences of cellular configuration along the rabbit juxtamedullary descending limb, will be significant cannot be ascertained at this time. The situation in other species has proven to be quite different. Both *Schwartz* and *Kriz* found considerable intraspecies heterogeneity when they examined the epithelium lining the descending limbs of juxtamedullary nephrons in the rat, a finding that has been extended by *Kriz* to the hamster and Psammomys. In these species the initial segment of the descending limbs of long-looped nephrons is lined by a relatively complex epithelium – corresponding to the type I epithelium of *Schwartz* and *Venkatachalam* (1974). This segment of the descending limb is, of course, located in the inner stripe of the outer medulla. As the descending limb courses on into the inner medulla the epithelium changes its appearance completely, assuming the simple characteristics of the type II epithelium (Fig. 3). Studies of the thin ascending limbs have shown no intra or interspecies differences in their ultrastructural organization. They are lined by a relatively complex epithelium showing the features of type I epithelium, i.e., complex cellular interdigitations and short tight junctions.

The morphology of the thick ascending limb of Henle has not received as much attention as has the thin loop of Henle. Nevertheless, the morphology of the medullary thick ascending limb (MTALH) is entirely different from the cortical thick ascending limb of Henle (CTALH). The MTALH has thick cuboidal epithelial cells while the cells of the CTALH have a lower overall height. The transition between these two types of epithelia is abrupt at the corticomedullary junction. The epithelium characteristic of CTALH extends somewhat beyond the macula densa. There also exist differences in the surface morphology of the MTALH as contrasted to CTALH. While both medullary and cortical TALH have two types of cells, the MTALH has a preponderance of the smooth surfaced cells, while in the CTALH there is a marked increase in the relative number of the rough surfaced cells, cells with prominent microvilli (*Allen* and *Tisher*, 1976). The relative distribution of the rough versus smooth surfaced cells is the same in rats and rabbits (*LeFurgey* and *Tisher*, personal communication). The characteristics of these two cell types are not known at the present.

The considerable intra and interspecies heterogeneity of their morphology suggests to us that functional differences also exist between these spe-

cies. When all the anatomic and functional information has been presented an attempt will be made to assimilate these facts into our current concept of the renal concentrating mechanism.

C. Vascular Bundles and Tubulovascular Relationships

In order to elucidate the interrelationships between nephron segments and vasa recta, *Kriz* et al. (1972) made a careful study of the position of short and long loops of Henle in the rat kidney and related these to the positions of other medullary structures. Similar extensive studies have also been carried out in the mouse (*Dieterich* et al., 1975), Psammomys (*Kaissling* et al., 1975), and rabbit (*Kriz* and *Kaissling*, 1978). In each case the histotopographic relations of the nephron segments were determined by tracing histologic serial sections through the medullary zones following the microinjection of a silicone rubber into individual nephrons. The results of these studies indicate certain characteristic differences when the different animal

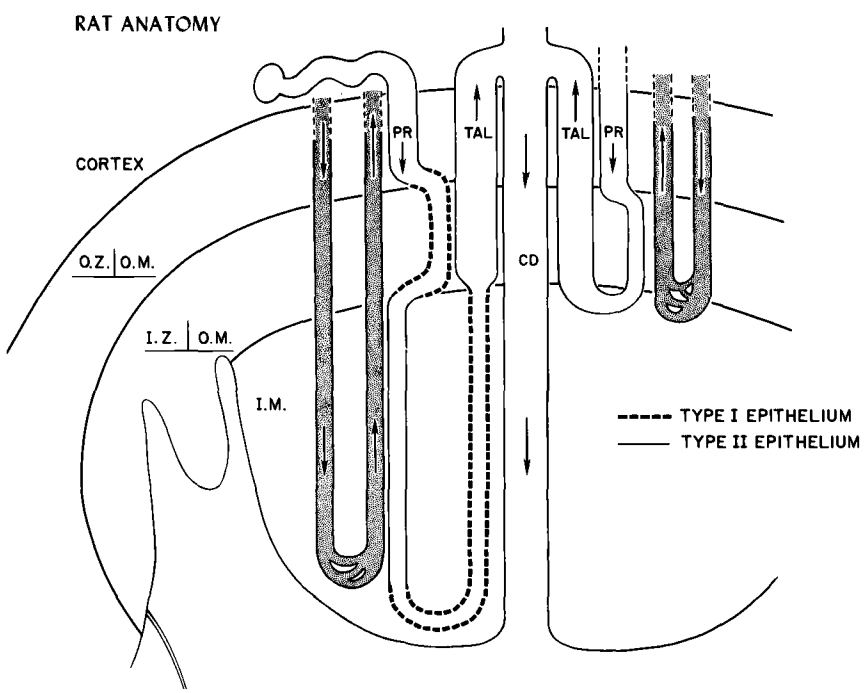

Fig. 4. Representation of the tubulovascular relationships in the rat medulla

species listed above are examined. The rat and Psammomys demonstrate a very similar tubulovascular organization in the medulla. The rabbit differs in a number of ways, most notably in the tubulovascular associations to be found in the inner stripe of the outer medulla. The arrangement of the nephron and vasa recta segments in the outer and inner medullary zones of the rat and the rabbit has been depicted in tabular form (Table 1). This table is intended to clarify the histotopography of these nephron segments and to highlight the considerable heterogeneity that exists between these two animal species and between different nephron populations in the same animal species. A schematic representation of these structural relationships is shown in Figures 4 and 5.

The vascular supply to the medulla originates from efferent arterioles of juxtamedullary nephrons which divide to form arterial (descending) vasa recta. These vessels descend unbranched to varying depths of the medullary zones and then form a capillary plexus which in turn surrounds the tubular structures in that area. Each plexus drains into a venous (ascending) vas rectum which then returns to the corticomedullary border. Vascu-

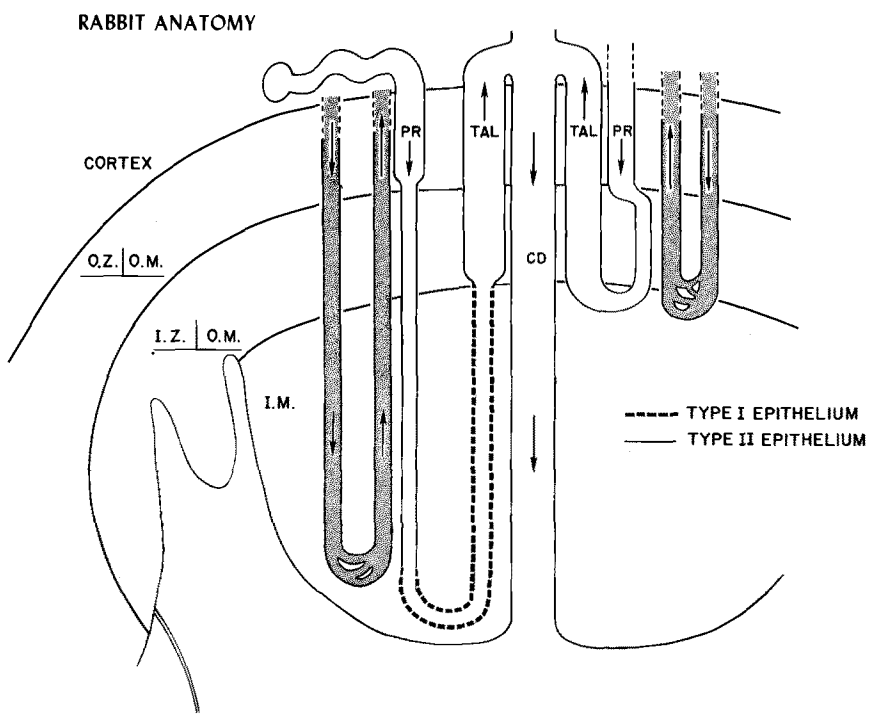

Fig. 5. Representation of the tubulovascular relationships in the rabbit medulla

Table 1. Comparison of histotopography of rat and rabbit medullary structures

	Segment	Rat	Rabbit
I. Outer medulla			
A. Outer stripe			
Superficial nephrons	Pars recta Thick ascending limb	Both segments found *within the medullary rays* along with the collecting duct. Distant from the vascular bundles. *Surrounded by venous vasa recta.*	Same
Juxtamedullary nephrons	Pars recta Thick ascending limb	In the deeper nephrons these segments lie outside the medullary rays. The JMN pars recta runs a tortuous course in the outer stripe.	Same
B. Inner stripe			
Superficial nephrons	Descending limb	*Found in the periphery of the vascular bundles* adjacent to venous (ascending) vasa recta.	*Distant from the vascular bundles.* Close to TAL, CD and also venous VR originating from the inner stripe.
	Thick ascending limb	Distant from the vascular bundles, in the vicinity of the collecting ducts in the medullary rays.	Lie near to vascular bundles.
Juxtamedullary nephrons	Descending limb	Found exclusively in a position *distant* from the vascular bundles.	Descend in a tortuous manner *in the immediate vicinity* of the vascular bundles.
	Thick ascending limb	Closer to the vascular bundles than SFN-TAL but not incorporated into them.	Lie near to vascular bundles.
II. Inner medulla			
	Descending limb	Occupy a bundle near position in the initial portion. Subsequently have varying positions.	Same
	Thin ascending limb	Lie near collecting duct at junction of inner and outer medulla. No definite position in rest of inner medulla.	Same

lar bundles are formed by ascending and descending vasa recta, and the interrelationships between these vascular structures and the adjacent nephron segments varies between animal species and even between different zones of the kidney in a single species. The histologic characteristics of the two limbs appear to be relatively constant however, with the arterial vasa recta endothelial cells showing microvilli on their luminal surfaces and intercellular tight junctions. Venous vasa recta have extremely thin endothelial cells which are separated by many fenestrations.

Kriz et al. (1978) have demonstrated more complex inner stripe vascular bundles in animals that are capable of producing highly concentrated urine (such as the rat, hamster, Psammomys) as compared with simpler bundles in those animals with less concentrating capacity (man, rabbit, dog). The simple vascular bundles are composed of arterial and venous vasa recta only whereas the complex type possess in addition descending thin limbs of superficial nephrons. *Kriz* et al. have speculated that this arrangement may enable those animals with superior concentrating abilities to recycle solute (notably urea) from inner medulla to outer medulla, via entry into superficial nephrons.

D. Pelvic Space

The possible role of the pelvis in the renal concentrating mechanism will be examined by reviewing the present knowledge of the features of the pelvic space, an area which has been largely ignored in previous reviews of the concentrating mechanism.

1. Gross Anatomic Features. The presence of considerable interspecies differences in the complexity of the structure of the renal pelvis was emphasized by *Narath* (1951). The possibility of functional significance relating to these differences was raised at that time and was subsequently examined in some detail by *Pfeiffer* (1968). An excellent analysis of this feature has recently been written by *Schmidt-Nielsen* (1977).

The basic difference in the two main types of pelvis is the extent to which pelvic extensions occur back into the body of the kidney as shown in Figure 6. In the simplest type (Pfeiffer type I) there are no extensions and the only part of the kidney bathed by pelvic urine is the area cribrosa of the renal medulla. This type of pelvis is found in the beaver, pig, and mountain beaver and has been described as a simple expansion of the upper end of the ureter. Kidneys possessing a type I pelvis have no inner medullary zone and have a poorly developed pelvic musculature.

In contrast to this simple type of pelvis, the type II pelvis is characterized by pelvic extensions which penetrate the inner and outer zones of the

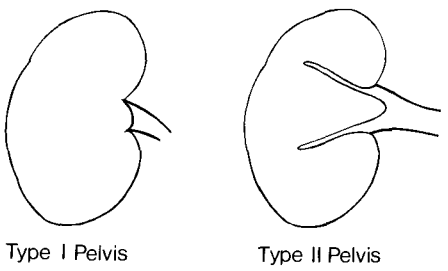

Fig. 6. Representation of simple (type I) and complex (type II) pelvic arrangements

medulla, a feature that results in these areas being bathed by pelvic urine. The type II pelvis has been demonstrated in both unipapillate and multipapillate kidneys, as in the rat, dog, sheep, and man. Kidneys with this type of pelvis have well defined inner as well as outer medullae and possess a well developed pelvic musculature. Studies of the type of pelvis in rabbits have produced disparate findings. *Narath* (1951) described the rabbit pelvis to be relatively simple with a short calyx emptying directly into the ureter. *Sheehan* and *Davis* (1959), on the other hand, reported that the rabbit pelvis extends out into the renal parenchyma forming a series of secondary pouches. Observations that we have made on the New Zealand white rabbit are in agreement with *Sheehan* and *Davis* (1959).

The degree of complexity of the renal pelvis may be of great importance in the renal concentrating mechanism. Those animals possessing a type II pelvis have much more renal parenchyma bathed by pelvic urine. If solutes back diffuse from the urine into the parenchyma, recycling of such solutes could occur via this route into the inner and outer stripes of the outer medulla. The most important solute from this aspect is urea, as shown in Figure 1.

If diffusion of urea and other solutes from the pelvic urine to the renal parenchyma is important, it is essential that a mechanism should exist to propel the urine into these pelvic extensions. Consideration will now be given to the mechanism by which this occurs. In 1951, *Narath* reviewed the muscular arrangement of the pelvi-calyceal system in a number of animals, including man. He described the manner in which the calyceal muscle arrangement in man is well suited to the task of emptying the pelvis (Fig. 7). This involves a well coordinated interaction between the muscle groups, as shown in Figure 8, which results in most of the pelvic urine being discharged into the ureter but some being forced upwards into the fornices as the intrapelvic pressure rises. In studies on rats and hamsters, *Schmidt-Nielsen* (1977) made the observation that urine colored with lissamine green was swept from the tip of the renal papilla upwards toward the cortex. This demonstration of the ability of the urine to flow retrograde confirms the previous studies of *Narath* and others in which backflow of contrast media into the specialized fornices was seen to occur dur-

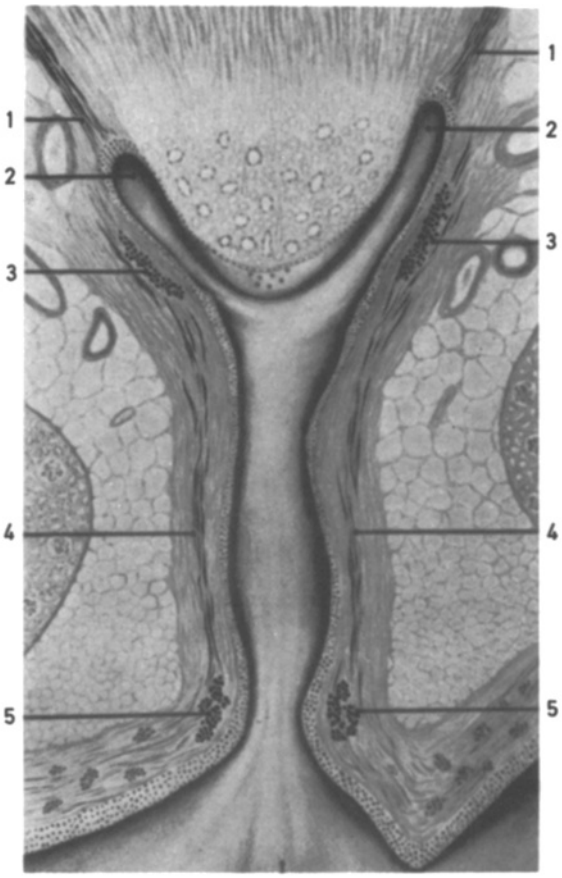

Fig. 7. Explanatory drawing of a calyx and its muscular arrangement. *1*, Musculus levator fornicis; *2*, fornix; *3*, musculus sphincter fornicis; *4*, musculus longitudinalis calycis; *5*, musculus sphincter calycis. (From *Narath*, 1951)

ing fluoroscopy. *Narath* concluded that reabsorption of solute and water probably occurred across the epithelium of these fornices. This may well be true in a number of species. Before considering the direct evidence for this solute back diffusion we will describe the epithelial lining of the renal areas in question as this will be of vital importance in determining whether diffusion of solutes is possible.

2. Histology of Pelvic Epithelium. A number of investigators have examined the type of epithelium lining the renal parenchyma that is exposed to the pelvic urinary space. Most of these studies have been carried out in rats, an animal that exemplifies the type II pelvis. In general, the results have been consistent with the findings of *Pfeiffer* (1968) that the epithelium covering the papilla is simple cuboidal in type and appears to be a continuation of the type of epithelium lining the papillary collecting ducts. In a study of the hamster, *Lacy* and *Schmidt-Nielsen* (1976) reported that the epithelium covering the inner and outer stripes of the outer medulla was also simple in type, and they made the observation that the thickness

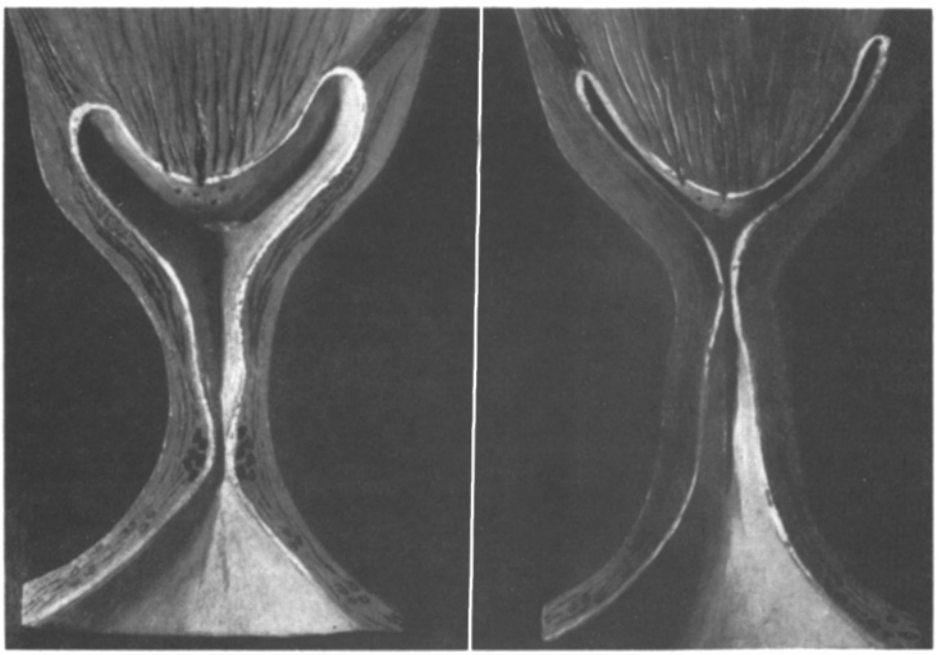

Fig. 8. Models of collecting and emptying phases of calyx. (From *Narath*, 1951)

of the epithelium covering the outer stripe was only half of that covering the inner stripe.

These observations have recently been extended by *Bonventre* et al. (1978); these investigators studied the microscopic appearance of the pelvic epithelium under conditions of antidiuresis and water diuresis. In antidiuretic rats the papillary cells were separated by widely dilated intercellular spaces (Fig. 9) whereas in water diuresis they were closely apposed (Fig. 10). However, it was not possible to detect this difference in the epithelium overlying the outer medullary segments. They concluded that the widely dilated intercellular spaces seen in antidiuresis resulted from increased water flux from pelvic urine into the papilla. Recent studies in our laboratory have demonstrated that this phenomenon also occurs in the papillary epithelium of the New Zealand white rabbit (Figs. 11 and 12) (*Worthen* and *Hogg*, 1978).

The change in morphology seen in papillary epithelial cells is very similar to that observed in the rabbit cortical collecting tubule by *Ganote* et al. (1968), and in the rat medullary collecting ducts by *Tisher* et al. (1971) following ADH induced osmotic water flow. *Bonventre* et al. (1978) proposed that the change from water diuresis to antidiuresis may also be accompanied by an increased transepithelial flux of urea from the pelvic space into the papillary interstitium. However, this correlation must be

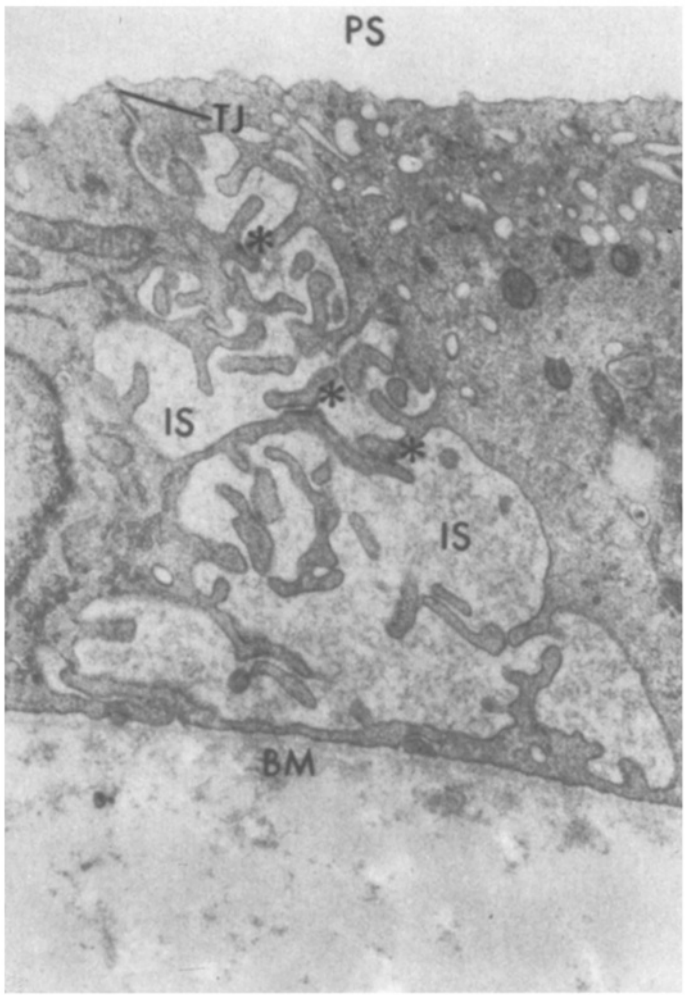

Fig. 9. Electron micrograph of rat papillary epithelium in antidiuresis (U_{Osm} = 1880 mOsm/kg). Fixative solution was 2.5% glutaraldehyde 2000 mOsm. Note widely dilated intercellular space *(IS)* with closed apical tight junction *(TJ)*. Magnification = X 20,000. *Bar* = 0.5 μm. *PS* = Pelvic space. *BM* = Basement membrane. (From *Bonventre* et al., 1978)

viewed with caution as *Grantham* and *Burg* (1966) showed that ADH has no effect on urea permeability in the cortical collecting tubule despite a similar dilatation of the intercellular spaces in this epithelium.

3. Solute Recycling from the Pelvic Space. Although caution is needed in assuming a direct correlation between dilatation of intercellular spaces and increased back-flux of urea, there is certainly evidence that urea back-flux

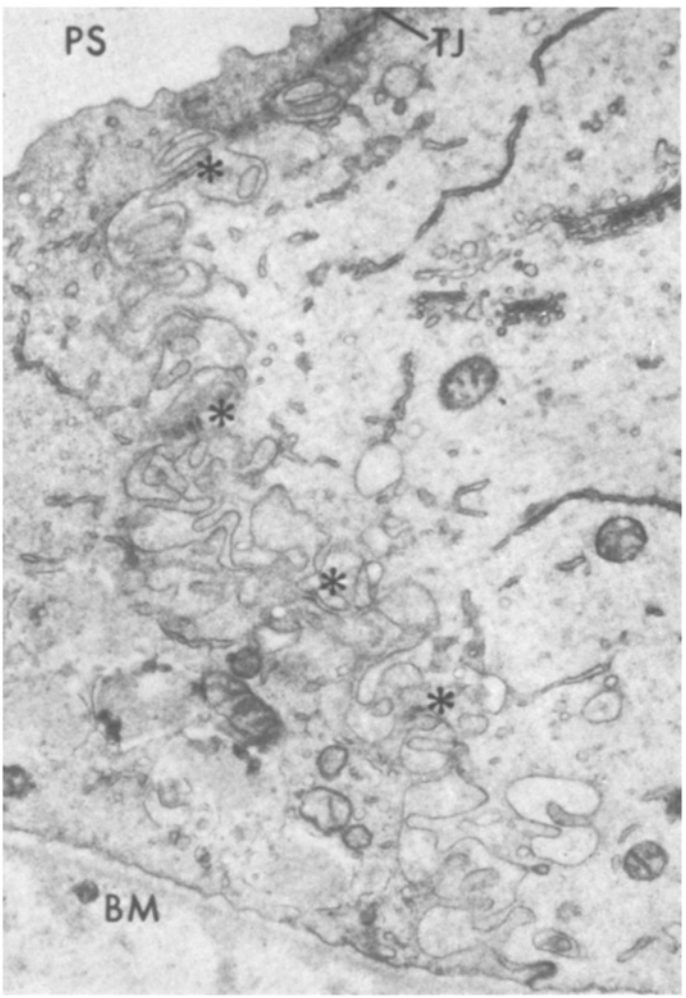

Fig. 10. Electron micrograph of rat papillary epithelium in water diuresis (U_{osm} = 115 mOs/kg). Fixative solution was 2.5% glutaraldehyde, 2000 mOsm. Note closely apposed cells. (Mag. X 20,000). *Bar* = 0.5 μm. *PS* = Pelvic space. *TJ* = apical tight junction. * Desmosomes. *BM* = Basement membrane. (From *Bonventre* et al., 1978)

into the papilla does occur. The original demonstration of urea and water exchange between the pelvic urine and the papilla was provided by *Gertz* et al. (1966). Their preliminary work was amplified by the studies of *Schutz* and *Schnermann* (1972) who showed that the failure to concentrate urine which occurs when the renal papilla is exposed can be compensated almost completely by superfusing the papilla with hypertonic solutions that resemble pelvic urine. Additional evidence of solute transfer from pelvic urine to renal medulla has now established that not only urea, but also

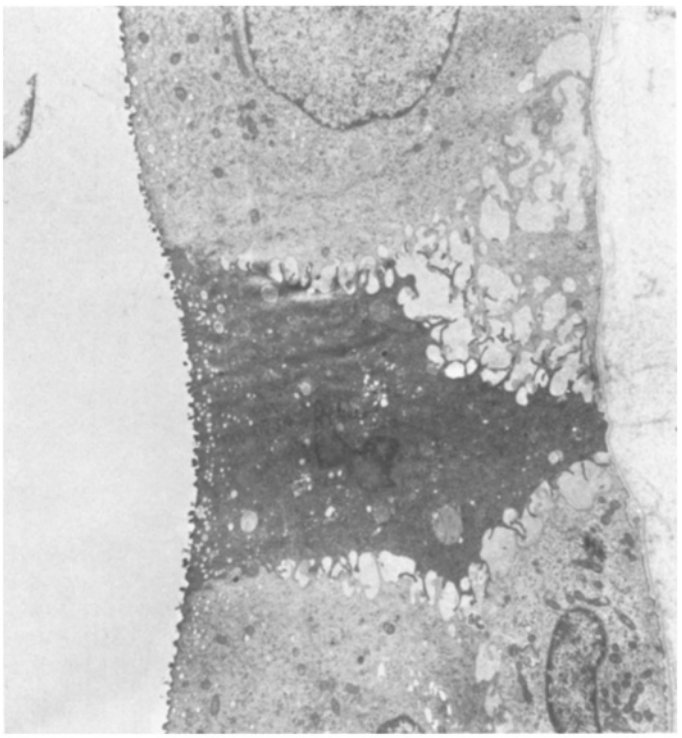

Fig. 11. Electron micrograph of rabbit papillary epithelium in antidiuresis (U_{Osm} = 1665 mOsm/kg). Fixative = 3% glutaraldehyde in 0.1 M phosphate buffer. Osm = 517 mOsm/kg (mag. X 3000)

larger molecules such as inulin and ferrocyanide are reabsorbed from the pelvic urine, particularly in antidiuretic states (*Lechene* et al., 1976).

E. The Importance of Compartmentalization of the Inner Medulla

Recent work by *Lacy* and *Schmidt-Nielsen* (1976) and by *Schmidt-Nielsen* (1977) has brought into question the long-held belief that the inner medulla is composed of renal tubules, vasa recta, and a relatively homogenous interstitial matrix. They have demonstrated the presence of a very narrow space (1–2 micron diameter) lying beneath the papillary epithelium. This space connects with similarly sized channels running around the collection ducts, as shown in Figure 13. *Schmidt-Nielsen* and *Lacy* analzyed the composition of the fluid present in this space and their results suggest that it is in equilibrium with pelvic urine. They speculate that collecting duct fluid may equilibrate with this collecting duct channel fluid rather than with

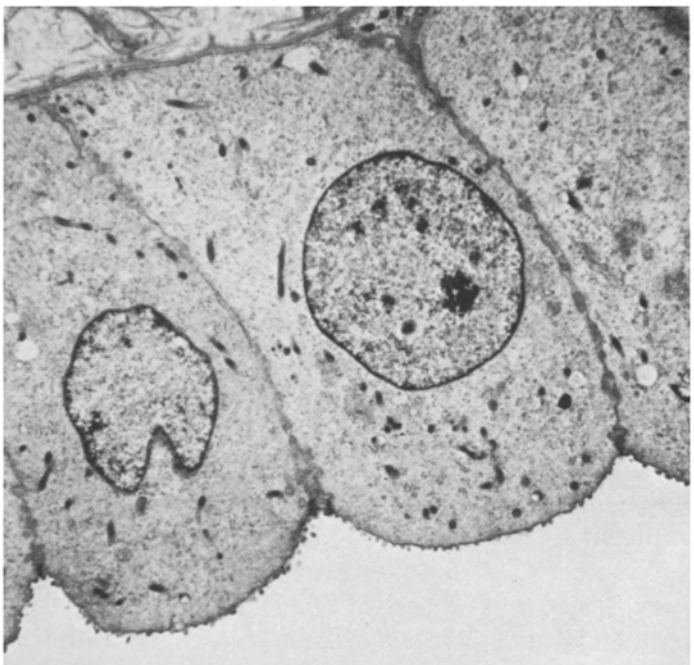

Fig. 12. Electron micrograph of rabbit papillary epithelium in water diuresis (U_{osm} = 104 mOsm). Fixative = 3% glutaraldehyde in 0.1 M phosphate buffer. Osm = 517 m Osm/kg (mag. X 3000)

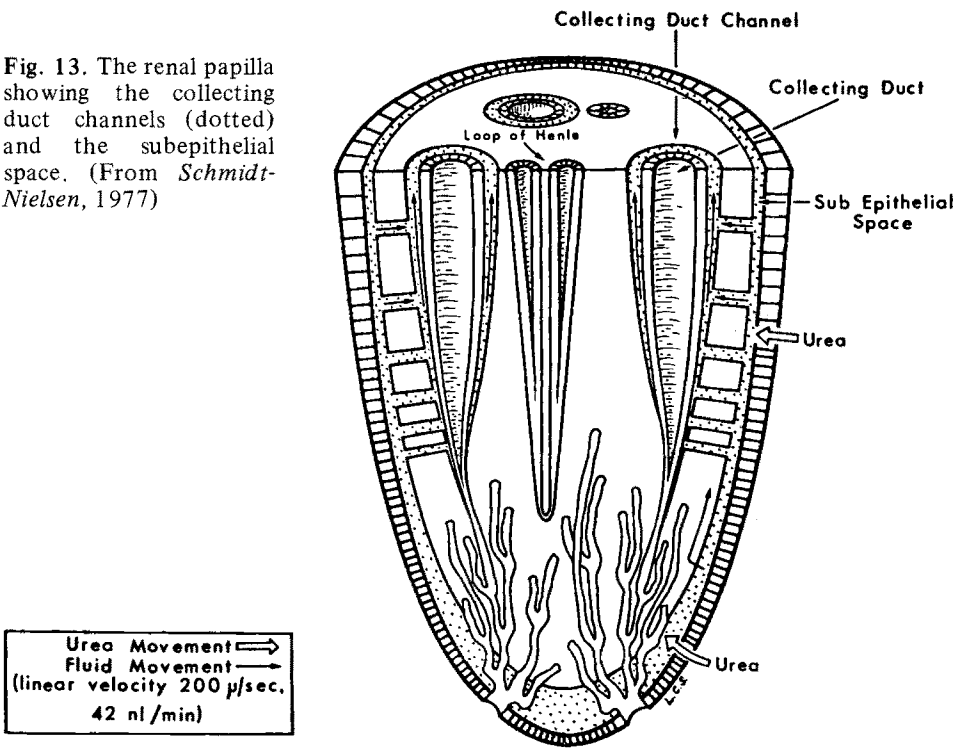

Fig. 13. The renal papilla showing the collecting duct channels (dotted) and the subepithelial space. (From *Schmidt-Nielsen*, 1977)

"interstitial fluid". This would explain the finding of urine osmolalities that are higher than "interstitial fluid osmolality" under certain circumstances. Previous explanations of this phenomenon have invoked differential urea and electrolyte permeabilities and reflection coefficients in collecting tubules but the results of *Schmidt-Nielsen* and *Lacy* provide an alternative explanation for this finding. The demonstration of collecting duct channels and subepithelial spaces further increases the potential importance of solute and water transfer from pelvic urine to the renal medulla.

F. Conclusion

From this review of the morphology of structures that may be important in the renal concentrating process, it is apparent that considerable advances in our knowledge have occurred in recent years. The importance of solute back diffusion from pelvic urine, increased medullary compartmentalization, and intra and interspecies heterogeneity with regard to nephron morphology is currently under further investigation in a number of laboratories.

IV. Physiology of Various Nephron Segments

We will now consider in detail physiologic data that exists concerning nephron segments that are involved in the countercurrent process.

A. Pars Recta

It is becoming increasingly evident that the straight portion of the proximal tubule, the pars recta, may have a role in the overall operation of the countercurrent multiplication system. Support for this concept comes from both morphological and physiologic considerations. As shown in Table 1, the pars recta descends into the outer medulla where it is closely surrounded by ascending vasa recta. Thus, the terminal pars recta is surrounded by fluid which has an osmolality which is significantly higher than that of plasma. Also it is reasonable to postulate that the urea concentration around the pars recta is more closely reflected by the urea concentration in the ascending vasa recta than by systemic blood.

The function of the pars recta has been examined most directly by the technique where isolated segments are perfused in vitro. Using these tech-

niques it has been determined that the pars recta has a high hydraulic conductance to water (*Schafer* et al., 1978a; *Kawamura* et al., 1974). It is of interest that the water permeability of the juxtamedullary pars recta is alone twice as great as the superficial pars recta (*Kawamura* et al., 1974). Because of the inaccessibility of the pars recta to micropuncture studies, there are no studies which have measured the osmolality of the fluid issuing out of the pars recta. However, due to its high osmotic water permeability it is reasonable to suggest that the fluid entering the descending limb of Henle is not isotonic with systemic blood, but rather, is hypertonic due to a combination of water abstraction and solute addition. Most previous considerations of the countercurrent multiplication system have assumed that the fluid coming out of the pars recta is isotonic to blood and containing a low concentration of urea. This is a gross oversimplification, due in part to our previous lack of knowledge concerning the function of the pars recta, and in part because it has simplified the consideration of the countercurrent multiplication system

The net fluid reabsorptive capacity of the pars recta is about a third of the convoluted segment when perfused with ultrafiltrate of rabbit serum (*Kawamura* et al., 1975; *Lutz* et al., 1973; *Grantham* et al., 1973; *Burg* and *Orloff*, 1968; *Schafer* et al., 1978; *Schafer* and *Andreoli*, 1976; *Schafer* et al., 1975, 1977). The mechanism of this fluid reabsorption is not entirely clear, but seems to depend on both active and passive transport processes. Experiments strongly suggest that the pars recta can actively transport sodium. Passive efflux of NaCl also probably occurs in this segment, as a result of a favorable tubule to blood chloride gradient set up by more proximal preferential bicarbonate reabsorption. Thus, if the pars recta only absorbs fluid by active and passive mechanisms, then the tubular fluid-to-plasma (TF/P) volume marker should rise to a lesser extent in the pars recta than in an equivalent length of the convoluted segment. However, what is of extreme interest and potential importance is the fact that the pars recta is also a secretory organ. Initially it was shown that the pars recta can actively secrete para-aminohippurate (*Tune* et al., 1969), but a variety of other organic acids can be secreted by the pars recta (*Grantham* et al., 1973). If isolated segments of pars recta are bathed in uremic serum they can actively screte fluid (*Grantham* et al., 1973). Presumably the secretion of fluid is due to secretion of various osmotically active organic acids present in uremic serum which subsequently cause osmotic influx of water. Since the pars recta is surrounded by ascending vasa recta, and therefore is presumably in contact with a high urea concentration, it is not clear whether the terminal pars recta is a reabsorptive or a secretory tubule. Certainly forces exist around the pars recta for both secretory and reabsorptive processes.

Recently it has been recognized that high papillary urea concentrations are associated with the ability to form concentrated urine. If there were no urea recycling, then it would be difficult to conceive how a high urea concentration could be generated in the papilla. Evidence for urea recycling has been provided by recent in vitro perfusion studies that have noted urea influx to be about twice as great as urea efflux in the pars recta. Furthermore, the urea influx was inhibited by cooling, phloretin, and cyanide (*Kawamura* and *Kokko*, 1976). *Herrmann* in a recent abstract has taken an entirely different approach and analyzed urea to inulin ratios in various nephron segments by enzymatic techniques from kidneys which were quick frozen (*Herrmann*, 1978). In these studies *Herrmann* did not use inhibitors of active transport but his study, and the study of *Kawamura* and *Kokko*, suggests that urea is actively secreted by the straight portion of the proximal tubule. Since these segments are juxtaposed to the ascending vasa recta, it is possible that urea may recycle back to the papilla through the pars recta transport processes and therefore contribute to the high urea concentration found in vivo at the bend of the loop of Henle, and may also play a part in the ultimate trapping of urea in the papillary interstitium by mechanisms to be discussed later.

B. Descending Limb of Henle

Descending limb of Henle (DLH) function can be examined either by in vitro microperfusion or in vivo micropuncture techniques. Neither of these techniques are without limitations. Though the in vitro technique does have the major advantage that the entire length of the DLH can be examined, it also has the disadvantage that it is impossible to impose a gradual osmotic gradient along its axial length. On the other hand, the in vivo micropuncture techniques are difficult to interpret because it is only possible to perform either a single puncture, or two punctures which are relatively close together in a given tubule. It is technically not feasible to perfuse in vivo a segment of the DLH and control all potential variables, such as the composition of the fluid which bathes the DLH in question. Nevertheless, given these limitations, significant new information has been put forth which has advanced our understanding with respect to the function of the DLH.

Since it is now generally accepted that the DLH is not capable of active outward salt transport (*Kokko*, 1970), the most important issue with respect to DLH function is the mechanism by which osmotic equilibration occurs across its epithelium. In broad terms osmotic equilibration can occur by solute addition, water abstraction, or a combination of these two

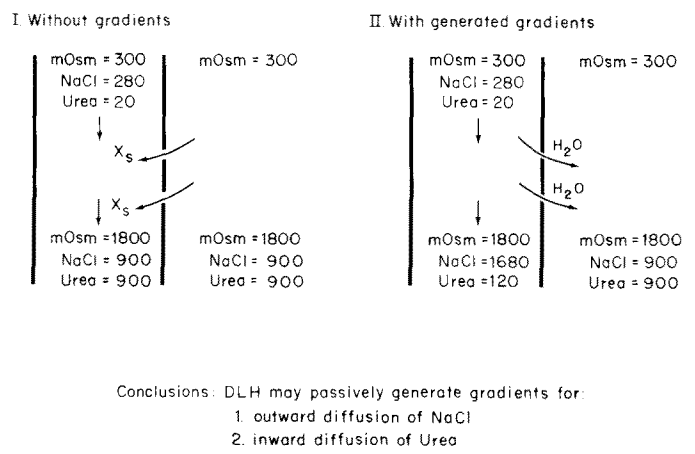

Fig. 14. Schematics to illustrate the mechanism by which the NaCl and urea gradients are generated passively by the thin DLH

mechanisms. Figure 14 illustrates these two extreme mechanisms of osmotic equilibration and shows that while the osmolality rises to the same extent under both circumstances, the luminal concentration of urea and salt are entirely different. In each case it is assumed that approximately 50% of the total tissue osmolality of the inner medulla during hydropenia is made up of NaCl while 50% is composed of urea. If the DLH is permeable to solutes, as depticted in left panel of Figure 14, then the intraluminal constituents approximate the interstitial concentrations of solutes. However, if the DLH is permeable to water but impermeable to solutes, then the osmolality of the fluid still rises towards the papillary tip but now the intraluminal constituents are concentrated in the same ratio as the fluid entering the DLH. For the sake of illustration, Figure 14 assumes the fluid entering the DLH is mainly NaCl containing 20 m*M*/liter urea. The osmolality of fluid entering the DLH is not known, but it is reasonable to postulate that the main osmotically active constituent is NaCl. As this fluid then courses through more hypertonic surroundings, water is abstracted and the NaCl concentration rises to levels above the interstitium. If there is any water abstraction out of the DLH, it is apparent from Figure 14 that NaCl cannot passively diffuse into the DLH because the intraluminal concentration of NaCl will always be higher, if the fluid entering the DLH has a higher concentration ratio of NaCl to urea than exists in the interstitium. From these considerations it becomes evident that the main issue of importance with respect to the DLH is the mechanism of its osmotic equilibration, since this mechanism dictates the nature of fluid entering the thin ascending limb of Henle.

The mechanism of osmotic equilibration is dictated by the relative solute-to-osmotic water permeability coefficients. If the DLH were highly permeable to solute but not water then solute entry would predominate as the primary mechanism of osmotic equilibration. The converse would be true if the DLH were highly permeable to water and relatively impermeable to solute. A quantitative estimate of the osmotic water permeability coefficient has been made, in vitro, across the DLH of rabbit (*Kokko*, 1970) and rat (*Morgan* and *Berliner*, 1968) by perfusing segments of DLH with fluids which were less concentrated than the ambient bath. Both of these studies have disclosed that the DLH has a much higher water permeability than other segments similarly examined.

Isotopic permeability to various solutes has also been determined for the DLH by measuring the rate of efflux of a given isotope which had been added to the perfusate. These studies have indicated that the DLH is relatively impermeable to all solutes tested (*Kokko*, 1974). Because micropuncture studies have generally found more urea at the bend of the loop of Henle than could be predicted by the direct ^{14}C-urea permeability measurements (*Kokko*, 1972), *Abramow* and *Cogan* (1978) have recently measured systematically the ^{14}C-urea permeability of the early and late portions of the rabbit DLH. They were able to show that not only was urea impermeable across the entire length of the DLH but also that the electrically measured resistance of the DLH was high, 873 Ω cm^2. Thus the direct isotopic permeability of electrical studies have indicated that the descending limb of Henle, at least of rabbit, has a high permeability to water and low permeability to solute. In agreement with this view are the reflection coefficient measurements where the reflection coefficients of NaCl (*Kokko*, 1970) and urea (*Kokko*, 1972) have been shown to be close to one. Thus the passive permeability characteristics of the DLH are ideal for osmotic equilibration to occur principally by water abstraction. Indeed, direct measurements of the mechanism of osmotic equilibration in the in vitro perfused DLH of rabbit have shown that osmotic equilibration occurs primarily due to water efflux without significant influx of solute (*Kokko*, 1970). This finding, coupled with the assumption that urea concentration at the end of the pars recta is low, would lead to the in vivo prediction that the urea concentration at the end of the DLH is low and the NaCl concentration is high, and therefore, there would exist a large outward gradient for NaCl efflux between the DLH and the adjacent vasa recta (Fig. 14). However, in vivo micropuncture studies have found much higher urea concentrations in the DLH (up to 300 m*M*/liter) than would be predicted by simple water abstraction (*Pennell* et al., 1974; *Marsh*, 1970; *de Rouffignac* and *Morel*, 1969). Also the Na (*Johnston* et al., 1977) and Cl (*Gelbart* et al., 1978) concentrations near the bend of the loop of Henle, though

higher than vasa recta, are not as high as would occur if osmotic equilibration along pars recta and DLH were to occur solely by water abstraction. However, it should be emphasized that the in vivo micropuncture studies cannot determine the entry site of urea along the pars recta, early DLH, late DLH or even the pre-bend region of the loop, which in most species has the anatomic characterisitcs of the thin ascending limb of Henle. Direct evidence of urea entry into the DLH of the hamster was provided by *Marsh* (1970) who compared urea delivery to two sites in the DLH. It should be noted however that this finding only pertains to urea entry in the terminal DLH. Therefore the in vivo micropuncture studies are not necessarily at variance with the in vitro studies, since the higher urea concentration in vivo at the bend of the loop may reflect urea secretion by the pars recta (as discussed in Sect. IV.A) and/or the terminal DLH. In vivo studies, which have suggested that a large fraction of osmotic equilibration in vivo occurs by solute entry, are difficult to interpret due to the fact that the composition of fluid entering the DLH is not known. The presence of significantly more urea at the bend of the loop of Henle in rat (*Pennell* et al., 1974), hamster (*Marsh*, 1970), and Psammomys (*de Rouffignac* and *Morel*, 1969) than would be predicted from the DLH studies in rabbit may also reflect species differences. As described earlier, the rat juxtamedullary DLH has morphologically two types of epithelia along its length, the proximal segment appearing very similar to the urea permeable tALH, (type I epithelium) while the rabbit DLH has similar morphological characteristics along its entire length (type II epithelium). However, with respect to the overall operation of the countercurrent multiplication system (CCMS), it does not make any difference where the urea enters the loop (pars recta, early or late DLH). The main issue is the final concentration of urea and NaCl entering the thin ascending limb of Henle (*Andreoli* et al., 1978).

C. Thin Ascending Limb of Henle

The function of the thin ascending limb of Henle (tALH) has also been examined by both in vitro microperfusion and in vivo micropuncture techniques. These two techniques have been complementary and have advanced our knowledge significantly. However, some controversy still persists. The main unresolved question is whether there is active salt transport out of the tALH. It is generally accepted that the fluid in the tALH has an osmolality less than the fluid from the adjacent vasa recta (*Jamison* et al., 1967; *Jamison*, 1968); however, this decrease in luminal osmolality could occur either by active or passive transport mechanisms (Fig. 15). Clearly the fluid

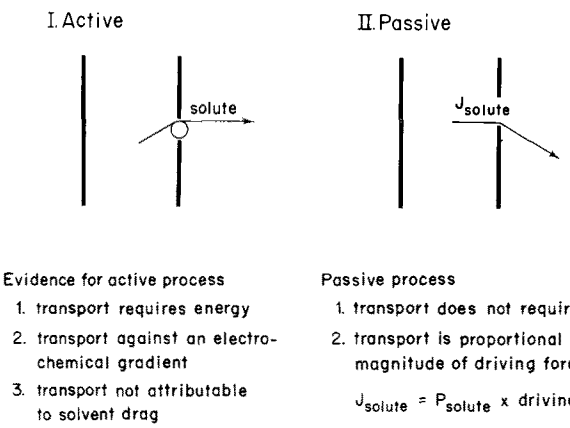

Fig. 15. The two fundamental mechanisms of solute penetration across renal tubules

within tALH can become less concentrated by active outward transport of solute if the tALH is water impermeable (Fig. 15, left panel). On the other hand, the tALH can also decrease its osmolality by passive outward diffusion of NaCl if indeed this segment is highly permeable to salt and impermeable to water. These events are depicted on the right panel of Figure 15 and assume that the tALH receives fluid with a higher concentration of salt than is contained in the adjacent vasa recta. In fact, micropuncture studies have shown that both Na (*Johnston* et al., 1977) and Cl (*Gelbart* et al., 1978; *Hogg* and *Kokko*, 1978) concentration in the tALH are higher than in the surrounding vessels.

The main unresolved question with respect to the function of the tALH is whether salt is actively transported out of the tALH. To date there is no convincing evidence to suggest the presence of an active transport mechanism in the tALH. A number of in vivo micropuncture studies have examined this issue. Initial attempts were by stopped-flow microperfusion techniques where varying concentrations of salt were injected into the tALH between two oil droplets (*Gottschalk*, 1964; *Marsh* and *Solomon*, 1965). After equilibration, these droplets were reaspirated and analyzed for electrolyte concentration. Neither *Gottschalk* (1964) nor *Marsh* and *Solomon* (1965) were able to find a lower concentration of salt in the tALH as compared to vasa recta. Thus, these experiments suggested that tALH did not have active ion transport capabilities. However, *Gottschalk* (1964) was careful to examine his own data and expressed a word of caution, suggesting that the scatter of results was such that one should be reluctant to accept his data as definitive proof against the existence of active transport. *Morgan* and *Berliner* (1968), while measuring the permeability properties of various nephron segments, were unable to find evidence for active out-

ward transport of NaCl from the tALH despite an extensive series of studies in which segments of tALH were perfused in an isolated papilla preparation. Although their data failed to show the presence of active transport, they cautioned that "some essential condition or requirement for sodium transport" was missing in their experimental protocol. *Marsh* (1970) next measured the sodium and urea concentrations in paired collections from the bend of the loop of Henle and tALH which on an average was one mm from the bend. In these studies he noted net NaCl reabsorption between these points and some urea addition. However, *Marsh* concluded that these studies cannot be used as an index of active transport especially since he repeated his earlier (*Marsh* and *Solomon,* 1965) microperfusion studies and reconfirmed that there was no reabsorption of salt from the split drop. In a more recent study *Marsh* and *Azen* (1975) again found no concentration difference of sodium between tALH and AVR during antidiuresis. However, they did find the sodium concentration of tALH to be lower than the adjacent vasa recta during saline diuresis when the tubular flow rate was decreased by simultaneous collection at the bend of the loop. *Marsh* and *Azen* (1975) feel that the most likely explanation for these latter findings is the presence of active transport mechanisms in the tALH. These results, however, should be regarded with caution as evidence of active transport because it is difficult to prevent upstream contamination of collected fluid from tALH under these conditions. In fact, *Johnston* et al. (1977), *Gelbart* et al. (1978), and *Hogg* and *Kokko* (1978) have found higher concentrations of sodium and chloride in tALH as compared to vasa recta. These latter findings would be in accord with the predictions of in vitro microperfusion studies. Thus, it is fair to conclude, that in spite of significant efforts no firm evidence exists to suggest the presence of active salt transport out of the tALH.

Because of the complexities in experimental design and difficulties in knowing the papillary interstitial electrolyte concentrations in in vivo microperfusion studies, in vitro microperfusion studies have also been designed to determine whether active salt transport occurs in the tALH. The initial studies of *Imai* and *Kokko* (1974) were conducted in the rabbit tALH using both isosmolar solution and hyperosmolar solutions in which osmotically equivalent amounts of NaCl was added to the perfusate and bath. The perfusion rates in these studies ranged from 1.9 to 17.9 nl/min. The parameters of active transport which were determined included measurements of transepithelial potential difference (P.D.), net movement of solute (gravimetric determinations), net movement of Na and Cl, and net movement of water. The PD was zero in these studies and there was no net movement of solute or water. Thus these studies showed no evidence for active transport (*Imai* and *Kokko,* 1974). Although the mean perfusion rate in these studies was higher than physiologic, it should be noted that a

number of tubules were perfused at physiologic rates with the same findings as tubules which were perfused at higher rates. *Imai* (1977) has extended these studies more recently by examining in vitro the function of the tALH of the rat and hamster. He determined that the membrane characteristics of the rat and hamster tALH were similar to the tALH of rabbit in that there was no evidence of active transport in these species.

Quantitative estimates of passive permeability measurements across the tALH can only be made in vitro due to the uncertainties of knowing the interstitial concentrations of various solutes and the difficulties inherent in maintaining perfect tissue-pipette seals during in vivo microperfusion studies of loop of Henle structures. When 200–300 mOsm/liter gradients are imposed across the tALH in vitro there is no net movement of water across the tALH of rabbit, rat or hamster (*Imai* and *Kokko,* 1974; *Imai,* 1977). Thus, the tALH is impermeable to osmotic water flow. Isotopic permeability coefficients for Na, Cl, and urea have been measured across the tALH under conditions of zero net fluid movement and zero transtubular PD. The results of these studies (*Imai* and *Kokko,* 1974, 1976) indicate that the tALH of rabbit, rat, and hamster is quite permeable to Na and Cl and moderately permeable to urea. These are the predicted permeability characteristics that would allow for passive dilution of intraluminal fluid in vivo by the efflux of NaCl down a concentration gradient. Indeed *Imai* and *Kokko* (1974) observed a decrease in luminal Cl concentration and osmolality when segments of tALH were perfused with NaCl solution that was initially isosmotic to a bath solution made up of approximately 50% NaCl and 50% urea. These latter bath conditions were chosen to simulate hydropenic in vivo papillary interstitial NaCl and urea concentration ratios.

Because of the unique membrane characteristics of the tALH, studies have been conducted to examine the nature of the passive transport mechanisms. Four different types of studies have been carried out across the rabbit tALH (*Imai* and *Kokko,* 1976). These studies disclose that transport of sodium occurs by simple passive diffusion. However, transport of chloride occurs by both simple diffusion and a saturable facilitated process which is competitively inhibited by bromide (*Imai* and *Kokko,* 1976).

The in vitro permeability characteristics would predict that in vivo the PD across the tALH is lumen positive due to preferential efflux of Cl^- with respect to Na^+. Early measurements, however, found a lumen negative PD (*Windhager,* 1964; *Marsh* and *Solomon,* 1965), but these studies failed to allow sufficiently for tip potentials and liquid junction potentials in vivo. Indeed when these precautions are taken, more recent in vivo studies by *Marsh* and *Martin* (1977) in the hamster and by *Hogg* and *Kokko* (1978) in the rat, have found a small positive PD across the tALH. Thus significant agreement now exists between the in vitro and in vivo studies.

D. Thick Ascending Limb of Henle

The function of the thick ascending limb of Henle (TALH) has been examined only by in vitro microperfusion techniques. These direct studies have demonstrated that both the medullary (MTALH) and cortical (CTALH) thick ascending limbs are capable of diluting the intraluminal fluid when perfused with solutions identical to the bath. The dilution of fluid requires specific active and passive transport characteristics.

Net solute transport out of the TALH occurs by active processes since solute is transported against significant concentration gradients. Though it is recognized that TALH epithelium has a high concentration of Na^+:K^+-activated ATPase, current evidence suggests that chloride, not sodium, is the principal ion which is actively transported, and that sodium is then transported via passive diffusion down a favorable electrochemical gradient.

There are two lines of evidence which are consistent with the view that chloride is the principal ion which is actively transported: measurement of transepithelial PD and comparison of Na and Cl flux ratios to simultaneously measured transepithelial PDs. *Rocha* and *Kokko* (1973) and *Burg* and *Green* (1973) noted initially that the luminal PD was positive when segments of MTALH (*Rocha* and *Kokko*, 1973) and CTALH (*Burg* and *Green*, 1973) were perfused with ultrafiltrate of the same rabbit serum which was used as the bath. In the broadest terms the most likely source of a lumen positive PD is either primary cation secretion or anion reabsorption. Since both the medullary and cortical TALH are capable of net solute reabsorption, it was argued that the most likely source of the lumen positive PD was primary anion reabsorption. Since Cl^- is, in the TALH, the predominant anion, the most reasonable source of the PD was primary Cl^- reabsorption. In support of this view are studies in which the lumen positive PD was eliminated by substitution of Cl^- with CH_3SO_4 in MTALH (*Rocha* and *Kokko*, 1973) and by SO_4 in CTALH (*Burg* and *Green*, 1973a). Furthermore, complete removal of HCO_3 from the perfusate in CTALH did not obliterate the positive PD (*Burg* and *Green*, 1973a). On the other hand, substitution of Na by an impermeant cation made the PD transiently more positive (*Rocha* and *Kokko*, 1973; *Burg* and *Green*, 1973a). Thus these results show that active Cl transport is responsible for the generation of the lumen positive PD. This active transport mechanism can be reversibly inhibited by various diuretics from the luminal side (*Kokko*, 1974; *Burg* and *Green*, 1973b, c; *Burg* et al., 1973) and ouabain from the blood side (*Rocha* and *Kokko*, 1973; *Burg* and *Green*, 1973a).

The passive permeability characteristics of the TALH are ideally suited for operation of the CCMS. Both the medullary (*Rocha* and *Kokko*, 1973) and cortical (*Burg* and *Green*, 1973a) TALH are impermeable to osmotic water flow. Thus NaCl can be added to the medulla without water follow-

ing. Furthermore, the water impermeability is maintained in the presence of a high concentration of antidiuretic hormone (*Burg* and *Green*, 1973a) even though it has been demonstrated that vasopressin increases the adenosine 3′:5′ monophosphate (cyclic AMP) content of the MTALH (*Imbert* et al., 1975). One of the requirements of an efficient active transport system is that the ion which is actively transported be relatively impermeant across the epithelium in question. If it were permeant, then the transported species would leak back to the side from which it emanated. In this regard it is interesting to note that the medullary (*Rocha* and *Kokko*, 1973) and cortical (*Burg* and *Green*, 1973a) segments of the TALH are quite impermeable to chloride with respective permeability coeffients of 1.4 and 1.1×10^{-5} cm/s. In contrast, if an ion is passively transported across an epithelium then its net transport would be more efficient if the epithelium were relatively permeable to that ion. Indeed the sodium permeability of cortical and medullary TALH is two to four times greater than that of chloride (*Rocha* and *Kokko*, 1973; *Burg* and *Green*, 1973a). Thus the TALH possesses ideal active and passive transport properties to allow for the separation of salt and water, and therefore, the generation of a hypertonic medullary interstitium and dilution of tubular fluid.

V. Discussion

Having reviewed the ultrastructure, histotopography, and transport characteristics of the individual nephron segments that comprise the loop of Henle, we will now consider how the experimental data agrees with the proposed models for the countercurrent multiplication system. The concept of countercurrent flow is not unique to the renal medulla. A number of examples occur in other biologic systems with perhaps the most important being the countercurrent blood flow in the human fetoplacental circulation, Figure 16. In this system it is possible to combine greatly differ-

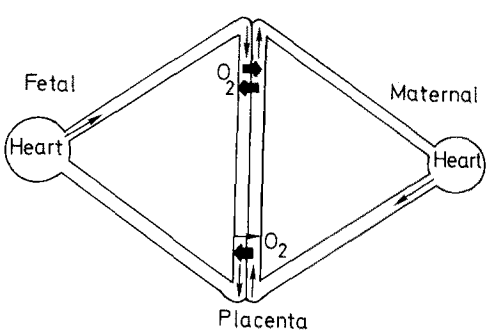

Fig. 16. Diagrammatic representation of countercurrent flow in feto-maternal circulation

ing oxygen pressures at the inflow and outflow sites in this vascular bed ("separating effect"), with equilibrium oxygen concentrations at the opposite end by the process of passive diffusion of oxygen along its concentration gradient. The two requirements for the mechanism to operate are (a) a countercurrent arrangement of the fetal and maternal vessels, and (b) the presence of a high concentration of oxygen in the afferent limb of the maternal circulation. These two requirements are applicable to all countercurrent multiplication systems, including that operating in the renal concentrating mechanism. In general terms they may be described as (a) countercurrent flow in closely apposed channels running parallel to each other, and (b) an initial active mechanism ("single effect") that generates a concentration difference between the two channel systems. It is the work performed by the maternal cardiopulmonary system that generates this high oxygen concentration in the afferent limb, and hence enables the countercurrent exchange system to evolve the concentration profile that is shown.

The salient architectural features of the renal countercurrent multiplication system were first put forth by *Hargitay* and *Kuhn* (1951) and by *Wirz* et al. (1951). These models were based on earlier theoretical developments of *Kuhn* and *Ryffel* (1942) and an appreciation of the then available physiologic data and anatomic descriptions of the renal medulla. The concept of CCMS soon received experimental support from data generated by *Wirz* (1953, 1954). The observations that distal tubule fluid is hypotonic to plasma (*Wirz*, 1956) and that fluid from the bend of the loop of Henle is hypertonic to plasma (*Gottschalk* and *Mylle*, 1959) led to the suggestion that the single effect, or active salt transport mechanism, is located throughout the length of the ascending limb of Henle (*Wirz*, 1956; *Gottschalk* and *Mylle*, 1959). There is now general agreement that the "single effect" or active mechanism that is primarily responsible for generating the countercurrent multiplication system in the kidney is active chloride transport in the thick ascending limb. However, as discussed earlier, there is no convincing evidence of active salt transport in the tALH. The failure to demonstrate active transport out of the tALH led *Kokko* and *Rector* (1972) and *Stephenson* (1972) to propose a model of CCMS which removed the necessity of active transport out of the tALH. Although certain modifications are required when other species are considered, the functional characteristics found in individual segments of the rabbit nephron conform precisely to those proposed in this model. The model is depicted in Figure 1. Its major features are as follows:

1) Active transport of sodium chloride out of the thick ascending limb, resulting in the delivery of a hypotonic fluid to the distal tubule and collecting tubule.

2) Osmotic equilibration of tubular fluid via reabsorption of water in the cortical and outer medullary segments of the collecting duct.

3) Generation of a high concentration of urea in the tubular fluid as it courses through the urea impermeable cortical and outer medullary segments of the collecting duct – as a result of the water reabsorption described (2).

4) Reabsorption of urea from the urea-permeable inner medullary segment of the collecting duct to the medullary interstitium.

5) Maintenance of a hyperosmotic inner medullary interstitium as a result of the entry of urea and sodium chloride as described in (1) and (4).

6) Equilibration of the descending limb fluid (as a result of water abstraction) with the hypertonic interstitium in the inner stripe of the outer medulla and the inner medulla. This abstraction of water produces end-descending limb tubular fluid that is isosmotic with the surrounding interstitium but which differs considerably in the solutes that comprise its osmolality. The major osmotic component of the tubular fluid is sodium chloride with urea providing a relatively small contribution to this osmolality. The situation that arises therefore, as a result of the processes described above, is a favorable gradient for the outward diffusion of sodium chloride from the thin ascending limb and the presence of a smaller, but still significant concentration gradient favoring the diffusion of urea into the thin ascending limb. Because of the greater permeability of the thin ascending limb for chloride, (and to a lesser extent, sodium) than for urea, there is a net efflux of solute resulting in dilution of the tubular fluid as it courses along the thin ascending limb of the loop of Henle (as demonstrated in vitro by the experiments of *Imai* and *Kokko,* 1974).

The pivotal role of urea in the passive model is readily apparent from this description. In order to account for the urea component of the medullary tonicity it was formerly considered that urea reabsorption from the collecting duct was solely responsible for urea recycling into the interstitium. It would now appear that urea recycling from the pelvic urine may also be important (cf. Fig. 1).

As noted previously, the experimental data that have been obtained using the technique of in vitro perfusion of isolated rabbit tubules are concordant with the passive model. Studies of this species in vivo have been rather scarce however. In vivo data concerning the role of urea in the rabbit concentrating mechanism was obtained by *House* et al. (1963) who compared the maximal concentrating capacity of normal rabbits and rabbits maintained on a low protein diet. They showed that rabbits maintained on a low protein diet had impaired concentrating capacity. We have recently confirmed these findings using female New Zealand white rabbits (*Hogg* and *McNatt,* unpublished results). More specific in vivo validation of the membrane characteristics of rabbit nephron segments detected in vitro would require micropuncture studies to reveal the urea, sodium, and

chloride concentration gradients, and electrical determinations in the thin limbs of Henle's loop in the rabbit. This data cannot be obtained by conventional papillary micropuncture because the rabbit papilla does not protrude from the main body of the kidney and hence is not available for micropuncture. Hence, direct in vivo validation (or repudiation) of the model in the rabbit is not possible.

When the passive model is applied to data obtained in species of animals in which in vivo papillary micropuncture is possible, a number of the findings are not entirely consistent with all details of the model as originally described. These experiments have been conducted primarily in the rat, hamster, and Psammomys and have been considered in detail in Sect. IV. There are obviously two major causes that may be responsible for such different findings. These involve the methodologic differences in the experimental models used and the different species that have been studied. Investigators who have been involved in studies of the concentrating mechanism have until recently been inclined to consider methodologic problems as the most likely cause – with particular consideration usually being given to the technical problems of other investigators. The findings which do not readily adhere to the passive model include the following: (a) fractional urea delivery to the bend of the loop of Henle in juxtamedullary nephrons is greater than that which can be accounted for by glomerular filtration alone, inferring urea "secretion" into a segment of the descending limb (*de Rouffignac* and *Morel,* 1969; *Marsh,* 1970; *Pennell* et al., 1974); (b) in concert with this is the finding of smaller concentration gradients for urea, sodium, and chloride between the thin limb tubular fluid and adjacent vasa recta than would be expected if hypertonicity of descending limb fluid were due to water abstraction alone (*Marsh,* 1970; *Pennell* et al., 1975; *Imbert* and *de Rouffignac,* 1976); and (c) the finding by *Marsh* (1970) of significant urea entry into the final millimeter of the thin descending limb in the in vivo hamster papilla preparation.

While these findings necessitate certain modifications of the passive model of the CCMS when applied to these species, they do not invalidate the basic mechanism as outlined above. As described in the first section, an examination of the ultrastructure and histotopography of medullary structures in rodents is highly suggestive that certain differences should exist between the quantitative aspects of these mechanisms in rats and Psammomys on the one hand, and the rabbit on the other. However, it should be noted that conditions that are necessary for the passive model to operate have in fact been observed in those species that have been examined in vivo. The conditions can be listed as follows:

1) Thin ascending limb sodium and chloride concentration greater than interstitial concentrations of sodium (*Johnston* et al., 1977) and chloride (*Gelbart* et al., 1978; *Hogg* and *Kokko,* 1978).

2) Interstitial urea concentration greater than end descending limb urea concentration (*Marsh*, 1970; *Penell* et al., 1975; *Imbert* and *de Rouffignac*, 1976).

3) Small positive electrical potential difference in the thin ascending limb consistent with the in vitro demonstration of high chloride permeability (*Marsh* and *Martin*, 1977; *Hogg* and *Kokko*, 1978).

4) Evidence of reversibility of polarity of this potential difference when the direction of the chloride concentration gradient is reversed (*Hogg* and *Kokko*, 1978).

These results in the hamster, rat, and Psammomys support the theories of water abstraction in the descending limb and passive chloride reabsorption in the thin ascending limb. They also demonstrate the presence of urea secretion into a segment of the juxtamedullary nephron proximal to the hairpin bend, but not in an amount that is sufficient to dissipate the urea gradient.

With regard to the question of urea entry into the descending limb, two points deserve reiteration along with the point that they are *not* mutually exclusive. (a) Urea "secretion" into a segment of the juxtamedullary descending limb definitely occurs in rats, hamsters, and Psammomys; and (b) the presence of urea entry does not invalidate the passive mechanism in the thin ascending limb, providing that there remains an outward concentration gradient for sodium chloride and an inward gradient for urea.

It is concluded therefore that the passive model, as originally described, is entirely consistent with recent experimental data concerning the rabbit nephron, but may require certain quantitative modifications in order to accomodate recent data pertaining to rodent kidneys. The question therefore arises as to which modifications will enable the passive model to encompass the recent in vivo micropuncture data and thus make the basic model a suitable representation of the renal concentrating mechanism in all animals. The only change that must be made in terms of permeability characteristics involves the incorporation of a urea entry segment in the terminal descending limb and also in the proximal DLH or pars recta of the proximal tubule. The pars recta has been examined in the rabbit and, as discussed earlier, active urea secretion has been shown to be present in this species (*Kawamura* and *Kokko*, 1976). Similar in vitro studies have not been carried out, however, in either the pars recta or thin descending limb of those species in which urea addition has been demonstrated in vivo. Hence it is not readily apparent where this urea entry occurs. It is probable that some urea secretion occurs in the pars recta and this may then be supplemented by further urea entry into the initial segment of the thin descending limb. Although it is very tempting to correlate functional differences with these striking differences in both structural organization and

ultrastructure, attempts to make such correlations without direct physiologic studies of the segments involved should be tempered with caution.

Figure 17 shows a schematic representation of the mechanisms by which urea entry into thin limbs of the loop of Henle of rodent kidneys may occur. It will be noted from the figure that three possible entry sites into the descending limb have been depicted. The first of these is the prebend DLH – a nephron segment whose epithelial wall shows the characteristics of the type I epithelium (solute permeable, water impermeable) that

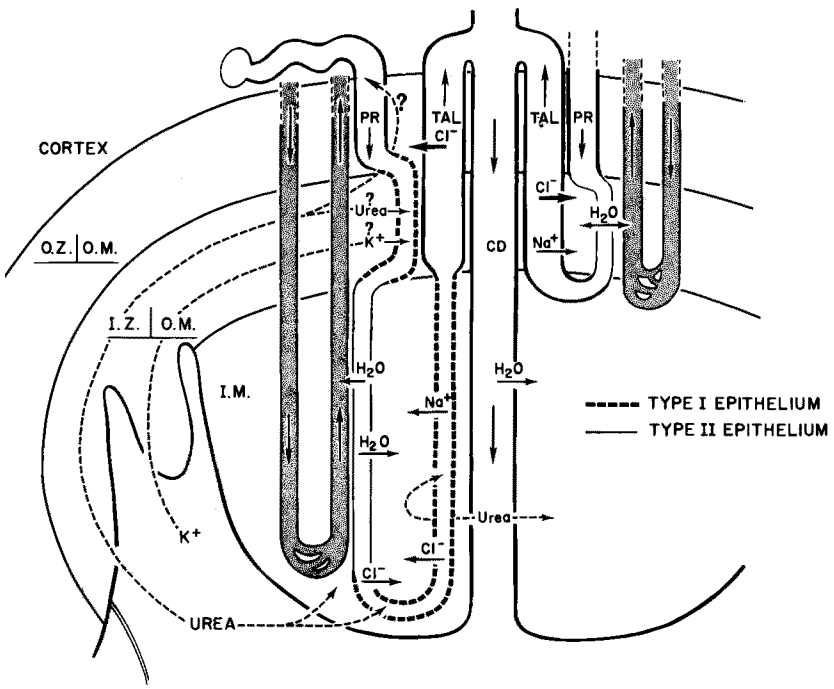

Fig. 17. Schematic representation of the sites by which urea may enter into thin limbs of the loop of Henle of rodent kidneys

lines the tALH. The other two possible sites of entry shown in the figure are the pars recta and the initial segment of the DLH (also type I epithelium) – the contribution of each of these being unknown at present. It must be stressed that the concept of differential urea permeability along the DLH of rodent kidneys has not been measured directly in vivo or in vitro because of technical problems. Caution must therefore be exercised in promoting this concept. It is proposed however that some form of sequential urea secretion and water abstraction in the descending limb is necessary to

explain the following findings: (a) end DLH urea delivery rates greater than the filtered load, and (b) end DLH tubular fluid NaCl concentrations greater than adjacent vasa recta concentrations. However, until further data is available the exact site of entry will remain speculative.

The question of species heterogeneity of function? The species in which solute entry into the descending limb (including pars recta and thin descending limbs of Henle) has been suggested (rat, hamster, Psammomys) have been studied primarily in vivo. In such circumstances it is not possible to examine segments from the whole length of the descending limb to test for homogeneity of function. Hence it cannot be stated whether the early DLH in such species possesses intrinsic membrane characteristics similar to those in the tALH, a segment which it resembles ultrastructurally.

Information which may assist in this questionof structure-function correlation has been extracted from the study carried out by *Jamison* (1968) in rats, a study which utilized the Sakai technique of exposing the inner medullary structures for micropuncture (*Sakai* et al., 1965). In this study the investigators were able to analyze tubular fluid from different lengths along the DLH. The puncture sites were in the segment of DLH which in the rat is characterized by type II epithelium i.e., simple epithelium with few interdigitations and long tight junctions. This is similar to the epithelium which lines the entire length of the rabbit JM-DLH. The data are shown

Table 2. TF/P inulin versus TF/P Na/inulin in DLH

Rat number	Puncture site to papilla tip distance (mm)	Distance between puncture sites (μ)	TF/P inulin	ΔTF/P inulin	TF/P Na/In	ΔTF/P Na/In
1	not given	–	4.6 5.2	0.6	0.30 0.29	– 0.01
2	2.80 2.20	600	4.8 6.2	1.4	0.38 0.32	– 0.06
4	2.50 2.03	470	4.0 4.7	0.7	0.35 0.34	– 0.01
6	2.90 2.40	500	4.0 4.5	0.5	0.45 0.31	– 0.14
17	2.50 2.33	170	3.6 4.0	0.4	0.39 0.38	– 0.01
$\bar{X}$ from last 4 rats		435		0.75		– 0.05

Data extracted from *Jamison* (1968).

in Table 2 and demonstrate that along this segment the fractional delivery of sodium remains relatively constant whereas the TF/P inulin increases, suggesting that water abstraction is occurring in the absence of solute entry. This in vivo situation is analogous to the in vitro findings along the whole length of the rabbit DLH and is compatible with the model in Figure 17.

The road ahead. Future investigations of the concentrating mechanism will hopefully require less assumptions and extrapolations than have been necessary in the present studies. The use of electron probe analysis will provide more specific ion concentration profiles of the inner medulla under varying circumstances. The approach of *Schmidt-Nielsen* (1977) in studying specific subcompartments of the inner medulla is to be encouraged. Knowledge of solute concentrations in the thin limbs, vasa recta, interstitial space, and possibly the collecting duct channels and epithelial spaces (*Lacy* and *Schmidt-Nielsen,* 1976) at different levels will hopefully enable investigators to settle the questions of (a) the site of solute entry into the descending limbs of rodents; (b) the need for active transport in the thin ascending limb as it approaches the outer medulla; (c) the appropriateness of the structure-function correlations that have been made; and (d) the extent to which interspecies heterogeneity exists in renal concentrating mechanisms.

Consideration must also be given in future analyses to the importance of the pelvic urine in the concentrating process. Control mechanisms and possible importance of the renal pelvis pacemaker activity, backflow of urine into the pelvic fornices, back diffusion of water and solutes into inner and outer medulla and the physical, and possibly hormonal, influences on these phenomena must be carefully studied if a fully composite picture of the renal concentrating mechanism is to be realized.

Acknowledgments. This work was supported in part by NIAMDD Grant No. R01AM 14677 and by NIH Training Grant No. 1-T32-AMO7257. The authors gratefully acknowledge the critical review and suggestions of Drs. M.S. Lucci and M.J. Schwartz.

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Rev. Physiol. Biochem. Pharmacol., Vol. 86

Mechanisms of Gas Exchange in Bird Lungs

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Contents

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I. Introduction

Scientific descriptions of the anatomy and physiology of avian respiration date back to the sixteenth century (cf. *Duncker*, 1971). While most of this work remained qualitative and many topics controversial, application in recent years of modern techniques in a number of laboratories has helped to obtain a much clearer picture of the structure and function of the respiratory system in birds. It is not the intention of this article to provide a comprehensive review of the physiology of avian respiration; some excellent textbook articles have recently appeared (e.g., *Fedde*, 1976). Rather it will highlight mechanisms of gas exchange in the avian parabronchial lung for two reasons. First, considerable progress has been achieved in our understanding in this area, yet many recent reviews have omitted its description; secondly, the physiology of gas exchange in birds has occupied the author's own interest for some time.

In thus restricting the scope of the report, many topics which are closely related to avian respiration and which have progressed considerably over the past years are omitted. The interested reader will find, however, a number of reviews on several aspects of avian respiration (*Romanoff* and *Romanoff*, 1949; *Romanoff*, 1967; *King* and *Molony*, 1971; *Jones* and *Johansen*, 1972; *Jones*, 1972; *Lasiewski*, 1972; *Calder* and *King*, 1974; *Freeman* and *Vince*, 1974; *Dawson*, 1975; *Dejours*, 1975; *Schmidt-Nielsen*, 1975; *Fedde*, 1976; *Jones*, 1976; *Piiper* and *Scheid*, 1977; *Bouverot*, 1978; *White*, 1978) and may consult the proceedings of recent conferences (*Piiper*, 1972, 1978a; *Scheid*, 1974). References to the many papers on gas exchange during development of birds may be obtained from *Piiper* (1978a).

This review is mainly written to address physiologists who are familiar with the general principles of respiratory physiology in mammals, and will therefore concentrate mainly on those aspects in respect of which birds differ from mammals. Emphasis is, moreover, laid on those factors which appear to be common for all birds; species differences will generally not be addressed. Values for physiologic parameters will only be quoted as far as they help the understanding of basic principles.

The anatomical terminology used is adopted from *King* (1979); for physiologic terminology, the proposals of *Piiper* et al. (1971) are followed.

II. Anatomoy of the Respiratory System

Application of modern techniques has led to a considerable advancement in our understanding of the structure of the avian respiratory system. Of

particular interest is the work of *Duncker* who has studied casts of the respiratory apparatus in about 150 bird species (*Duncker,* 1971) and has thus helped to identify common features in the structure, which may be of particular interest for functional considerations. In this paper we will only briefly describe those elements of the system which form the basis for discussing the way in which the system works. The reader is referred to detailed and comprehensive reviews of the anatomy (*Akester,* 1960; *King,* 1966, 1975; *King* and *Molony,* 1971; *Duncker,* 1971, 1972, 1974).

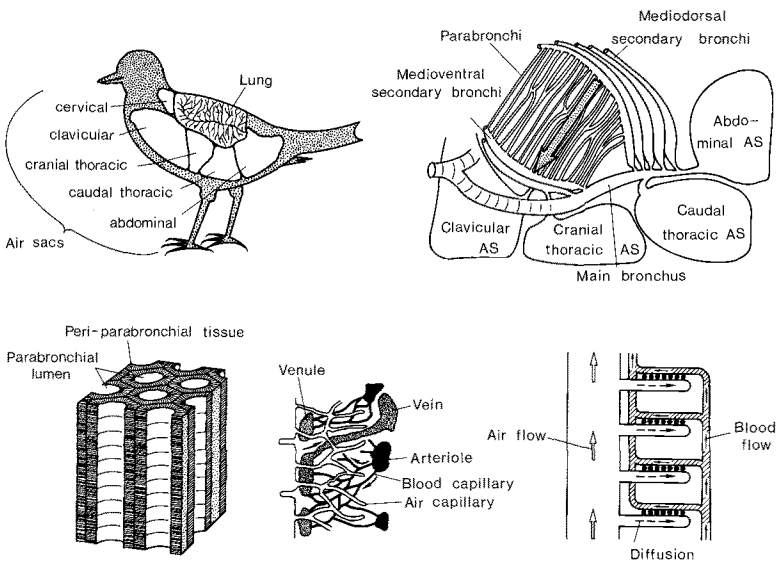

Fig. 1. Schema of the respiratory system in birds. It comprises the lung and a number of air sacs. The lung is composed of long narrow tubes (parabronchi), through which gas flows in the same direction during both inspiration and expiration: from mediodorsal to medioventral secondary bronchi (arrow in upper right diagram). The peripara-bronchial tissue, a dense network of air capillaries and blood capillaries, constitutes the site for respiratory gas exchange. The cross-current model *(lower right)* is suited for analysis of gas exchange

The respiratory tract comprises two components (Fig. 1), the *parabronchial lung,* which serves gas exchange, and the *air sacs,* which allow the volume changes required for tidal ventilation without significant gas exchange across their walls (*Magnussen* et al., 1976). Unlike in the mammalian lung, the structural elements subserving ventilation and gas exchange are thus separated.

A. Location of Lungs and Air Sacs

The avian lungs are compact, small structures which cannot be subdivided macroscopically into subunits such as lobes. They occupy the dorsal portion of the thoracic cavity, the cavum pulmonale, where the ribs and vertebrae incise deeply into the dorsolateral and medial lung surfaces. The cavum pulmonale is limited ventrally by a membrane composed mainly of connective tissue, the horizontal septum. The space underneath this cavum is subdivided by a similar membrane, the oblique septum, into a medial compartment, containing the visceral organs, and a lateral compartment which houses the air sacs. The horizontal septum contains some muscle fibres originating from the ribs (Mm. costopulmonales). However, neither the horizontal nor the oblique septum may be viewed as homologous to the mammalian diaphragm. In fact, thoracic and abdominal cavities are not separated by a subdivision which would allow different pressures in both.

In most birds there exist nine air sacs, four paired and one unpaired. Two pairs, the *cranial* and *caudal thoracic air sacs,* each have well defined and smooth walls, mainly provided by the body wall and the two septa. The unpaired *clavicular air sac,* which is easily accessible to a puncturing needle between the claviculae, has a very complex configuration with many diverticula and extensions even into the surrounding bones. The trachea, main bronchus, esophagus, nerves, and muscles traverse this sac. The small and diverticulated *cervical sacs* have not received much attention by physiologists yet. Care must, however, be taken not to rupture their walls in the course of a tracheotomy. The *abdominal air sacs* lie behind the oblique septum. They occupy the space between the intestinal loops, and their maximum capacity exceeds by far their actual volume under normal conditions.

B. Bronchial System

The *trachea* divides in the lower neck into the right and left *main bronchi.* After entering the lung, each main bronchus gives off a series of secondary bronchi, the *medioventral secondary bronchi* (referred to here as *ventrobronchi*), which occupy with extensive ramification the ventral surface of the lung and are thus in close proximity to the horizontal septum. Between the ventrobronchi and the second set of secondary bronchi, the *mediodorsal secondary bronchi* (referred to here as *dorsobronchi*), there is only a short stretch of the main bronchus without openings to the secondary bronchi. The dorsobronchi and their branches form the dorsolateral surface of the lung. These two sets of secondary bronchi, ventrobronchi and dorsobronchi, are connected by the tertiary bronchi or *parabronchi*

which are long, narrow tubes displaying only a mild degree of anastomosing, around their origins from secondary bronchi and around the middle of their length (Fig. 1). The periparabronchial tissue is the site where gas exchange occurs with blood, and the assembly of parabronchi will be addressed as the *parabronchial lung* of birds.

The air sacs are usually divided into two groups according to their bronchial connections. The cranial group (cervical, clavicular, and cranial thoracic air sacs) connects to the ventrobronchi, while the sacs of the caudal group have direct communication with the main bronchus: the laterobronchus to the caudal thoracic air sac departes from the main bronchus opposite to the origins of the large, cranial dorsobronchi, while the main bronchus itself opens caudal to the lung into the abdominal sac.

The cervical sacs connect to the first ventrobronchus. Both the clavicular and the cranial thoracic air sacs originate from the third ventrobronchus on each body side, very close to its origin from the main bronchus. Aside from these connections, there exist ostia to the cranial air sacs connected by a lateral branch to the first ventrobronchus and, variable among species, by branches or a parabronchial network to the second and fourth ventrobronchi. The ventrobronchi appear to communicate by short branches such that functionally all cranial air sacs are connected to all ventrobronchi (*H.-R. Duncker,* personal communication).

Parabronchi are several cm in length and their lumen is about 1 mm wide, there being a considerable variability among species. The number of parabronchi in both lungs of a chicken is about 300 to 500 (*King* and *Cowie,* 1969). The length of the parabronchi within the lungs of a given animal appears to be roughly equal.

The features of the respiratory system so far described have been found to be present in all birds investigated (*Duncker,* 1971). Figure 1 represents a rough schema of the lung and its bronchial connections to both air sac groups (cranial and caudal). *Duncker* (1971) has proposed the term *paleopulmo* for this basic arrangement of the lung with parabronchi extending exclusively between ventrobronchi and dorsobronchi. It is the only arrangement occurring in penguins and emus.

In all other birds an additional network of parabronchi, the *neopulmo,* is developed, to varied degrees, which extends from the main bronchus and dorsobronchi to the caudal air sacs, entering particularly into their bronchial connections. The neopulmonic parabronchi are laterally apposed to the main bronchus and dorsobronchi which are thus no more directly accessible from the lateral body wall. In song birds and fowl-like birds the neopulmo is particularly well developed and has thus disqualified the domestic hen for studies involving direct measurements in the dorsobronchi. In the duck, on the other hand, the modest development of the neopulmo allows access to the dorsobronchi from the lateral body wall.

Unlike in the paleopulmo, the parabronchi in the neopulmo form a meshwork. Aside from that, the histologic structure of both types of parabronchi appears to be identical. Some functional implications of the difference in the bronchial connections between both lung regions will be discussed later (Sect. VII. E).

In the schema presented above, neopulmonic parabronchi would originate only from dorsobronchi and from the main bronchus. However, with highly developed neopulmo (e.g., in fowl-like and song birds) there exist also some parabronchial connections with ventrobronchi. The functional significance of all these paths is not entirely clear yet.

C. Microscopic Structure of the Parabronchi

Whereas the air sac walls, particularly the membranes between adjacent sacs, are only poorly vascularized, the tissue around the parabronchi contains a rich supply of *blood capillaries.* These blood capillaries originate from arterioles in the tissue between neighboring parabronchi and traverse the periparabronchial tissue in radial direction towards the parabronchial lumen, where they are collected in venules and drained into larger veins that run in the tissue between the parabronchi.

From the parabronchial lumen radiates a network of very fine (some μm in diameter) tubular *air capillaries,* interposed into the system of blood capillaries. Air capillaries, blood capillaries, and their walls, forming the blood/gas membranes, make up most of the periparabronchial tissue, which may be viewed as a *gas exchange mantle* around the parabronchial tubes. The thickness of this mantle is of the same order of magnitude as the radius of the parabronchial lumen, displaying considerable variability among species.

In some orders of birds, the air capillaries are functionally blind-ending tubes and adjacent parabronchi are thus well delimited, whereas in others, the air capillaries of neighboring parabronchi interconnect. However, the lack of a pressure difference between adjoining parabronchi prevents significant convective gas movement through these communicating air capillaries.

The excact arrangement of the blood capillaries – degree of ramification, degree of deviation from a purely radial direction – is open to some controversy (*Akester,* 1971; *Abdalla* and *King,* 1975; *Duncker,* 1972, 1974; *West* et al., 1977; cf. *Scheid,* 1978a). However, all authors agree that a given blood capillary contacts the parabronchus for gas exchange, via the air capillaries, only along a fraction of the total parabronchial length. This point is of particular interest, as it constitutes the structural

basis for the cross-current model of parabronchial gas exchange (see Sect. V. B).

For mammalian lungs, morphometric techniques have been very successfully applied to obtain quantitative estimates of morphological parameters (*Weibel,* 1963, 1973; *Gehr* et al., 1978). Comparatively little is known about quantiative lung morphology in the parabronchial lung (*Policard* et al., 1962). Estimates of *Duncker* (1972) suggest a higher area of the gas exchanging surface (per unit body weight) in active species, being about five times larger in the carrion crow than in the chicken. The extremely high value reported by *Stanislaus* (1937) for the hummingbird should be reexamined. The data are simply too scanty to invite a fruitful discussion about differences between species or comparison with lungs of other vertebrate classes.

The problem of stability of and exudation into the narrow air capillaries has not yet been solved (cf. *Macklem* et al., 1979). Lung surfactant has been demonstrated which is physically, chemically, and morphologically similar to that of mammalian lungs, and which may prevent accumulation of liquid in the air capillaries (*Pattle,* 1965, 1978).

III. Ventilation of Respiratory Tract

Inspired air moves into the respiratory system as a result of the expansion of the thoracoabdominal cavity executed by the inspiratory muscles; and during expiration, air is expelled by the action of expiratory muscles. To this extent, the situation is not different from that in mammals, apart from the lack of the diaphragm in birds. Due to the peculiar structural arrangement of airways, however, the distribution of the respired gas inside the lung-air sac apparatus is not easy to predict and has been debated among scientists for a long time.

The volume of gas in the parabronchial lung is small compared with that in the air sacs. Anatomic measurements suggest that about 10% of the total volume of the respiratory system is located in the parabronchial lungs (*Campana,* 1875; *Zeuthen,* 1942; *King* and *Payne,* 1958, 1962; *Burton* and *Smith,* 1968; *Duncker,* 1972). The fractional volume of gas exchanging airways in the avian respiratory tract is thus considerably smaller than in mammals, where it constitutes more than 95% of the total lung volume (*Weibel,* 1963). The implications for gas exchange will be considered below (Sect. VII. B). The parabronchial lung appears to undergo only small volume changes in the respiratory cycle. Recent measurements (*Macklem* et al., 1979) suggest that the parabronchial tissue is distensible so that changes in parabronchial volume might be expected with changing volume

of the thoracoabdominal cavity in the respiratory cycle. However, such changes appear to be counteropposed by phasic activity of the Mm. costopulmonales (*Fedde* et al., 1964) which connect the ribs with the horizontal septum.

It appears thus as a justified approximation to view the air sacs as bellows which provide the tidal air flow. Part of this air flow is directed through the parabronchial lung, which may be assumed to be rigid.

A. Ventilation of Air Sacs

Earlier authors contended that only the caudal air sacs were ventilated to a significant degree (*Vos,* 1935; *Zeuthen,* 1942). However, more recent investigations agree that all air sacs are effectively ventilated, the ratio of ventilation to volume being similar in all air sacs (*Shepard* et al., 1959; *Schmidt-Nielsen* et al., 1969; *Bouverot* and *Dejours,* 1971; *Bretz* and *Schmidt-Nielsen,* 1971; *Scheid* et al., 1974b). *Scheid* et al. (1974b) have, moreover, estimated functional volumes and ventilation of the various air sacs in the duck using inert gases of low solubility.

B. Air Flow Pattern in Respiratory Tract

Air reaches the alveoli of mammalian lungs after passing through a number of branching bronchiolar tubes, the airways thus forming a dead-end, to-and-fro system for air flow. The flow of air in the avian lung, on the other hand, cannot easily be predicted from structural considerations. Since the parabronchial lung is open at both ends, air can flow through it in either direction, and the path taken by the air between trachea and the air sac is likewise unpredictable. In fact, this problem has long been a matter of fierce controversy and imaginative speculation. Indeed, one finds in the literature, which dates back to *Coitier* (1573) and *Harvey* (1651), almost all possible patterns proposed for air flow in the avian lung. We will outline some of the older theories and hypotheses and refer to more comprehensive reviews (*Biggs* and *King,* 1957; *King* and *Farner,* 1964; *King,* 1966; *Bretz* and *Schmidt-Nielsen,* 1971).

1. Earlier Views. The theory of *Zeuthen* (1942) appears at first sight to be the most plausible. He regarded the assemblage of the parabronchial tubes (of the paleopulmo) to be in parallel to the main bronchus and thus postulated alternating flow direction through the lung, from ventrobronchi to dorsobronchi on inspiration, and vice versa during expiration. Lung and main bronchus shared ventilation in accordance with their relative flow re-

sistance. This theory has received little attention. In fact, authors before and after *Zeuthen* assumed that air passed through the lung in only one direction, from dorsobronchi to ventrobronchi, either in inspiration or in expiration or in both.

All hypotheses were based on indirect experiments and observations. Distribution of inhaled particles were observed (*Dotterweich,* 1930a, b; *Walter,* 1934; *Vos,* 1935; *Graham,* 1939; *Hazelhoff,* 1943); gas partial pressures in the air sacs were compared with those in arterial blood (*Dotterweich,* 1933; *Vos,* 1935; *Makowski,* 1938; *Scharnke,* 1938; *Graham,* 1939; *Zeuthen,* 1942; *Shephard* et al., 1959; *Cohn* and *Shannon,* 1968; *Schmidt-Nielsen* et al., 1969); normal breathing was compared with breathing through a transected humerus (*Biggs* and *King,* 1957); or the flow pattern was observed in structural models of the respiratory tract (*Dotterweich,* 1936; *Hazelhoff,* 1943).

Controversial results were obtained, and even with agreement in results, conclusions would often differ according to the conceptual models utilized. To interpret partial pressures in air sacs and in arterial blood in terms of the flow of respired air, the model used for gas exchange in the parabronchial lung appears to be crucial. *Shephard* et al. (1959) assumed the alveolar lung model to hold for parabronchial gas exchange (P_{CO_2} in gas leaving the parabronchi equal to arterial blood P_{CO_2}); *Cohn* and *Shannon* (1968) implied a co-current model, whereas *Schmidt-Nielsen* et al. (1969) found their results to agree with the assumption of a counter-current model for exchange between parabronchial gas and blood. Since none of these models appears to be in agreement with lung anatomy (see Sect. V.B) the conclusions drawn had to be viewed as dubious. Recently, *James* et al. (1976) employed various radiographic and X-ray techniques to study air movements in the respiratory tract.

2. Direct Measurement of Flow Direction. A few years ago, several investigators attempted to measure airflow in the avian respiratory tract by direct techniques.

Bretz and *Schmidt-Nielsen* (1970, 1971) devised a flow sensitive catheter probe of two configurations, incorporating two thermistors as sensing elements. A straight probe could directly be inserted into the main bronchus, and a curved probe could be advanced through the main bronchus into a ventrobronchus or dorsobronchus. They observed flow in awake ducks during rest and thermal panting as well as in anesthetized birds.

Scheid and *Piiper* (1970b, 1971) devised a flowmeter tube, containing a heat source and a thermocouple element, which they could implant through the lateral body wall into the larger dorsobronchi of the duck. Recordings were made in awake animals at rest and during heat induced panting and also in pump ventilated birds after relaxation.

Brackenbury (1971) constructed small tubes in which flow could be measured manometrically. He implanted the tube from the lateral body wall into the major dorsobronchi in geese. He observed air flow in anesthetized, spontaneously breathing animals.

All these authors observed air to flow in the dorsobronchi during both inspiration and expiration, flow direction being the same in these bronchi in both respiratory phases, viz. from the main bronchus into the dorsobronchi. The anatomy of the bronchial connections implies that air flow through the parabronchi of the paleopulmo is also in the same direction during inspiration and expiration, from dorsobronchi towards ventrobronchi. This pattern is usually referred to as *unidirectional air flow* in the avian parabronchial lung. These authors have thus, in respect of parabronchial flow direction, confirmed the hypothesis of *Bethe* (1925), and have disproved the proposal of *Zeuthen* (1942).

The techniques used could be criticized for various reasons. It cannot easily be ruled out that the implanted devices disturb the normal flow pattern. In particular, the flow probe of *Bretz* and *Schmidt-Nielsen* (1971), which was advanced through the orifices of the secondary bronchi, could have obstructed or distorted the tissue with consequences for air flow pattern. Attention should also be directed to the position of the experimental animals. The supine position used by *Brackenbury* (1971) is certainly unphysiologic, but a support to keep the animal in an upright position (*Bretz* and *Schmidt-Nielsen,* 1971) may also limit free respiratory movements. The methods of *Bretz* and *Schmidt-Nielsen* (1971) and of *Scheid* and *Piiper* (1971) allow measurement of direction of flow but are inappropriate to quantify the flow rate. Although this quantification may be accomplished with the device used by *Brackenbury* (1971) its usefulness is limited, as only one or a few of the larger bronchi may be investigated, while the combined flow rate of all these bronchi is the interesting parameter as it is closely related to the total parabronchial ventilation.

Support for the unidirectional flow thesis was also obtained by observations of inert or respiratory gases at various sites in the respiratory system after bolus injections of the gases at key sites (*Schmidt-Nielsen* et al., 1969; *Bouverot* and *Dejours,* 1971; *Bretz* and *Schmidt-Nielsen,* 1972).

Although the unidirectional flow through the parabronchi appears to have been demonstrated beyond resonable doubt, there are still controversies about the pattern of flow in other parts of the respiratory system. In particular, direction of inspiratory flow across the ventrobronchial orifices into the main bronchus is much debated, ranging from flow into ventrobronchi (*Portier,* 1928; *Vos,* 1935; *Dotterweich,* 1936; *Zeuthen,* 1942; *Scheid* et al., 1972), flow into the main bronchus (*Hazelhoff,* 1943), to no flow at all (*Bethe,* 1925; *Dotterweich,* 1930b, 1933; *Cohn* and *Shannon,* 1968; *Schmidt-Nielsen* et al., 1969). Of particular interest is the "in-

spired loop hypothesis" of *Hazelhoff* (1943) by which parabronchial gas may flow more than once over the parabronchi during inspiration. Such loop would in fact lead to a higher gas exchange rate for a given total ventilation (*Scheid*, unpublished) and would thus increase the overall gas exchange efficacy of the lung. It could also explain the finding of relatively high CO_2 and low O_2 levels in the caudal air sacs (see Sect. VII. E).

Recent measurements in the spontaneously breathing duck, by mass spectrometry of the partial pressure profiles for CO_2 and O_2 in the main bronchus and the ventrobronchi, led to the conclusion that there is no flow across the ventrobronchial orifices during inspiration (*Powell* et al., 1978; *Scheid* et al., 1978), in accordance with the findings of *Bretz* and *Schmidt-Nielsen* (1971).

Debate is also about whether on expiration all flow from caudal air sacs is directed into the (paleopulmonic) lung or whether some gas passes the direct way out through the main bronchus. The best evidence to date suggests that this flow bypassing the lungs is small if not negligible (Fig. 2) (*Bretz* and *Schmidt-Nielsen*, 1971; own unpublsihed observations).

Figure 2 is a diagram of air flow in the resting bird according to the results outlined above.

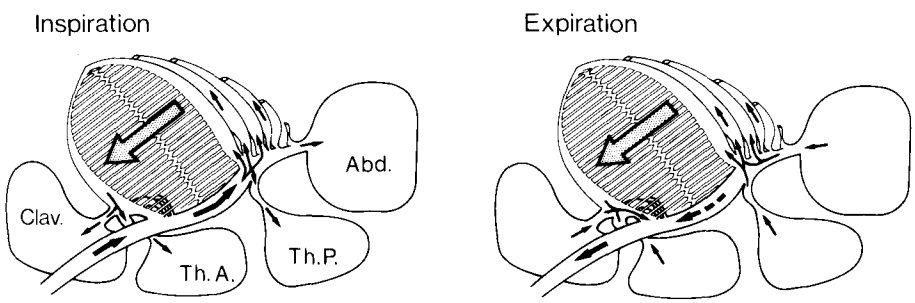

Fig. 2. Representation of air flow in the respiratory tract of birds during both phases of ventilation. Broken arrow, flow uncertain

C. Mechanisms Involved in Rectifying Lung Air Flow

The simplest explanation for the unidirectional air flow would be the existence of anatomic valves, opened and closed in phase with breathing. Although claimed by a number of authors in the past (*Brandes*, 1924; *Bethe*, 1925; *Portier*, 1928; *Dotterweich*, 1930a, b, 1933; *Vos*, 1935), valves or similar anatomic elements that would cause unidirectional air flow have never been found by anatomists (*King* and *Payne*, 1960).

Sequential filling and emptying of the air sacs would be another potential mechanism. In contrast to earlier observations (reviewed by *Bretz* and *Schmidt-Nielsen*, 1971), small pressure differences appear to exist between the cranial and caudal air sacs, as a result of differences in the time constants for emptying and filling of the sacs, and they may play a role in the rectification of flow (*Brackenbury*, 1972a). According to *Brackenbury* (1979) the cranial air sacs are responsible for driving air flow in the caudocranial direction through the lung during inspiration, whilst the caudal air sacs determine the flow direction during expiration.

Scheid et al. (1972) have shown that the unidirectional dorsobronchial flow persists in the paralyzed, pump ventilated, and even in the dead animal. These authors have also experimented with isolated parts of the bronchial system, excised from an animal that was fixed by glutaraldehyde. Their conclusion was that aerodynamic mechanisms, notably the Bernoulli effect, boundary layer detachment, and local jet formation, are involved. Similarly, *Brackenbury* (1972b) concluded from his experiments that aerodynamic mechanisms are involved in the rectification of respiratory flow. There is certainly more work to be done in this field, which appears to call for cooperation between physiologists and fluid dynamicists.

Recently, *Molony* et al. (1976) found air flow resistance across the ventrobronchial orifices into the main bronchus to be CO_2 dependent, high at low CO_2, and vice versa. The anatomic correlate of such a CO_2 dependent flow resistance is not identified. The authors suggested that this dependence could provide part of a functional valving mechanisms.

D. Significance of Unidirectional Flow

It is tempting to assume that the unidirectional air flow in the parabronchi is of benefit for gas exchange with blood. This would in fact be the case if the parabronchial lung operated as a counter-current system as had been proposed earlier (*Schmidt-Nielsen*, 1971). However, the actual arrangement of blood and gas flow in the parabronchi suggests a different model for gas exchange, the cross-current, the efficiency of which does not depend on the direction of flow. Thus rectification of parabronchial gas flow is not required for the functioning of the gas exchange system.

Piiper and *Scheid* (1973) have suggested that flow reversal would create a functional breath-holding situation during the time required for flow reversal. They have indicated that the rates of drop in P_{O_2} and rise in P_{CO_2} could be intolerably high due to the small parabronchial gas volume. However, direct evidence shows that gas exchange with intermittent ventilatory flow is only little impaired compared with gas exchange during continuous ventilatory flow, probably because parabronchial gas is mixed during

breath-holding with that in the adjoining airways by way of convection and diffusion. Hence, the functional residual volume in the gas exchange region appears to be larger than the parabronchial volume (see Sect. VII. B).

During panting, air flow in the dorsobronchi, and thus in the lung, is still unidirectional (*Bretz* and *Schmidt-Nielsen,* 1971; *Scheid* and *Piiper,* 1971). In fact, the oscillations in flow rate within a respiratory cycle appear to be largely attenuated at high breathing rates. Reversal of flow at the extremely high respiratory rates during panting could indeed be detrimental as suggested by *Piiper* and *Scheid* (1973).

It is interesting to note that intrapulmonary CO_2 receptors seem to be located at the caudal (inflow) end of the parabronchus (*Scheid* et al., 1974a; see also *Fedde,* 1976; *Bouverot,* 1978). At this location, the receptors are exposed to a rather low P_{CO_2} where their sensitivity curve is steep. Reversal of flow, on the other hand, would raise the P_{CO_2} in their microenvironment and would possibly shift the receptors into an unfavorable sensitivity range.

In *conclusion,* the phenomenon of unidirectional gas flow in avian lungs appears to hold during rest and panting conditions. The underlying mechanisms and the significance are not yet conclusively identified.

IV. Gas Transport Properties of Blood

For a quantitative treatment of pulmonary gas exchange, the properties relevant for O_2 and CO_2 transport in blood must be known. These are mainly determined by the chemical properties of the hemoglobin molecule (its reversible O_2 binding and buffer properties) and can be described by the dissociation curves for O_2 and CO_2. The differences in the O_2 and CO_2 transport characteristics between avian and mammalian blood, and in their control by physiologic variables like $[H^+]$, temperature, and organic phosphates, are mainly quantitative rather than qualitative. Reviews on mammalian blood (*Bauer,* 1974; *Antonini* and *Brunori,* 1971) may thus be consulted by students of avian physiology as well.

Avian red cells are nucleated, as are those of most vertebrates with the notable exception of mammals. This appears to be the main reason for the much higher O_2 consumption of avian compared with mammalian erythrocytes, which is nonetheless considerably smaller than that of resting skeletal muscle cells. The view that neglect of this O_2 consumption leads to errors in the determination of the O_2 dissociation when classic techniques are applied (*Lutz* et al., 1973) has not been confirmed (*Scheid* and *Kawashiro,* 1975; cf. *Baumann* and *Baumann,* 1977).

Recent investigations have revealed that many birds possess multiple hemoglobins (*Huisman* and *Schillhorn*, 1964; *Borgese* and *Bertles*, 1965; *Simons*, 1966; *Hashimoto* and *Wilt*, 1966; *Allen*, 1971).

A. Oxygen Dissociation Curve

Studies in hemoglobin (Hb) solution and in whole blood (cf. *Vandecasserie* et al., 1971, 1973; *Clausen* et al., 1971; *Ochiai* et al., 1972; *Lutz* et al., 1973, 1974; *Milsom* et al., 1973; *Scheipers* et al., 1975; *Isaacks* et al., 1976a; *Hirsowitz* et al., 1977) have shown that the O_2 dissociation curve in birds has the S-shape that is well known for mammals (Fig. 3). The O_2

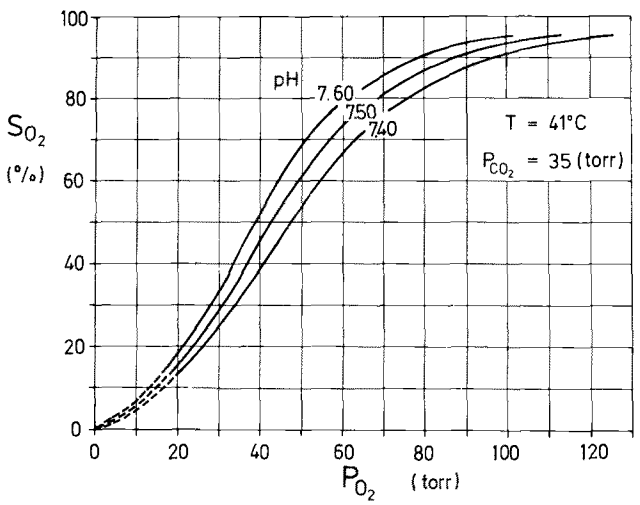

Fig. 3. O_2 dissociation curves of the duck. Three levels of pH around the normal arterial pH value; all curves at constant temperature (41 °C, approximate body temperature of the resting duck) and normal arterial P_{CO_2} (*Kawashiro* and *Scheid*, 1975). The shape of the curve is taken from *Scheipers* et al. (1975) and corrected for the P_{50} value (43 torr at P_{CO_2} = 35 torr, pH = 7.50, T = 41 °C) obtained by *Meyer* et al. (1978). The curves at pH 7.40 and 7.60 are calculated using the Bohr factor obtained by *Meyer* et al. (1978)

half saturation pressure, P_{50}, of chicken and duck blood is substantially higher than the human value. However, this is in part due to a negative correlation of P_{50} with body weight (*Lutz* et al., 1974), the P_{50} of smaller mammals being similarly high, and in part to the action of other physiologic factors controlling P_{50} (*Holle* et al., 1977; *Baumann* and *Baumann*, 1977).

Among these factors which affect the O_2 affinity, the organic phosphate, myoinositol 1, 3, 4, 5, 6-pentaphosphate (IPP; *Johnson* and *Tate,* 1969; *Bartlett,* 1970), is the most effective, thus functionally replacing 2, 3-diphosphoglycerate (2, 3-DPG) of mammalian blood. However, this compound appears to be rather stable in adult birds and thus constant under most physiologic conditions (*Wells,* 1976), and its effect on the O_2 dissociation appears to be saturated at physiologic conditions (*Petschow* et al., 1977). Hence, changes in the O_2 affinity due to changing IPP concentration are of minor significance in the study of gas exchange under normal physiologic conditions (*Holle* et al., 1977).

In the duck embryo 2,3-DPG appears to be the major organic phosphate compound, but it is virtually completely replaced by IPP soon after hatching (*Oshima* et al., 1964; *Borgese* and *Lampert,* 1975; *Bartlett* and *Borgese,* 1976). Changes in P_{50} during embryonic development and after hatching (*Bartels* et al., 1966) have recently been attributed to changes in the pattern and quantities of organic phosphates, including ATP (*Misson* and *Freeman,* 1972).

Among the other ligands to Hb, H^+ and CO_2 display the physiologically most important interaction with O_2, which is usually referred to as the Bohr effect. The Bohr factors reported for avian blood at half-saturation (*Danzer* and *Cohn,* 1967; *Lenfant* et al., 1969; *Lutz* et al., 1973, 1974; *Milsom* et al., 1973; *Lomholt,* 1975; *Scheipers* et al., 1975; *Isaacks* et al., 1976b; *Baumann* and *Baumann,* 1977; *Meyer* et al., 1978; *Weingarten* et al., 1978) are similar to those of mammalian species. In chicken and duck whole blood, the Bohr factor is independent of O_2 saturation; furthermore, there exists no difference between the Bohr factors induced by changes in CO_2 and in H^+ concentration, and thus there appears to be no oxilabile carbamate binding to the Hb of these species (*Meyer* et al., 1978). Investigations on stripped Hb suggest that this lack of oxilabile carbamate is due to the strong binding of IPP to the Hb molecule which appears to block the binding site for oxilabile carbamate; in fact, in the absence of IPP, oxilabile carbamino CO_2 is formed at the Hb molecule (*Weingarten* et al., 1978). In human blood, oxilabile carbamino CO_2 binding is suppressed at supranormal levels of 2,3-DPG (*Duhm,* 1976). The physiologic importance of oxilabile carbamate binding for CO_2 transport in blood has not yet been determined.

Since O_2 binding to Hb is an exothermic reaction, elevation of temperature reduces the O_2 affinity of avian blood. The determination of blood P_{O_2} and P_{CO_2} by standard blood gas electrodes should thus preferably be conducted at the body temperature of the experimental animal, which for many birds is above 40°C. Temperature correction factors for bird blood have not been established yet, but preliminary measurements in our labo-

ratory suggest that they are close to those for mammals (*Haab* et al., 1964; *Severinghaus*, 1964).

B. Carbon Dioxide Dissociation Curve

Total blood CO_2 content increases with increasing P_{CO_2}, mainly by an increase in HCO_3^- which is made possible by the buffer power of Hb (Fig. 4). Nothing is known about the contribution of carbamino CO_2 to the CO_2 dissociation curve. The buffer value of true plasma in birds is very similar to that in human blood (cf. *Scheipers* et al., 1975) and so is the shape of the CO_2 dissociation curve.

Interaction among O_2 and H^+ binding to Hb is the main cause for the Haldane effect, as for the Bohr effect. Thus the CO_2 dissociation curve is shifted to the right when blood is oxygenated (Fig. 4). Due to the peculiar arrangement of blood and air flow in the parabronchial lung, the Haldane effect exerts a particularly favorable action on pulmonary CO_2 transfer (see Sect. VI. C).

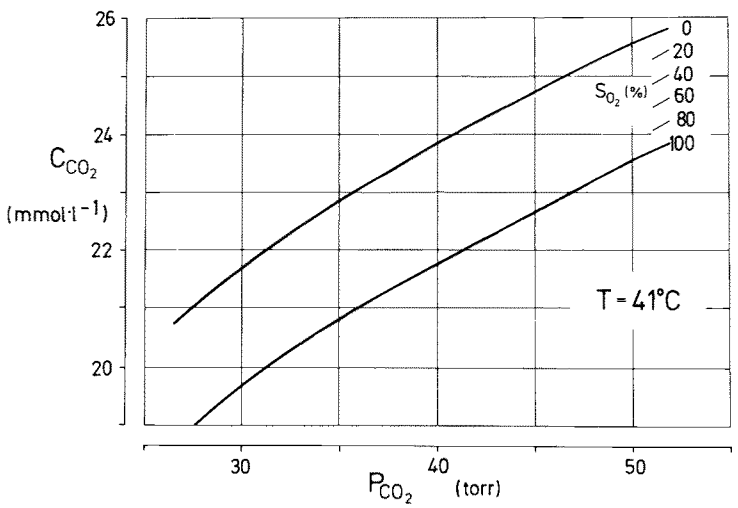

Fig. 4. CO_2 dissociation curve for duck blood, at 41 °C and at different levels of O_2 saturation (Haldane effect). (After *Scheipers* et al., 1975)

C. Effective Dissociation Curves

Using arterial blood gas values in resting chickens and ducks (*Kawashiro* and *Scheid,* 1975), which these authors derived by a remote-controlled sampling technique (*Scheid* and *Slama,* 1975), *Scheipers* et al. (1975) have constructed effective dissociation curves for O_2 and CO_2 which account for the mutual interactions provided by the Bohr and Haldane effects. These curves are steeper than those derived while neglecting these interactions. Hence, the Bohr-Haldane effect favors both O_2 and CO_2 exchange, as is also known in mammals (see Sect. VI. C).

V. Basic Concepts for Parabronchial Gas Exchange

The transport of O_2 from the ventilating gas into the pulmonary capillary blood, and vice versa for CO_2, involves a number of steps which may be defined by their underlying transport mechanisms: *convection* within the parabronchial lumen, *diffusion* (in gas phase) within the blind-ending air capillaries, *diffusion* (in liquid phase) across the gas/blood separating tissue membrane and within the capillary blood, *convection* with the blood stream. A further important factor for a quantitative analysis of gas transfer is the *structural arrangement* of the system which determines the physical model that is best suited for analysis (*Piiper* and *Scheid,* 1975). This model should be simple enough to allow mathematical treatment for generalized conditions, yet should be faithful enough in respect of those details that are critical for the analysis.

In this section we shall identify the basic elements needed for analysis of parabronchial gas exchange. In Sect. VI, we shall start from the simplest model of the avian parabronchial lung deriving the quantitative relationships for gas exchange, and shall then discuss some properties of this system that render it distinct from other vertebrate gas exchange organs. In discussing the validity of the simplifying assumptions made, we will consider, in Sect. VII, the parabronchial lung under more realistic conditions.

A. Basic Parameters

The following variables are required for a quantitative description of gas exchange in the avian lung (typical units in brackets). The terminology, the system of units and the dimensions used are in accordance with *Piiper* et al. (1971). Figure 5 serves to illustrate schematically the meaning of the symbols used.

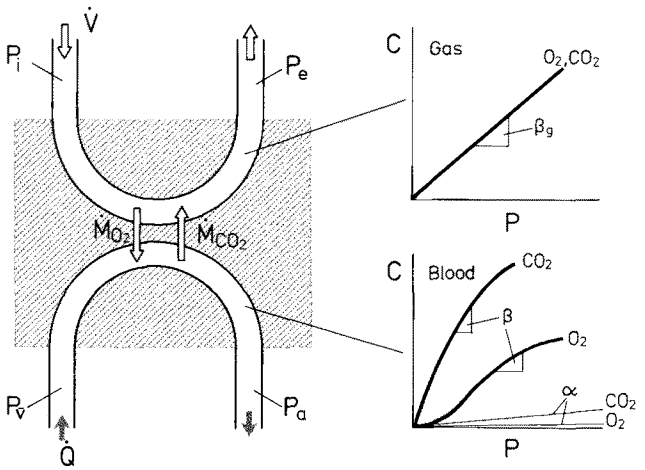

Fig. 5. Representation of a gas exchange system to define the important parameters. See text for details

1) *Transfer rate,* $\dot{M}$, of O_2 and CO_2, i.e., the amounts of these gases exchanged per unit time between the gas phase and the blood (mmol·min^{-1}). These transfer rates are identical with the metabolic rate of the body, provided the animal is in steady state, since the parabronchial lung appears to be the only site of significant gas exchange (*Magnussen* et al., 1976).

2) *Partial pressure,* P, of O_2 or CO_2 in the gas entering (P_i) and leaving the parabronchus (P_e) and in mixed venous ($P_{\bar{v}}$) and arterial blood (P_a) (torr or kPa). P_i and P_e differ in general from the corresponding partial pressures in the inspired and expired gas mixtures, P_I and P_E, which are experimentally easy to measure. Relations amongst these variables will be considered later.

3) *Capacitance coefficient,* β, defined as the increment in concentration per increment in partial pressure, for both the gas and the blood phase [mmol·l^{-1}·torr^{-1}]. For gaseous medium and for exclusively physical solution, β is independent of P (constant solubility). In particular, in the *gas phase,* β_g is identical for all (ideal) gases and is only dependent upon temperature. For 41°C, the body temperature of many experimental birds, β_g = 0.0510 mmol·l^{-1}·torr^{-1}. For *physical solution,* β equals the solubility coefficient, α. For O_2 and CO_2 in *blood,* β is dependent on P, and is equal to the slope of the respective dissociation curve.

4) *Flow rates,* $\dot{V}$ and $\dot{Q}$, of parabronchial gas and lung capillary blood [ml·min^{-1}]. While $\dot{Q}$ is nearly identical with cardiac output (neglecting the blood shunt, see Sect. VII. B), the parabronchial ventilation may differ significantly from total ventilation, $\dot{V}_E$, due to the peculiarities of air flow in the avian respiratory system (see Sect. III).

5) *Conductance,* G [mmol·min^{-1}·torr^{-1}]; defined as transfer rate, $\dot{M}$, per driving partial pressure difference, ΔP:

$$G = \dot{M} / \Delta P \tag{1}$$

The mass balance for the gas side of the gas exchange system (Fig. 5) requires

$$\dot{M} = \dot{V} \cdot \beta_g \cdot (P_i - P_e) \tag{2}$$

In blood, when the slope of the dissociation curve may be approximated as linear between P_a and $P_{\bar{v}}$,

$$\dot{M} = \dot{Q} \cdot \beta \cdot (P_a - P_{\bar{v}}) \tag{3}$$

For the convective transport provided by parabronchial ventilation and lung perfusion, the respective conductances, G_{vent} and G_{perf} are easily obtained from Eqs. (1), (2), and (3):

$$G_{vent} = \dot{V} \cdot \beta_g \tag{4}$$

$$G_{perf} = \dot{Q} \cdot \beta \tag{5}$$

For diffusive transport across the blood/gas separating membrane, an expression for ΔP is not readily obtained and, in fact, depends on the structural arrangement of the system (see below). However, the diffusive conductance, G_{diff}, may be obtained from Fick's law of diffusion:

$$G_{diff} = K \cdot A / l \tag{6}$$

where A and l are area and thickness of the membrane, and where Krogh's diffusion constant, K, is dependent on the diffusing gas species, the material of the membrane, and the temperature, but is independent of the partial pressures that drive diffusive flux. G_{diff} is often referred to as the diffusing capacity, D, although G_{diff} constitutes a conductance rather than a capacity.

For diffusive transport in the gas phase of the air capillaries, Eq. (6) applies as well, A and l in this case being (combined) cross-sectional area and length of the air capillary, and $K = d \cdot \beta_g$, where d is the diffusion coefficient of the gas under study in the air capillary gas.

B. Structural Arrangement of the Parabronchial Lung

The essential structural elements to be considered for deriving a model of the parabronchus are (Fig. 6):

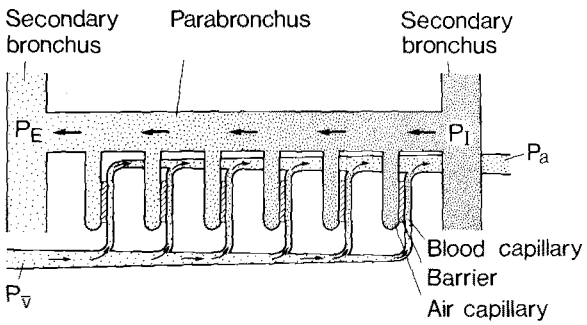

Fig. 6. Schema of the parabronchus with radially departing air capillaries and blood capillaries running from the periphery towards the lumen of the parabronchus and contacting air capillaries of only a small fraction of the parabronchial length

1) The parabronchial lumen through which gas flows by convection.

2) The blind-ending air capillaries, departing in radial direction from the parabronchial lumen into the periparabronchial tissue. Gas transport in the air capillaries occurs primarily by virtue of diffusion in the gas phase.

3) The blood capillaries which, like the air capillaries run in a radial direction, the capillary blood flowing from the periphery towards the parabronchial lumen.

4) The small fraction of the parabronchial length at which each blood capillary contacts the parabronchus (via its air capillaries).

5) The walls of the air capillaries and blood capillaries which constitute the membrane through which gas exchange takes place between lung gas and blood.

VI. Cross-Current Model for Gas Exchange in the Ideal Parabronchus

We will restrict the analysis by a number of assumptions and discuss their impact on the results in Sect. VII. These assumptions will make the analysis simple enough to enable derivation of some general relationships which are useful for understanding the basic properties of gas exchange in parabronchial lungs.

A. Assumptions

The following assumptions will be made in this Section:

1) Radial diffusivity, within the parabronchial lumen, and diffusivity

along the air capillaries, is infinite. Thus, the air capillaries offer no diffusive resistance to gas transfer.

2) Transport of gases along the parabronchial axis occurs exclusively by convection, diffusivity in this direction being neglected.

3) The system is in steady state, meaning constancy in time of all parameters listed in Sect. V. A. In particular, both flow rates, $\dot{V}$ and $\dot{Q}$, are assumed to be constant in time, as are the partial pressures P_i and $P_{\bar{v}}$.

4) β is constant, independent of P (linear blood dissociation curves).

5) The parabronchial lung is perfectly homogeneous. It may thus be represented by one single parabronchus, which receives all blood and gas flows and is equipped with the total diffusing capacity.

Neglect of air capillaries, and of all radial concentration gradients, leads to the model of Figure 7 in which the parabronchial gas contacts, in serial order, the blood capillaries, themselves being arranged in parallel. This model may be termed *serial multicapillary* system to signify the structural arrangement, or *cross-current* system (in analogy with models for heat ex-

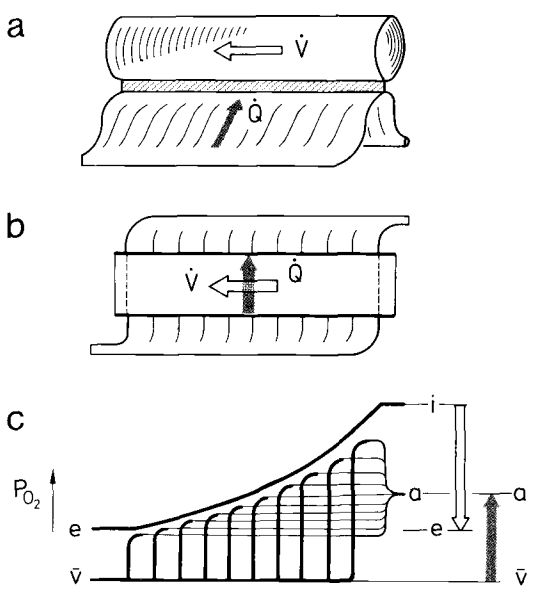

Fig. 7a–c. Simplified model for parabronchial gas exchange. View from side (**a**) and top (**b**). The schema illustrates that ventilatory gas flow ($\dot{V}$) and blood flow ($\dot{Q}$) cross each other in the exchange region *(cross-current system)*. (**c**) Partial pressure profile (illustrated for O_2) in the gas phase, from initial parabronchial *(i)* to end-parabronchial values *(e)*; and in the blood of the blood capillaries, arterial blood *(a)* deriving as a mixture from all blood capillaries. Arrows to the right show the overlap in gas *(open arrow)* and blood *(closed arrow)* partial pressures

change; cf. *Hansen,* 1950) to underline the relative direction of parabronchial gas flow and capillary blood flow at the site of gas exchange.

B. Quatitative Relationships

The differential equations and their solutions for the homogeneous parabronchus have been derived by *Scheid* and *Piiper* (1970a). These equations consider the gas transfer through an infinitesimal element of the blood/gas membrane, at a distance z along the parabronchial tube, into the capillary at the distance x along its contact with the parabronchus. Integration is then performed along the capillary, x, at given z, and along the parabronchial length, z, to yield the partial pressures in both gas and blood at any site, with coordinates x and z, in the gas and blood phases of the model.

The result of this analysis is qualitatively shown in Figure 7 for O_2; but the same applies for CO_2 when $P_{\bar{v}}$ is the highest, P_i the lowest value. Some features deserve attention:

1) The air, which flows through the parabronchus, gives off O_2 to, and accepts CO_2 from, all blood capillaries. Thus P_{O_2} and P_{CO_2} change continually along the parabronchus. The lowest levels of P_{O_2}, and the highest of P_{CO_2}, in parabronchial gas are those at the end of the parabronchus, P_e.

2) The degree of arterialization in capillary blood decreases along the parabronchial axis, the arterial blood being a mixture from all capillaries.

These two features enable P_{O_2} in end-parabronchial gas to fall below the arterial level (Fig. 7), and P_{CO_2} in end-parabronchial gas to exceed the value in arterial blood.

3) The amount of gas exchanged per unit parabronchial length is highest at the gas inflow end and diminishes continuously in the direction of gas flow, as the driving blood/gas partial pressure difference diminishes.

Of particular interest for applications of the model analysis to physiologic measurements are the relationships between the end-parabronchial, P_e, or arterial, P_a, partial pressures to the inflow values, P_i and $P_{\bar{v}}$, and the other parameters, e.g., G_{vent}, G_{perf}, and D. These relations can be expressed in a general form using relative partial pressure differences, Δp, as shown by *Piiper* and *Scheid* (1975):

$$\Delta p_{vent} \equiv \frac{P_i - P_e}{P_i - P_{\bar{v}}} = 1 - \exp\left\{-\frac{1}{X} \cdot [1 - \exp(-Y)]\right\} \tag{7}$$

$$\Delta p_{perf} \equiv \frac{P_a - P_{\bar{v}}}{P_i - P_{\bar{v}}} = X \cdot \Delta p_{vent} \tag{8}$$

$$\Delta p_{tr} \equiv \frac{P_e - P_a}{P_i - P_{\bar{v}}} = 1 - \Delta p_{vent} - \Delta p_{perf} \tag{9}$$

$$\text{where } X = G_{vent}/G_{perf},\ Y = D/G_{perf} \tag{10}$$

For application of these formulae to experimental conditions it is useful to consider the mass balance [see Eqs. (2), (3)]:

$$\dot{M} = G_{perf} \cdot (P_a - P_v) = G_{vent} \cdot (P_i - P_e) \tag{11}$$

whereby X in Eq. (1) may be replaced by

$$X = G_{vent}/G_{perf} = (P_a - P_{\bar{v}})/(P_i - P_e) \tag{12}$$

If partial pressures P_i, P_e, P_a, and $P_{\bar{v}}$ and gas exchange rate, $\dot{M}$, are known, the equations may be used to calculate D: rearrangement of Eq. (7) with Eqs. (11) and (12) yields (cf. *Burger* et al., 1979)

$$D = -\frac{\dot{M}}{P_a - P_{\bar{v}}} \cdot \ln \left\{ 1 + \frac{P_a - P_{\bar{v}}}{P_i - P_e} \cdot \ln \left(\frac{P_e - P_{\bar{v}}}{P_i - P_{\bar{v}}} \right) \right\} \tag{13}$$

Applicability of this equation to experimental situations will be discussed below.

C. Some Peculiarities of the Cross-Current System

In this section we will discuss some properties which make the cross-current model distinct from other systems that are realized for gas exchange in vertebrates.

1. Dependence of Gas Exchange on Direction of Parabronchial Gas Flow

Gas exchange in the parabronchial cross-current system is independent of direction of gas flow. In fact, reversal of gas flow would reverse the sequence in which the blood capillaries attain contact with the gas flowing through the parabronchus. But since arterial blood constitutes a mixture of blood from all capillaries, their sequence is immaterial. In fact, reversal of

gas or of blood flow would retain the flow directions of both media relative to each other, and thus retain the cross-current system. On the other hand, reversal of the relative flow directions in the counter-current model would turn that system into a co-current system and would seriously interfere with the gas exchange efficiency. *Scheid* and *Piiper* (1972) have experimentally reversed gas flow direction through the parabronchial lung of ducks, and have concluded that the cross-current rather than the counter-current system be the adequate model to describe parabronchial gas exchange.

2. Efficiency

In this discussion we shall restrict the term efficiency to the gas exchange itself and shall disregard other parameters which may affect the efficiency of the entire system (e.g., pattern of air flow; air flow resistance). Efficiency in this sense may be defined as being proportional to the total conductance, G_{tot}, of the gas exchange system:

$$G_{tot} = \dot{M}/(P_I - P_{\bar{v}}) \tag{14}$$

which relates the total gas exchange rate to the entire partial pressure span, between inspired medium and mixed venous blood. G_{tot} can be expressed as a function of the component conductances, G_{vent}, G_{perf}, and G_{diff}, as has been elaborated by *Piiper* and *Scheid* (1975). It is evident that the absolute value of G_{tot}, and the effectiveness of gas transfer, increases with all three component conductances, the actual value of G_{tot} being dependent on the actual values in those parameters.

Of particular interest is, however, a comparison between the parabronchial system and those gas exchange systems that are realized in other vertebrates, notably the alveolar system in lungs of mammals and the counter-current system in gills of fish. Comparison between these systems is best performed for given conductances (G_{perf}, G_{vent}, and G_{diff}), as differences in G_{tot} will then only reflect differences in the structural arrangement. It has been shown by *Piiper* and *Scheid* (1975) that for any set of values of the component conductances the sequence in gas exchange efficacy is:

Counter-current $\geqslant$ Cross-current $\geqslant$ Alveolar.

It should be noted, however, that this sequence in efficiency is valid only when G_{tot} values of the three systems are compared at identical values of the component conductances. That means that under experimental conditions fish may utilize their *potentially* superior system at a lower efficiency than birds or mammals (*Piiper* and *Scheid*, 1975).

The high gas exchange efficiency of the parabronchial system is reflected in the potential cross-over of partial pressures in parabronchial gas and blood. As is exemplified in Figure 7 for O_2, arterial P_{O_2} may exceed the expired level which is impossible in the alveolar lung (negative alveolar-arterial P_{O_2} difference). Thus, for identical ventilation, perfusion, diffusing capacity, and blood gas properties, the parabronchial system will reach a higher arterial P_{O_2} than the alveolar system. This cross-over is in fact observed under physiologic conditions, particularly for CO_2.

Other parameters have been used to compare the gas exchange performance of different system. The *convection requirement* has been found particularly useful for comparing water breathers with air breathers (cf. *Dejours*, 1975). The *extraction coefficient* (of respired air) has been used to assess the gas exchange efficiency of the avian lung and to compare it with that of the alveolar lung (*Bernstein* and *Schmidt-Nielsen*, 1974). This parameter appears, however, problematic for assessing gas exchange efficiency as it depends only on the ventilatory conductance and metabolic rate, and is independent of the other conductances and particularly of the structural arrangement realized in the system. Hence, the expectation of a higher extraction coefficient in avian than in mammalian lungs due to the higher gas exchange efficiency in the former (*Bernstein* and *Schmidt-Nielsen*, 1974) seems unjustified.

3. Stratification Along the Parabronchus

Concentration gradients for respiratory gases along the parabronchus are typical for the cross-current system. In alveolar lungs, these concentration gradients within the gas exchanging airways are commonly referred to as *stratification*. Although disagreement exists in the literature about the significance of stratification as limiting gas exchange in man under normal conditions, it can be shown that existence of stratification would reduce alveolar gas exchange, by imposing positive $(AaD)_{O_2}$ and $(aAD)_{CO_2}$ (gaps between gas and blood partial pressures; *Scheid* and *Piiper*, 1979). Stratification along the parabronchial axis, on the other hand, consequent upon the structural arrangement, is the decisive feature for the comparatively high gas exchange efficiency. In fact, if mixing processes (e.g., provided by mechanical agitation of lung tissue by the heart, or by diffusion along the parabronchial axis) attenuated the concentration gradients in the gas, the cross-current would approach the alveolar system with ensuing reduction in gas exchange efficacy. The essential difference between the effects of stratification in the alveolar and parabronchial systems resides in the mode of ventilation of the systems: reciprocal in alveolar lungs, serial in avian lungs (*Piiper* and *Scheid*, 1978; *Scheid* and *Piiper*, 1979). It may thus be concluded that stratification, in alveolar lungs a disadvantageous deviation

from the ideal system, occurs even in the ideal parabronchial lung and reflects there the particularly high gas exchange efficacy of the system.

4. Particular Enhancement of Carbon Dioxide Transfer

It is well established for alveolar lungs that the mutual interactions between H^+ and O_2 binding to Hb, expressed by the Bohr and Haldane effects, enhance pulmonary exchange of both O_2 and CO_2. This increased gas exchange efficiency may be quantitated by increases in the slopes, β, of the O_2 and CO_2 dissociation curves in the presence of Bohr and Haldane effects, and applies to the avian lung as to the mammalian lung. However, the Haldane effect may exert a particularly high increase of gas exchange efficiency in the avian lung due to the peculiar structural arrangement of the cross-current system.

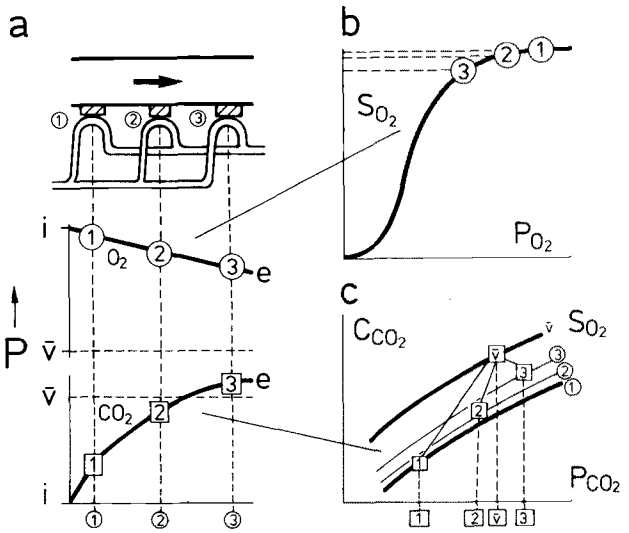

Fig. 8a–c. Schema to illustrate the peculiar action of the Haldane effect in the parabronchus. As a result, P_{CO_2} in end-parabronchial gas (P_{eCO_2}, site ③) may exceed mixed venous P_{CO_2}, $P_{\bar{v}CO_2}$. For details, see text

Figure 8 serves to illustrate the underlying mechanisms. The gas exchange rate per unit parabronchial length depends on the component conductances for the gases under study. Although G_{vent} is identical for O_2 and CO_2, both D and G_{perf} are significantly larger for CO_2 than for O_2, due to the higher solubility (D) and steeper dissociation curve (β in G_{perf}) for CO_2 than for O_2. Thus the fractional CO_2 release (CO_2 released per unit length divided by total CO_2 release) will exceed the fractional O_2 up-

take in initial parts of the parabronchus, while the relationship is reversed towards the end. This is reflected in a steeper gas partial pressure gradient along initial parts of the parabronchial axis for CO_2 than for O_2 (Fig. 8a). P_{O_2} in end-capillary blood, which is close to the gas P_{O_2} at the corresponding site in the parabronchus, stays thus relatively high toward the end of the parabronchus, and this results, by virtue of the O_2 dissociation curve (Fig. 8b), in rather high O_2 saturation, S_{O_2}, in end-capillary blood all along the parabronchus. In Figure 8c are schematically shown the CO_2 dissociation curves corresponding to S_{O_2} in mixed venous blood and in the end-capillary blood of the three capillaries shown in Figure 8a. It can be seen that by virtue of the Haldane effect CO_2 may be released ($C_{\bar{v}CO_2}$ exceeding end-capillary C_{CO_2} at site ③) while $P_{\bar{v}CO_2}$ is smaller than end-capillary P_{CO_2} at this site.

In the limiting case, when there is no CO_2 exchange at the end while O_2 uptake still continues, the blood of the last capillaries will be oxygenated whithout change in CO_2 content. Hence, the P_{CO_2} in blood leaving these capillaries will approach oxygenated mixed venous P_{CO_2} which exceeds true mixed venous P_{CO_2} by virtue of the Haldane effect (*Meyer* et al., 1976).

Hence, P_{eCO_2} may not only exceed P_{aCO_2}, consequent upon the cross-current model, but also $P_{\bar{v}CO_2}$, as a result of the special action that the Haldane effect exerts in this system. For given conductances, this effect further enhances CO_2 output as it allows the blood P_{CO_2} values to be lower than in the absence of the effect.

Davies and *Dutton* (1975) and *Meyer* et al. (1976) have in fact observed end-expired P_{CO_2} to exceed $P_{\bar{v}CO_2}$ in the chicken. *Meyer* et al. (1976) have proposed the Haldane effect, as outlined above, to cause this phenomenon and have criticized the conclusions of *Davies* and *Dutton* (1975) who had advocated the Wien effect as explaining the phenomenon (cf. *Piiper* and *Scheid*, 1979).

Zeuthen (1942) in his comprehensive account on avian respiration has qualitatively deduced a number of features of the parabronchial gas exchanger based on a model that is very similar to ours (compare his Figure 4 with our Figure 6). He has shown that the CO_2 concentration rises, in a curvilinear fashion, as air flows through the parabronchus; that the P_{CO_2} in end-parabronchial gas can exceed the arterial level, and even the mixed venous level, for which he proposed the Haldane effect. Although we disagree with a number of statements in his paper (see e.g. Sect. III. B and VII. A), he was the first to discover many of the peculiarities of the avian gas exchange system.

VII. Applicability of Cross-Current Model to the Parabronchial Lung

For a quantitative description of gas exchange in the cross-current model (Sect. VI) a number of idealizing assumptions had to be made in order to solve analytically the underlying differential equations and thus to arrive at simple relationships among the parameters involved. In this Section we will critically review these assumptions to define more closely the ranges for the parameters in which the equations hold.

A. Diffusion in Air Capillaries

The assumption was made that diffusional gas equilibration between the parabronchial lumen and the radially departing air capillaries is complete at any time. Since diffusivity of gases in the gas phase, although large compared with the liquid phase, is finite, this assumption can only approximately be true.

Zeuthen (1942) and *Hazelhoff* (1943) have attempted to assess the limitation offered by the air capillaries to O_2 and CO_2 exchange. Although not explicitely stated, both authors used a model which implies that gas uptake into blood is restricted to the blind end of the air capillary. In this system the resistance to diffusion would be directly proportional to the drop in partial pressure along the air capillary. They estimated the partial pressure drop for respiratory gases along the air capillary using data for numbers and size of parabronchi available at the time, and they concluded that these structures offered no measurable resistance to overall gas exchange at rest and even during swift flight. For the model used by these authors, the diffusion resistance inside the air capillaries would be directly comparable with the stratified resistance in alveolar lungs as both are in series with the resistance offered by the blood/gas membrane.

The main criticism of *Scheid* (1978a) was that the microscopic structure of the periparabronchial tissue (Sect. II. C) does not support the model used by these authors. The model utilized by *Scheid* (1978a; cf. *Piiper* and *Scheid*, 1973) is shown in Figure 9. It consists of an air capillary in contact, all along its length, with a blood capillary in which blood flows from the peripheral end towards the entrance end of the air capillary.

A particular feature of this system is that gases are exchanged with the blood all along the air capillary. This has two implications: (1) not all gas molecules are subjected to the total diffusional resistance of air capillary gas so that the peculiar arrangement of blood flow to the air capillary partially compensates the "stratified" resistance (*Scheid* and *Piiper*, 1979); (2) the concentration gradient along the air capillary is not directly related

to, and cannot be used to estimate, the diffusional resistance offered, as was performed by *Zeuthen* (1942) and by *Hazelhoff* (1943). In fact, if the blood/gas membrane were of infinite conductance, all gas would be taken up into blood at the entrance of the air capillary, the diffusive resistance of which would thus be immaterial; yet the partial pressure gradient along the air capillary in this case would be the highest possible, as the gas in the distal parts of the air capillary would equilibrate with mixed venous blood. A more reliable measure for the limitation to gas exchange offered by diffusion within the air capillaries is the degree of arterialization of end-capillary blood when diffusion resistance is finite or zero.

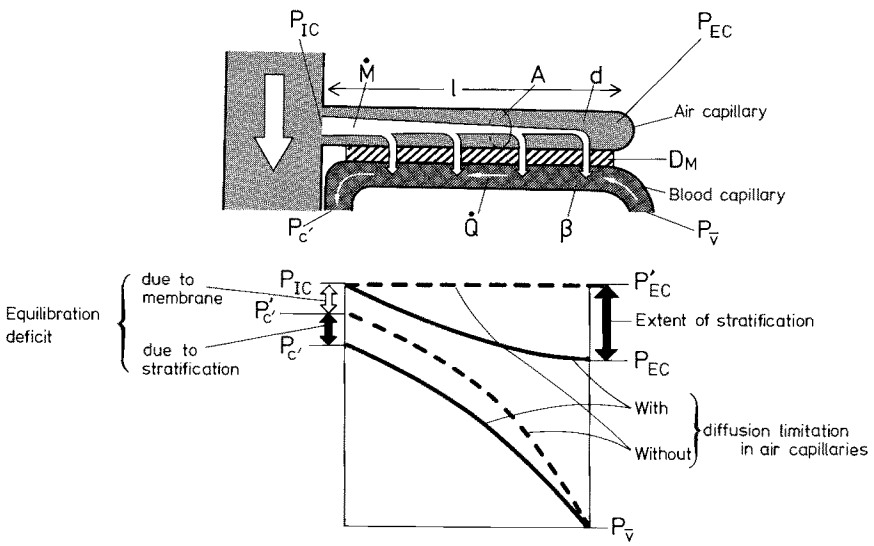

Fig. 9. Stratification in avian air capillaries. An air capillary, of length, l, and cross-sectional area, A, is shown to originate radially from the parabronchial lumen. A blood capillary contacts this air capillary in its course from the periphery towards the parabronchial lumen, both capillaries being separated by a tissue membrane, of diffusing capacity, D_M. Arrow in parabronchial lumen denotes gas flow direction; arrow in air capillary, O_2 transport, $\dot{M}$ (by diffusion); arrows in flow, direction of blood perfusion, $\dot{Q}$; P_{IC}, P_{EC}, partial pressures in gas at the origin and the end of air capillary; $P_{\bar{v}}$, $P_{c'}$, partial pressures in mixed venous and end-capillary blood. Diagram below shows partial pressure profiles in gas and blood with finite *(continuous curves)* or negligible *(dashed curves)* diffusion resistance in the gas phase of the air capillaries (realized, e.g., by infinite diffusivity, d). Calculations based on those morphometrical data which are most unfavorable for diffusion (cf. *Scheid*, 1978a)

This is schematically shown in Figure 9 by the partial pressure profiles in blood and gas along the air capillaries. The continuous lines are calculated for a finite value of diffusional resistance in air capillary gas, while for

the dashed curves this diffusional resistance was assumed to be zero, in which case gas P values would be identical throughout the air capillary. The difference, at the end of the air capillary, in P values between the continuous (P_{EC}) and the dashed curves (P'_{EC}) corresponds to the extent of stratification, which appears to be marked in this case. However, removal of diffusion resistance in air capillaries results in an only small increase in end-capillary blood partial pressure (compare $P'_{c'}$ with $P_{c'}$) and reveals the relative importance of air capillary diffusion and membrane diffusion in producing an equilibration deficit.

Calculations suggest that under resting conditions the air capillaries impose no significant resistance to parabronchial gas exchange (*Scheid*, 1978a), and this is confirmed by measurement of O_2 and CO_2 exchange when diffusivities of these gases in gas phase are increased about 2.5-fold by replacing air N_2 by He (*Burger* et al., 1979). However, under conditions of elevated gas exchange rates (e.g., exercise) the diffusion resistance in air capillaries may contribute significantly to the gas exchange resistance. There is substantial uncertainty in these estimates as the morphometric information needed for the calculations is incomplete (see Sect. II. C).

Recently, *Crank* and *Gallagher* (1978) have performed similar calculations with similar results. They have also considered diffusion of gases in axial direction within the parabronchus, and found it to contribute significantly to longitudinal gas transport only at extremely low parabronchial flow rates.

Scheid (1978a) has termed the model for gas exchange between air capillaries and blood capillaries "counter-current like" since the partial pressure profiles in gas and blood phases resemble those of a counter-current system. It should be noted, however, that there is convective flow only in the blood capillary, which makes this system distinct from a true counter-current system. It should also be noted that this model is not a substitute for the cross-current system, as the former describes gas exchange within the air capillary while the latter considers gas exchange between the bulk of parabronchial gas and capillary blood.

The counter-current like system takes account of the microscopic structure of the periparabronchial tissue observed by *Duncker* (1974). Other authors (*Abdalla* and *King*, 1975; *Akester*, 1971) have proposed slightly different structural relations amongst air capillaries and blood capillaries which lend themselves to different models for gas exchange. *Scheid* (1978a) has investigated these alternatives as well and found them to be inferior to the counter-current like system.

It may then be concluded that stratification may occur along the air capillaries, but that the adverse effects on gas exchange are partly removed by the structural arrangement of blood flow, constituting a counter-current like system.

B. Steady State Conditions

It was assumed that at any given location in the system all variables are constant in time. This may be replaced by the less rigid condition that the time constants of changes in parameters, for example in metabolic rates, $\dot{M}$, and in $P_{\bar{v}}$, are long compared with those of readjustment in the gas exchange system. Thus long-term changes, with time constants of several minutes, will not preclude application of the model equations provided all parameters needed are measured at the same time.

The assumption of steady parabronchial flow, continuous with time, is certainly not warranted under physiologic conditions, where parabronchial flow rate varies within the respiratory cycle. In the alveolar lung, gas exchange is usually also considered at constant ventilatory flow, since the large ratio of residual to tidal volume results in effective buffering of the cyclic changes of gas flow rates, resulting in only minor variations of alveolar concentrations with respiration (*Comroe,* 1965; *Piiper* and *Scheid,* 1979). However, in birds, according to anatomic estimates, parabronchial (i.e., residual) gas volume (*Duncker,* 1972) appears to be much smaller on the scale of tidal volume, and thus cyclic changes of parabronchial flow rate should result in considerably larger cyclic variations of parabronchial gas exchange. In fact, it has been suggested that the significance of unidirectional gas flow is to minimize the time of functional breath holding at the periods of flow reversal (*Piiper* and *Scheid,* 1973).

Scheid et al. (1977) have experimentally tested the effects of oscillating parabronchial flow on gas exchange in the duck. They found gas exchange rates at oscillation frequencies equal or above normal respiratory rates to be nearly identical to those at steady flow. *Scheid* (1978b) has utilized these data to calculate effective parabronchial volume, which turned out to be more than twice the anatomic prediction (*Duncker,* 1972). Aside from possible errors in both the anatomic and the physiologic estimate, the likely reason for the apparent discrepancy is that the effective (physiologic) parabronchial gas volume includes part of the volume of the adjoining larger bronchi with which the parabronchi are in open connection allowing for mixing by diffusion or convection (e.g., cardiogenic mixing).

The important conclusion is that functionally the parabronchial volume may be larger than suggested from anatomic data and that this volume may be quite adequate to buffer effects of periodic variations of parabronchial flow rates. Thus a time-averaged mean parabronchial flow rate may be used in the quantitative relationships for the idealized system (Sect. VI) to describe gas exchange when parabronchial gas flow is variable.

Nothing is known about the pulsations of blood flow in the pulmonary capillaries and their impact on gas exchange.

C. Linear Dissociation Curves

To derive the quantitative relationships of Eqs. (7) to (9), the O_2 and CO_2 dissociation curves in blood had to be assumed to be linear. In reality, however, both dissociation curves are nonlinear, and it is of interest to what extent the curvilinearity affects the validity of the quantitative expressions derived for gas exchange.

An estimate of the impact of the curvilinearity could be based on a comparison of the exchange rates, $\dot{M}$, of two systems with identical parameters except for the shapes of the dissociation curve used, curvilinear in one and straight, passing through the arterial and mixed venous points, in the other. Differences in $\dot{M}$ in these systems would indicate to what extent the assumption of a linear dissociation curve would underestimate or overestimate the gas exchange properties of the system.

Similar conclusions would be obtained by using Eq. (13) to calculate an apparent diffusing capacity, D_{app}, assuming a linear dissociation curve and comparing this apparent value to the true model value, D. A ratio of D_{app}/D exceeding unity would not only show that the D value, calculated from Eq. (13) with constant β, would overestimate true D but would indicate that the curvilinear nature of the dissociation curve is advantageous for gas exchange since it makes the system behave as if it had a larger diffusing capacity.

Calculations (*P. Scheid, H.-J. Wagner, J. Piiper*) suggest that the curvature of the O_2 dissociation curve leads to an overestimation of D and constitutes thus a factor which aids gas exchange. The extent of the overestimation increases with increasing values of true D. In the physiologic range of paramaters, overestimation in the resting duck could amount to about 20%. For CO_2, the effect is opposite, D_{app}, being below D, but the magnitude of this factor is insignificant.

These effects can easily be understood qualitatively. For any given amount of O_2 taken up by blood and leading to a given increase in blood O_2 concentration, the corresponding partial pressure will stay closer to the mixed venous value on the curved dissociation curve, and will thus preserve the pressure difference to the gas phase, than is the case for the straight dissociation line. In this respect, the curvature of the CO_2 dissociation curve is functionally in opposite direction, resulting in disadvantageous gas exchange performance when compared to the straight line.

These calculations suggest that the quantitative relationships derived, in particular Eq. (13), hold only approximately when the O_2 dissociation curve is nonlinear in the range of blood P_{O_2} values. The problem applies similarly to the alveolar lung, and it is partly for this reason that quantitative analysis of gas exchange is attempted in experimental hypoxia where the O_2 dissociation curve is more straight (see *Piiper* and *Scheid*, 1979). In

parabronchial lungs, however, the range of blood P_{O_2} values is larger, extending potentially to initial-parabronchial (≈ inspired) levels, as compared with alveolar levels in the alveolar system. Hence extremely deep hypoxia is advisable in experiments aimed at quantitative analysis of gas exchange in birds. The Bohr integral procedure may be applied as in alveolar lungs (see *Piiper* and *Scheid*, 1979). The effects expected from neglect of curved dissociation curves appears to be much attenuated when regional inhomogeneities (see Sect. VII. D) are present, as is the case under normal conditions.

D. Inhomogeneities

One of the most important deviations of the real parabronchial lung from the idealized model concerns possible regional inhomogeneities. These can be classified in two types (Fig. 10). The *series inhomogeneities* (Fig. 10a) pertain to unequal distribution of the diffusing capacity to blood flow along a given parabronchus (ventilation being identical in all parts), whereas the *parallel inhomogeneities* (Fig. 10b) pertain to variation in the distribution of ventilation (and of diffusing capacity) to blood in different parabronchi. In alveolar lungs, it is mainly the second type that has hitherto been recognized and analyzed; the first type may be of interest in the study of stratification.

1. Series Inhomogeneities

Calculations show that any degree of series inhomogeneity impairs the gas exchange efficiency (*Holle* et al., 1978). It is not important that both D

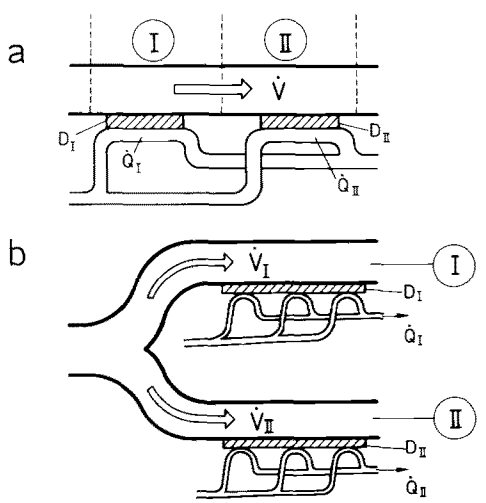

Fig. 10 a, b. Schematic representation of series (**a**) and parallel inhomogeneities (**b**), illustrated on a simplified two-compartment system (compartments I and II)

and $\dot{Q}$ are evenly distributed along the parabronchial length as long as they are equally distributed, the ratio $D/\dot{Q}$ being constant throughout. For a gas like CO_2, for which the diffusive conductance is large enough to result in virtually complete equilibration between parabronchial gas and mixed venous blood at some distance along the parabronchus, blood flow to this part would effectively constitute a venous admixture. *Duncker* (1974) has suggested that mechanisms that would redistribute the blood to more proximal regions of the parabronchus would reduce this shunt and would thus increase the gas exchange efficiency (cf. *Lutz* and *Schmidt-Nielsen,* 1977). However, this view conflicts with calculations of *Holle* et al. (1978). In fact, if blood from the distal end would entirely be shifted to more proximal parts, the resulting parabronchus would simply be deprived of a part of its exchange area which necessarily would constitute an impairment of gas exchange. The effective venous admixture provided by distal portions of the parabronchus is more than compensated by the high degree of arterialization in proximal parts.

Holle et al. (1978) have experimentally studied the distribution of blood flow along the parabronchus using the technique of injecting radioactive microspheres. In unanesthetized, spontaneously breathing ducks there was a slight decrease of blood flow in the direction of air flow through the parabronchus, which has recently been found in other birds as well (*Parry* and *Yates,* 1978, 1979). No morphometric data suggest a corresponding uneven distribution of D. *Holle* et al. (1978) estimated the resulting series inhomogeneity to be of insignificant influence on gas exchange.

The uneven allotment of blood flow to the parabronchial length is only in part attributable to a hypoxic vasoconstriction at distal parts of the parabronchus where P_{O_2} is low (*Holle* et al., 1978).

2. *Parallel Inhomogeneities*

As in alveolar lungs, parallel inhomogeneity of $\dot{V}$ and $\dot{Q}$ leads in general to an impairment of gas exchange (see *Piiper* and *Scheid,* 1979). It can be shown (*Burger* et al., 1979) that the effects of a given maldistribution increases with increasing ratio of $D/(\dot{Q}\beta)$. This has two implications:

1) Since under most experimental conditions this ratio is larger for CO_2 than for O_2, inhomogeneities impair CO_2 output relatively more than O_2 uptake. Similarly, D as calculated from Eq. (13) will in general underestimate true D if prevailing parallel inhomogeneities are not properly accounted for, and the underestimation is more severe for CO_2 than for O_2.

2) The larger β is, the smaller the effects of a given maldistribution on gas exchange, and the better the approximation of the apparent D value, calculated by neglecting the inhomogeneity [Eq. (13)], to the true D value. Hence, D_{O_2} should be measured in hypoxia where β is large. Unfortunate-

ly, hypoxia has to be very deep since the range of prevailing blood P_{O_2} values extends so far towards the initial-parabronchial level (see Sect. VII. C). As shown above, hypoxia is advisable as well for minimizing the effect of the curvature of the O_2 dissociation curve.

Burger et al. (1979) have in fact shown that D_{O_2} in unidirectionally ventilated ducks increases as inspired P_{O_2} is lowered. This dependence was virtually abolished when lung inhomogeneity was accounted for.

Recently, *Lutz* and *Schmidt-Nielsen* (1977) have found in the pigeon P_{O_2} differences between respiratory gas and arterial blood (corresponding to alveolar-arterial P_{O_2} differences in mammals) to diminish substantially when inspired P_{O_2} levels were reduced at altitude, and have proposed that birds have more than one mode of breathing with different inherent gas exchange efficiencies. We would rather suggest two mechanisms as mainly responsible for the observation:

1) β is larger in hypoxia, thus G_{perf} [Eq. (5)] and the total conductance increased. This, under experimental conditions, tends to reduce or even reverse the gas/blood P_{O_2} difference, even in the homogeneous system.

2) In real lungs, the effects of inhomogeneities, tending to increase the gas/blood P_{O_2} difference, would be diminished in hypoxia, where β is increased, leading to smaller gas/blood P_{O_2} differences.

It is thus the differences in range, in which the system operates, rather than differences in the mode of respiration which accounts for the observations of *Lutz* and *Schmidt-Nielsen* (1977).

3. Venous Admixture

Both series and parallel inhomogeneities produce shunt-like effects, in avian as in mammalian lungs. In some respects different from these effects are the effects produced by true venous admixture, provided, e.g., by pulmonary arteriovenous anastomoses. They tend to affect CO_2 much less than O_2 due to the steeper CO_2 than O_2 dissociation curve (cf. *Piiper* and *Scheid*, 1979).

Experimental evidence suggests that shunt flow through arterio-venous anastomoses is negligible (*Abdalla* and *King*, 1976; *James* et al., 1976; *Holle* et al., 1978; *Parry* and *Yates*, 1979).

The other extreme, ventilation of unperfused parabronchi (equivalent to alveolar dead space ventilation), is much more difficult to assess in the bird lung because of the peculiar flow pattern (Sect. III. B). In unidirectionally ventilated ducks, *Burger* et al. (1979) have used the highly soluble gas, chloroform, to estimate the ventilatory shunt, and this technique may be useful in the study of normal ventilation as well.

4. Conclusion

Series and parallel inhomogeneities as well as venous admixture (and ventilatory shunt) are disadvantageous for gas exchange. Their quantitative effects depend largely on the blood β values, being reduced when β is increased. Hence, D_{O_2} should be measured in hypoxia, where β is relatively large, while hyperoxia is suited for assessment of blood shunt flow (see *Burger* et al., 1979).

E. Neopulmo and Gas Composition in Caudal Air Sacs

Presence of the neopulmo in addition to the paleopulmo in most birds may be regarded as a special type of regional inhomogeneity. Not much is known about the significance of gas exchange in the neopulmo for total gas exchange. *Duncker* (1972) has suggested that neopulmo, when highly developed, constitutes the predominant or exclusive site for gas exchange at rest, and that, in this case, paleopulmo plays a significant role only during increased O_2 demand, particularly in exercise. *Holle* et al. (1978) found, however, very similar values for specific blood perfusion of neopulmo and paleopulmo in the resting duck. They concluded that paleopulmo must be ventilated in this condition, and hence contribute to gas exchange, considering the comparatively small venous admixture. *Jammes* and *Bouverot* (1975) had arrived at a similar conclusion from the observed differences in respired gas partial pressures between caudal air sacs and dorsobronchi in the awake Pekin duck.

Piiper (1978b) has reviewed and estimated the mechanisms that could be responsible for the relatively high CO_2 (and low O_2) concentrations in the caudal air sacs. He concluded that gas exchange in neopulmo constitutes one of the most important factors. Other potential mechanisms include:

1) Reinspiration of dead space gas. Unpublished observations from our laboratory suggest that this is a significant, yet not the only mechanism.

2) Gas exchange across the air sac walls with neighboring (cranial) air sacs or blood. This mechanism appears to be of minor importance (*Magnussen* et al., 1976).

3) The Hazelhoff loop does not appear to be realized under normal conditions (see Sect. III. B).

VIII. Measurement of Gas Exchange Under Various Conditions

The principles of avian pulmonary gas exchange developed in simplified models can be applied to study the performance of bird lungs under various physiologic conditions. A quantitative treatment is particularly desirable in an attempt to identify those processes which become rate limiting for gas exchange under a given condition. Unfortunately, technical difficulties have restricted the analysis mainly to the resting condition, and very little is known of how bird lungs cope with the demand of continuously high gas exchange rates during high altitude flight. Interesting aspects have been revealed in the coordination of respiration and singing (*Berger* and *Hart*, 1968; *Calder*, 1970; *Gaunt* et al., 1973a, b).

A. At Rest

Many authors have studied gas exchange parameters in birds at rest. In a number of these studies, the main aim was directed at aspects of control of breathing, and analysis was restricted to ventilation and partial pressures of respired gases in ventilated air and in arterial blood. Generally, mixed venous blood was not collected and cardiac output not measured. Hence, a detailed appraisal of the limitations to lung gas exchange could not be made. Allometric relationships have been determined for many respiratory parameters using data reported in literature (*Lasiewski* and *Dawson*, 1967; *Lasiewski* and *Calder*, 1971; *Lasiewski*, 1972; *Lutz* et al., 1974).

Piiper et al. (1970) have conducted experiments in unanesthetized, resting chickens in an attempt to quantitate the gas exchange performance of the lung. Their study included measurement of partial pressures of respired gases in air and blood, ventilation and pulmonary blood flow. The aim was to assess the various conductances, G_{vent}, G_{perf}, D, for the lung. The problem these authors faced was to estimate lung parameters from those measured at the trachea, viz. parabronchial from total ventilation; initial- and end-parabronchial partial pressures from those in in- and expiratory gas. They arrived at ranges for the conductances which they calculated using equations given in Sect. V, and concluded that the pulmonary diffusing capacity, D, for O_2, and particularly for CO_2, was high enough to exert no rate-limiting effect on gas exchange.

Burger et al. (1979) have applied the technique of unidirectionally ventilating ducks (*Burger* and *Lorenz*, 1960). In this technique, a steady flow of air is introduced into the caudal thoracic sacs, diverted through the paleopulmo by blocking balloons in the main bronchi, to leave the animal at

the trachea. This preparation allows direct measurement of parabronchial (i.e., total) ventilation and of initial- and end-parabronchial partial pressures, and eliminates problems deriving from nonsteady ventilation (see Sect. VII. B).

Their results confirmed the main findings of *Piiper* et al. (1970) in the chicken. Some of their results and calculations are summarized in Table 1 and compared with data in the dog (cf. *Piiper* and *Scheid,* 1973). The results suggested in particular that diffusion in air capillaries displayed no significant resistance to gas exchange in the resting condition (see Sect. VII. A).

Table 1. Oxygen diffusing capacity (DO_2) and exchange surface area (A) of lungs of a bird and a mammal.

		Mammal (dog)	
	Bird[a]	actual[b]	normalized[c]
Body weight (kg)	1.6	23	1.6
Exchange surface area, A (m^2)	2.88	72	5.28
Resting O_2 uptake, $\dot{M}O_2$ ($mmol \cdot min^{-1}$)	0.75	6.43	0.94
O_2 diffusing capacity, D_{O_2} ($mmol \cdot min^{-1} \cdot torr^{-1}$)	0.10	0.98	0.076
D_{O_2}/A ($mmol \cdot min^{-1} \cdot torr^{-1} \cdot m^{-2}$)	0.035	0.014	0.014
$D_{O_2}/\dot{M}O_2$ ($torr^{-1}$)	0.13	0.15	0.081
$A/\dot{M}O_2$ ($m^2 \cdot mmol^{-1} \cdot min$)	3.84	11.2	5.62

[a] Gas exchange data for the duck from *Burger* et al. (1979); morphometric data for the chicken of equal body weight from *Duncker* (1972).

[b] Gas exchange data from *Piiper* et al. (1969), morphometric data from *Siegwart* et al. (1971).

[c] Normalization to the avian body weight, using the allometric relations of *Weibel* (1972).

The preparation of unidirectionally ventilated birds, although particularly suited for measurement of pulmonary gas exchange, is certainly not easily applicable to conditions other than rest. Hence, the knowledge of the gas exchange performance of the lung under nonresting conditions is comparatively scarce.

B. Resting Conditions with Elevated Gas Exchange Rates

Attempts have recently been made in our laboratory (*J. Geiser, R.K. Gratz, P. Scheid,* unpublished) to study pulmonary gas exchange in resting, spon-

taneously breathing ducks when O_2 uptake, $\dot{M}_{O_2}$, was pharmacologically elevated with 2,3-dinitrophenol (DNP). When $\dot{M}_{O_2}$ was increased up to about sixfold, ventilation and perfusion increased almost proportionately, as did D_{O_2}, when calculated in a way similar to that of *Piiper* et al. (1970). However, this increase in D_{O_2} does not necessarily reflect an increase in the true diffusing capacity, as for example provided by opening of new lung capillaries. In fact, an increase of the ventilatory and/or perfusive conductances would diminish the effects of existing lung inhomogeneities (Sect. VII. D) which become manifest in the degree to which calculated (i. e., apparent) D values underestimate true diffusing capacity. Thus the increase of D_{O_2} with $\dot{M}_{O_2}$ could partly reflect an apparent increase towards the true D_{O_2} value. Similar results were obtained, and conclusions drawn, in experiments with DNP in the dog (*Piiper* et al., 1969).

C. In Running Birds

Recent experiments in ducks running on a treadmill (*Kiley* et al., 1978) revealed some interesting aspects of the way in which ventilation is adjusted to the elevated metabolism. Although no emphasis was given to the study of pulmonary gas exchange, blood gas and pH values show that the lung can easily cope with the elevated gas exchange rates. In fact, both arterial and mixed venous P_{O_2} values were higher, and P_{CO_2} values lower, at exercise than at rest. Unfortunately, O_2 uptake was not measured and hence it is not possible to determine which fraction of the maximal O_2 uptake rate had been reached with this experimental procedure. It may, however, be possible to elaborate the technique to allow a quantitative analysis of pulmonary gas exchange in birds running on the treadmill.

D. During Flight

Flight constitutes for most birds the natural condition of exercise. Particular demands become apparent during sustained, cruising flight. Altitude and speed of flight are mainly determined by aerodynamic parameters which have been studied in great detail (cf. *Pennycuick,* 1972, 1975; *Tucker,* 1974).

The conditions that birds flying at high altitude encounter are characterized by a combination of low barometric pressure, low O_2 partial pressure, and low temperature. They have been studied in simulation studies in varying combinations (*Tucker,* 1968a; *Butler,* 1970; *Berger* and *Hart,* 1972; *Jones* and *Holeton,* 1972a; *Bernstein* and *Schmidt-Nielsen,* 1974; *Berger,* 1974a; *Bouverot* et al., 1976; *Colacino* et al., 1977; *Lutz* and

Schmidt-Nielsen, 1977; *Escobedo* et al., 1978). A comprehensive review on various aspects of avian flight has been written by *Berger* and *Hart* (1974).

Measurements of gas exchange under natural flying conditions, particularly at high altitude, are scarce (*Berger,* 1974a). Face masks (*Tomlinson* and *McKinnon,* 1957; *Tomlinson,* 1963) and radiotelemeters (*Lord* et al., 1962) have been applied for measurements in birds during free flight. The study of hovering hummingbirds (*Berger* and *Hart,* 1972; *Berger,* 1974b) has been particularly successful. However, these techniques allowed only measurements during short flights. Study of respiratory parameters during sustained level flights became possible only with the introduction of wind tunnels to the experimental laboratory (*Tucker,* 1966). As the bird can be made to fly continuously at a point that is constant relative to the observer, rather sophisticated experiments may be performed during flight. Blood has been sampled with indwelling catheters for analysis of respired gas (*Tucker,* 1968a, b; *Bernstein,* 1976; *Torre-Bueno,* 1978; *Butler* et al., 1977). The technical problems with training the birds for use in the wind tunnel and with the experiments are phenomenally great and have as yet precluded any detailed study of pulmonary gas exchange under these conditions. The question remains thus yet unresolved, as to whether gas exchange in the lung becomes rate limiting for O_2 supply to the tissues in flight, or if, as suggested for man (*Rowell,* 1974), oxygen transport becomes limited by the circulatory system.

Lefebvre (1964) has used isotopic water ($D_2{}^{18}O$) to measure energy expenditure in pigeons flying over a long distance, up to 300 miles. His calculations show an eightfold increase in metabolism during flight compared with the resting value.

E. During Diving

Since birds possess no organs for aquatic gas exchange, apnea is a necessary condition during diving. This creates severe problems with the O_2 delivery. Readjustments in the pattern of perfusion of the body tissues, with a pronounced reduction in cardiac output (*Jones* and *Holeton,* 1972b), results in a reduction of the total O_2 consumption, which is derived from O_2 stored in the body. Of these stores, the blood and gas in the respiratory tract are the most prominent, and both have been shown to be utilized (*Andersen,* 1959a, b; *Kooyman* et al., 1973). However, these O_2 reserves cannot prevent a significant lactacidosis, which becomes particularly prominent in the circulating blood when the tissues regain their full perfusion shortly after emersion. Thus, in the course of diving, an initial respiratory acidosis is later complemented by a metabolic acidosis (*Andersen* et al.,

1965) which, by virtue of the Bohr effect, allows comparatively high values of blood P_{O_2} despite extremely low O_2 saturation (*Andersen* and *Løvø*, 1967).

A review on the physiologic adaptations during diving has been contributed by *Andersen* (1966).

F. Gas Exchange and Heat Exchange

When birds are exposed to hot or cold environments, respiration is adjusted to comply with the thermoregulatory and the metabolic demands. This is particularly so in birds, which possess no sweat glands. The upper airways appear to be the sites for evaporative cooling (*Schmidt-Nielsen* et al., 1970; *Murrish*, 1973; *Menuam* and *Richards*, 1975; cf. *Lasiewski*, 1972; *Schmidt-Nielsen*, 1972), and a counter-current arrangement between blood and air flow in this region appears to provide a very efficient system for adjustment of heat exchange under varying environmental conditions (*Jackson* and *Schmidt-Nielsen*, 1964).

Interesting aspects concern the adjustment of ventilation, and particularly of parabronchial ventilation, in panting birds. While arterial P_{CO_2} has been found to fall to extremely low levels, indicating parabronchial hyperventilation, in heat stressed birds (*Linsley* and *Burger*, 1964; *Calder* and *Schmidt-Nielsen*, 1966, 1968), unaltered arterial P_{CO_2} has been observed in a number of bird species (*Calder* and *Schmidt-Nielsen*, 1968; *Schmidt-Nielsen* et al., 1969; *Bouverot* et al., 1974; *Marder* et al., 1974; *Marder* and *Arad*, 1975). *Bouverot* et al. (1974) have suggested that parabronchial hyperventilation, with ensuing arterial hypocapnia, is prevented when ambient temperature is only moderately elevated, sufficiently little to prevent a significant increase in body temperature.

The mechanisms which prevent arterial hypocapnia with elevated total ventilation are not identified yet. *Zeuthen* (1942) has proposed that an increase in parabronchial smooth muscle tone could increase air flow resistance of the parabronchi and hence increase the amount of air bypassing the lung. *Molony* et al. (1976) found ventrobronchial, though not parabronchial, air flow resistance to increase with decreasing CO_2 in the ventilating gas. As during panting CO_2 might decrease in gas of the main bonchi, and possibly of the ventrobronchi, the ensuing increase in flow resistance could in fact prevent parabronchial hyperventilation.

An interesting hypothesis has recently been proposed by Bernstein and his colleagues (*Ramirez* and *Bernstein*, 1976; *Hudson* and *Bernstein*, 1978). They found in heat exposed pigeons, using special techniques, a compound pattern of ventilation comprising two components, (1) a slow component, at a rate similar to the respiratory rate at rest, with large am-

plitude, that was similar to the resting tidal volume; (2) a fast component, with a frequency close to the natural resonant frequency of the animal (*Crawford* and *Kampe*, 1971), with low amplitude, only about one-quarter of the dead space volume. The authors suggested that the slow, deep component serves mainly the gas exchange needs, while the fast, shallow component results in large ventilation of the upper airways and thus serves the heat exchange needs. The compound panting may thus prevent hyperventilation of deep lung regions, particularly of the parabronchial lung.

Various aspects of temperature regulation and respiration are discussed by *Lasiewski* (1972) and *Calder* and *King* (1974).

Acknowledgments. I appreciate gratefully the encouragement and advice of Dr. Johannes Piiper. In fact, most of the published accounts from our laboratory have grown from stimulating discussions with him. I would like to thank Mrs. Irmgard Barteczko for her unwearying and excellent help in preparing the manuscript.

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