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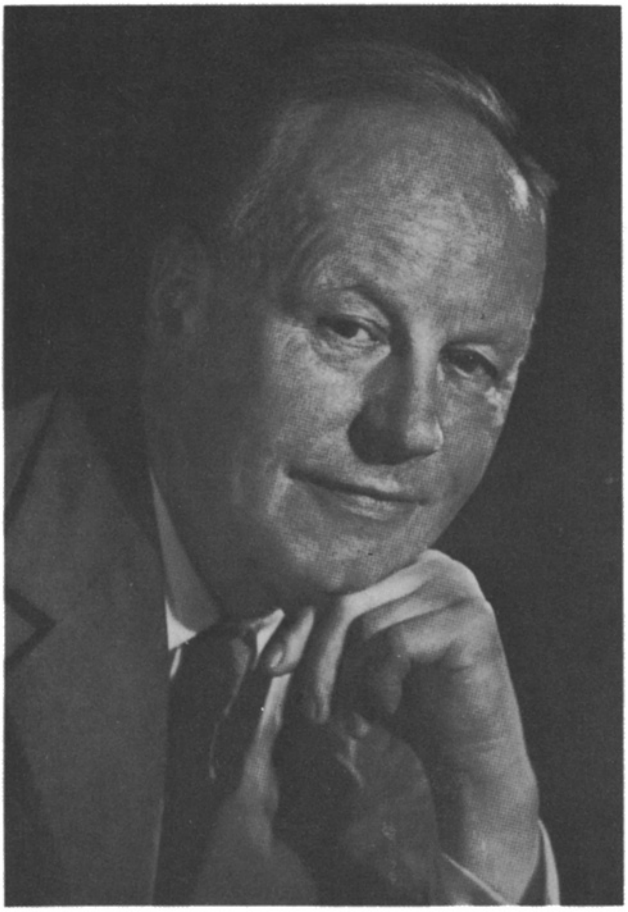

J. Harold Burn

With the death, on 13 July 1981, of Professor Joshua Harold Burn, pharmacological science lost a leader, medical and science students an eminent teacher, and pharmacologists everywhere a personal friend. Just before his 89th birthday, which was on 6 March 1981, his health started to deteriorate, but up to that time his interest in his own science, in local history, architecture and art remained lively, and he was able to enjoy sharing his cultural interests with Elizabeth Haslam-Jones, whom he had married in 1971.

His first wife died in 1927, and his second in 1971. There are two sons and four daughters from these two marriages; two daughters are married and living in the U.S.A.

Burn was born in Barnard Castle, Co. Durham, in 1892, and spent his school years there. He was the only child of J.G. Burn, who was the head of a family grocery business. His mother, a doctor's daughter, was described as "lively, cheerful and energetic". Burn's interest in science may have been aroused at school, since he later commented on its well-equipped chemistry and physics laboratories and its excellent teacher in chemistry.

On leaving school, Burn won a scholarship for Cambridge and entered Emmanuel College in October 1909; his tutor was F.G. Hopkins. In 1912 he took first class honours in part II of the tripos in physiology. Having been awarded a research grant by Emmanuel College, and the Michael Foster Studentship by the University, he started work with Joseph Barcroft in the Physiology Department. The results of his experiments on the oxygen capacity of the blood, showing that it remains unaffected by dilution, were published in the Journal of Physiology in 1913. On 1 January 1914 he moved to London to take up employment as a pharmacologist in the Wellcome Physiological Laboratories. He began working with H.H. Dale, but war broke out and he spent from October 1914 to 1918 in the army. After the war, he completed his medical training at Guy's Hospital, London.

In September 1920 he rejoined Dale, who had become Director of the National Institute for Medical Research in Hampstead, and remained there till 1925. This was also the year in which he took his M.D. degree and was awarded to Horton Smith prize for his dissertation. The publications from the years in Hampstead presage interests which recurred in later years. Two papers deal with sweating: one with its relation to blood flow and nerve supply, and the other with the action of pilocarpine. A first report on biological standards, by Burn and Dale, appeared in 1922. It is interesting that an entire series of papers, centred around insulin, deal not with its assay but with attempts at clarifying its mode of action.

On 1 January 1926 Burn became director of the Pharmacological Laboratories of the Pharmaceutical Society, in those days located in

Bloomsbury Square, London. He held this post for 12 years, during which period he was made professor of pharmacology at the University of London, in 1933. His papers till 1930 show the great effort he put into devising methods of standardization.

One of the tasks of the Pharmaceutical Society was to check on the suitability for patients of galenical preparations, vitamins and hormones, the composition of which could not be assessed by chemical means. Tests on isolated organs and small animals had to be made, and sound statistical principles applied. Burn's two books, *Methods of Biological Assay* (1928), and *Biological Standardization* (1937), have guided innumerable readers in the application of reliable methods. While chemical means of testing have since become possible for some of the substances discussed in these books, it is important to remember that some of the tests described remain useful in estimating the therapeutic action of newly developed drugs. This is why the 1950 edition of *Biological Standardization* should, as Burn states in its preface, really have been entitled "Quantitative Methods in Pharmacology and Chemotherapy".

From 1930 onward, Burn's interest in the function and actions of the autonomic nervous system and their modification by endogenous or exogenous substances became increasingly obvious. 1930–1933 was also the period in which he showed conclusively that the sympathetic nerves are capable of taking up adrenaline from the circulation, thus "replenishing their stores" and improving their performance whenever this has been impaired by lengthy experimental procedures, as for example, in pump perfusions of isolated organs. This uptake process later gained great importance when drugs capable of impairing it were discovered.

The expression of Burn's scientific interests was helped immensely by the arrival in his laboratory in 1933 of Edith Bülbring, a pharmacologist who had worked in Paul Trendelenburg's Institute in Berlin till his untimely death. In 1935/6 five joint papers by Bülbring and Burn appeared in the Journal of Physiology, several of these on sympathetic vasodilators. Then both authors moved to Oxford, where Burn occupied the chair in Pharmacology from 1937 till his retirement in 1959. It was in Oxford that Burn expanded to the full an activity which has been of the greatest importance to progress in pharmacology all over the world. In addition to having attracted a staff whose multidisciplinary expertise greatly widened the scientific scope of the laboratory, he continued and extended the excellent training of young pharmacoloists that he had begun in London.

The novice was given a problem, had to learn the appropriate technique(s), and was visited daily by Burn, who wanted to see what results he or she was getting. The regular visits, and the lunch-time discussions of the work, were the expression of Burn's boundless enthusiasm for the subject and of his personal concern for the progress of his charges.

Over the years about 200 scientists worked in Burn's Oxford laboratory. Some (H. Blaschko, E. Bülbring, D.B. Hope, H.R. Ing, H.W. Ling, E.M. Vaughan Williams and J.M. Walker) were on the staff and either are still there or remained in the Department till retirement, but the others were either beginners in training, or well-known scientists spending periods ranging from months to several years at Oxford. No other Department in Britain did as much as the one at Oxford, under Burn's professorship, for the training of future pharmacologists. Although these activities were somewhat restricted during the war years, they benefited colleagues in all parts of the world when international relations were restored.

Outstanding among the publications of the war years is the first evidence of release of acetylcholine from the central nervous system; it was obtained on the perfused spinal cord of the dog (Bülbring and Burn 1941). Before that, a recurring theme had been the modification of skeletal muscle activity by adrenaline, and by vasodilator nerves found in some species, particularly in the hare. Another topic concerned the smooth muscle of the nictitating membrane and the effect of denervation, which made the membrane highly sensitive to adrenaline, but lowered only very slightly, if at all, the threshold for tyramine (Bülbring and Burn 1938). It took two decades to reach a clear understanding of that difference (see below).

Many striking observations were made by Burn and his co-workers on the fact that the actions of acetylcholine and adrenaline vary with the dose and the condition of the tissue. Since we have learnt in recent years about multiple, and particularly about pre-synaptic, receptors, these phenomena have become less of a mystery, but their demonstration in Burn's laboratory preceded their general recognition and explanation by many years.

Interspersed among these academic papers were frequent articles written by Burn for the medical practitioner or the lay public. He wrote on asthma, on blood-pressure control, on antihistamines, on the evils of smoking, on fine chemicals in medicine and on the use of insecticides. He was as keen on preventing illness as on healing it, and had strong views on the beneficial effects of simple measures such as "an apple a day"; he was very persuasive on the power of cod-liver oil (*not* the more palatable halibut-liver oil) to prevent bronchitis in the elderly.

In 1946, von Euler found that sympathetic nerves contain noradrenaline, and in the following year, Gaddum and Goodwin obtained the release of noradrenaline by stimulation of the cat's hepatic nerves. The question whether the adrenal medulla might secrete noradrenaline as an admixture to adrenaline was answered by Bülbring and Burn in 1949. They stimulated the splanchnic nerves of the cat and tried to match the effects on the blood pressure, the innervated and the denervated nictitating

membranes, with injections of either adrenaline or noradrenaline, or a mixture of the two. Only a mixture of the two catecholamines reproduced the effect of splanchnic nerve stimulation, indicating that the adrenal secreted both compounds.

The next years brought much work on the synthesis and stability of catecholamines. Furthermore, the suggestion was made that the hypersensitivity of denervated iris and blood vessels to catecholamines might be due to a loss of amine oxidase. However, when the experiments were repeated on a large number of animals, the results were inconsistent and the suggestion was abandoned [Burn, Philpot and Trendelenburg (1954) Br J Pharmacol 9:423]. There were investigations of the actions of acetylcholine and eserine, particularly in situations when acetylcholine is not a transmitter of nerve impulses. This led to papers on its role in ciliary movement and in auricular fibrillation of the artificially driven heart. In the heart, acetylcholine release was always found to be linked to the beat, and therefore considered to be essential to rhythmic activity. Auricular and ventricular fibrillation, their origin, experimental production and response to drugs, was a prominent topic in 1956 and 1957. New ideas and concepts started to appear in the following 2 years.

In 1953, a publication (with Fleckenstein) dealt with the classification of sympathomimetic amines on the basis of whether or not their action on the nictitating membrane was enhanced or abolished by denervation. When reserpine, which removes catecholamines from nervous tissue without causing permanent damage, became available a few years later, the results of its administration were found to resemble those of denervation: tyramine lost its effect and noradrenaline became more potent. Both changes were abolished by an infusion of noradrenaline. The suggestion (Burn and Rand 1958) was that tyramine and congeners acted by releasing endogenous noradrenaline. The supersensitivity to noradrenaline after reserpine had its counterpart in the supersensitivity of denervated tissues.

The observations on the nictitating membrane were equally valid for other sympathetically innervated tissues, the blood vessels being the most important from the clinical point of view. New findings which were to dominate Burn's future thinking were published in his paper with Leach, Rand and Thompson (1959) entitled "Peripheral Effects of Nicotine and Acetylcholine Resembling those of Sympathetic Stimulation". The authors saw this resemblance in pilomotor muscles, nictitating membrane and rabbit ear vessels, and noticed that all effects were greatly reduced by administration of reserpine or by denervation.

The next step (Burn and Rand 1960) was to characterize the residual response to stimulation of postganglionic sympathetic fibres of animals treated with reserpine: the responses were all enhanced by eserine and abolished by atropine. There were obviously cholinergic fibres running

in the sympathetic nerve supply. Seeing an analogy to the situation in the adrenal medulla, where a cholinergic nerve impinges on the chromaffin cell, Burn suggested that cholinergic nerves caused the release of noradrenaline from the sympathetic terminals, and postulated that noradrenergic fibres depend for their activity on first being primed by acetylcholine. This view, also known as the "theory of Burn and Rand", prompted a great number of very valuable investigations of peripheral sympathetic activity, both by Burn and by those who did not accept his conclusions. We owe a great increase in knowledge of the autonomic system to this controversy, but for Burn it was a cause of unhappiness, because he had hoped for acceptance without reservation. In many ways he was ahead of his time, as in his suggestion that nerve fibres may contain more than one transmitter; although we have no evidence that noradrenaline and acetylcholine coexist in the same (adult) neuron, recent work on peptides has shown that monoamines can co-exist, and be released, together with peptides. Burn also demonstrated that cholinergic fibres are much more widespread in postganglionic sympathetic nerves than had ever been suspected. What many colleagues found difficult to accept, however, was Burn's disagreement with the view that the adrenergic fibre may liberate "noradrenaline in the same way as cholinergic fibres liberate ACh". His hypothesis implied that adrenergic fibres liberate noradrenaline exclusively through the "cholinergic link". Support for this extreme view was obtained by Chang and Rand (1960)[1] who abolished the effect of sympathetic stimulation in several organs by hemicholinium, and restored the effect by giving choline. Yet the theory that the cholinergic link is *always* involved when noradrenaline is being released is not proven; Consolo et al.[2], for example, did not find evidence for this existence of cholinergic neurons in the spleen and the iris of the cat.

A most interesting offshoot of this controversy is a paper on the phylogenetic and ontogenetic development of the response of the intestine to stimulation of its periarterial nerves (Burn 1968). This was Burn's last experimental paper; the work was carried out partly in Philadelphia and partly in Harrogate, since Burn had no laboratory facilities in Oxford. It showed that in the adult fowl, in contrast to the adult mammal, stimulation of the periarterial fibres of the gut causes contraction, as does ACh. In the new-born rabbit, as in the adult fowl, contraction is elicited, but the response changes to relaxation between the ages of 3 and about 8 days.

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1 Br J Pharmacol (1960) 15:588–600. Transmission failure in sympathetic nerves produced by hemicholinium.

2 Consolo S, Garattini S, Ladinsky H, Thoenen H (1972) J Physiol (Lond) 220:639–646. Effect of chemical sympathectomy on the content of acetylcholine, choline and acetyltransferase activity in the cat spleen and iris.

Burn was a skilled and imaginative experimenter and a master of difficult perfusion techniques, and he enriched pharmacological knowledge over many decades. Interpretation of some of his results would have required knowledge of the multiplicity of receptors, and structural analysis by the electron microscope, neither of which were available during the period of his scientific acitivity. The areas of research for which Burn would probably have liked to be remembered are suggested in his last two published lectures (1976 and 1977): the uptake of catecholamines by sympathetic neurons; the development of an adrenergic from a cholinergic fibre; and the synergism of acetylcholine and noradrenaline in the activity of the postganglionic sympathetic neuron ("the cholinergic link").

Burn had strong views on many subjects, moral as well as scientific. He always stood up for his convictions, irrespective of whether it would have been to his advantage not to express them. His helpfulness knew no bounds, and was most frequently offered to his many young visitors and their families. What some newcomers to the laboratory regarded as his strictness originated in his concern and feeling of responsibility for the future of the younger generation. He had strong views about minor issues as well as about moral priorities. To quote from the preface to *The Background of Therapeutics* (1948): "The care for a sick man in a bed is a good thing, but it is better to strive constantly to improve diagnosis and treatment in order to benefit one hundred other sick men who will occupy the bed after he has gone." His objections to smoking and to beards were openly admitted. Whoever wishes to enjoy his irrepressible sense of humor should read "Essential Pharmacology" (Burn 1969) where the following passage describes his impressions on entering Emmanuel College, Cambridge: "I discovered that, compared with those who taught physiology and physics, the chemists were an unattractive lot, particularly those who demonstrated in the practical class. These seemed very undistinguished, had cheerless faces and wore rather shabby clothes." Writing came easily to Burn, and he found time in the evening to write many books. In addition to one pamphlet not connected with science, "A defence of John Balliol", he published eleven books, some addressed to scientists, others to the general public. The subjects range from bio-assays, biological standardization, therapeutics and practical pharmacology to the autonomic nervous system and medicine in general. In 1964 his last book appeared, characteristically entitled *Our Most Interesting Diseases.*

Burn received honorary degrees from Yale, Mainz, Paris and Bradford Universities; the Schmiedeberg Plakette from the German Pharmacological Society; and the first Wellcome gold medal from the British Pharmacological Society – both societies also conferred honorary membership on him. He was an honorary member of the Czechoslovakian Medical Society of

J.E. Purkinje, a member of the Deutsche Akademie der Naturforscher Leopoldina, and a Fellow of the Indian National Science Academy. He became a Fellow of the Royal Society in 1942.

A last quotation from Burn's 1969 article in the *Annual Review of Pharmacology* may end this biographical sketch. In answer to the question whether he would choose a different career if he had his time again, his reply was, "I am quite certain that I would choose to have it all over again."

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Cardiovascular Sympathetic Afferent Fibers

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Contents

1 Introduction

In 1976, an important symposium on *Cardiac Receptors* was held in Leeds (*Hainsworth* et al. 1979). One of the topics was entitled *Electrophysiology and Reflexes of "Sympathetic" Afferents.* For the first time the term "sympathetic" was officially used to describe the afferent nerve fibers running in the sympathetic nerves. However, as indicated by the quotation marks, some uncertainty still existed. On that occasion I expressed the view that the new experimental data justified the use of this term

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(*Malliani* 1979). As a matter of fact, after that symposium the cardiovascular sympathetic afferent fibers became more widely accepted as part of the neural afferent pathways that participate in the regulation of the cardiovascular functions.

This review may seem premature. However, its main justification is that some concepts related to new findings may have general implications, and it does not attempt to draw simple conclusions from such new evidence. The aim of this review is to discuss three hypotheses that, I think, have adequate supporting data:

1. A similar organization characterizes the basic neural mechanisms of the somatic and visceral nervous systems: an organization that can be defined as Sherringtonian and that recognizes the fundamental role of the reflex arc.

2. Cardiovascular sympathetic afferent fibers mediate reflexes that are mainly excitatory and exhibit positive feedback characteristics.

3. The nociceptive function, considered for a long time as the unique property of these fibers, seems to be based, mainly if not exclusively, on their intense activation rather than on the recruitment of specific cardiovascular nociceptors.

2 Terms and History

Edgeworth (1892) first suggested the existence of afferent nerve fibers in the cardiac sympathetic nerves which he called "sympathetic sensory fibres." *Langley* (1903) also sporadically wrote about "afferent sympathetic fibres" but eventually rejected the expression with his definition of the autonomic nervous system being pure outflow. It is well known that, following Professor Jebb's suggestion, *Langley* (1898) coined the term autonomic, indicating that the structures supplied by the system are not subject to voluntary control but operate to a large extent independently. The afferent fibers in the sympathetic nerves were considered "somatic", because they had their cell bodies in the dorsal spinal ganglia together with somatic neurons, because they were thought to have no reflex role, and because their functions were assumed to be exclusively nociceptive (*Langley* 1903). Visceral pain also gave rise to much discussion, "the pain of visceral and somatic disease" being attributed, even several decades later, to "direct stimulation of a common system of pain nerves" (*Lewis* and *Kellgren* 1939–1942).

In short, during the same years that witnessed *Sherrington*'s enlightening experiments leading to the coexisting concepts of "proprioceptive reflex" and "dominance of the brain" (1898, 1906), the visceral reflex

spinal arc was considered either an oversimplification devoid of any functional significance or a basically wrong concept. That was only the beginning: in the years that followed, it was generally agreed that only the cardiovascular the afferent autonomic fibres to those which end in tissues which receive reflexogenic areas (*Heymans* and *Neil* 1958).

However, *Langley,* who was known for "intimating" his opinions (see *Ranson* and *Billingsley* 1918a, p. 422), must have had more doubts on "sympathetic" afferent fibers than we think. He said, "We might, however, restrict the afferent autonomic fibres to those which end in tissues which receive efferent autonomic fibres, i.e. in mammals to the afferent fibres of unstriated muscle, cardiac muscle and glands..." and "all that seems to me possible at present towards arranging afferent fibres into autonomic and somatic divisions is to consider as afferent autonomic fibres those which give rise to reflexes in autonomic tissues, and which are incapable of directly giving rise to sensation; and to consider all other afferent fibres as somatic" (*Langley* 1903). The crucial fact was that Langley could only count on negative experiments: "Such fibres ought when stimulated to produce reflexes of one sort or another even though slight. But in experiments made earlier I could not find with certainty reflex action of any kind..." (1896). In short, I would like to suggest that it is likely that Langley had a more open mind on this topic than is generally believed.

The term "sympathetic" afferent fibers has been proposed recently (*Malliani* et al. 1973b, 1975a) for several reasons which include simplicity and analogy with vagal afferent fibers. It is not simply a problem of terminology but a point essential to the concept that the visceral nervous system may have its basic functional unit in the spinal reflex arc: "The reflex arc is the unit mechanism of the nervous system when that system is regarded in its integrative function" (*Sherrington* 1906). Accordingly, the sympathetic input to the spinal cord may be as important to the regulation of the sympathetic outflow as the somatic spinal input is to the regulation of the somatic nervous outflow (*Malliani* et al. 1975a). In conclusion, the term reflects the original Winslow definition of sympathetic nerves as an ensemble of nerves "bringing about the sympathies of the body" (quoted by *Langley* 1915–1916), stresses their composite nature of efferent and afferent fibers, underlines the new experimental findings on sympatho-sympathetic reflexes (*Malliani* et al. 1975a), and is economical in the use of words in comparison with expressions such as "afferent nerve fibers running into the sympathetic nerves."

3 Morphology

Many anatomical studies have been carried out, over almost a century, on the sensory innervation of the heart, and yet, we have to admit that our knowledge is still remarkably scanty. There are many reasons that can justify the elusive results of so much work and a brief explanation of some of these difficulties will provide the most realistic introduction.

1. The heart possesses a double sensory innervation of afferent nerve fibers running in the vagi or in the sympathetic nerves: therefore, with the histological techniques in use until now, vagal and sympathetic endings can only be discriminated on the basis of selective degeneration studies.

2. As methods for specific staining of afferent neurons and their receptive endings are not available, the attribution of a sensory function to a morphological finding often, if not always, bears some uncertainty.

3. Such uncertainty may even become presumption in the case of electron microscopy. On the other hand, this is the only technique available that can adequately identify terminal endings (*Tranum-Jensen* 1975).

4. Finally, a minor difficulty is the fact that all staining techniques suffer from variability: they oscillate from a too generous visualization of neural and non-neural elements to an incomprehensible selection of only a few neural elements.

In more general terms, moreover, it is known that even though a morphological clear cardiac sensory ending can be identified, we have no information on where the graded electrogenesis of the generator potential occurs and on where propagated activity is initiated.

The existence of sensory endings in the heart was first suggested by *Berkeley* (1894), *Smirnow* (1895) and *Dogiel* (1898). But *Edgeworth* (1892), following *Gaskell*'s suggestion, was the first to describe large nerve fibers in the cardiac sympathetic nerves: fibers that he traced to the heart and that he considered to be sensory in function. It is remarkable that *Gaskell* (1886) had already recognized in the sympathetic white rami the presence of nonmyelinated fibers arising from the posterior root ganglia: however, he probably interpreted them as the efferent axons of autonomic cells contained in the spinal ganglia. Thirty years later, *Ranson* and *Billingsley* (1918b) indicated the sensory nature of these nonmyelinated fibers.

In short, early anatomical studies suggested that the sympathetic sensory supply of the heart was made up of both myelinated and nonmyelinated afferent nerve fibers. Recent anatomical studies have confirmed the existence of both types of afferent fibers in the cardiac sympathetic innervation (*Coggeshall* and *Galbraith* 1978; *Oldfield* and *McLachlan* 1978; *Seagard* et al. 1978).

In the heart, the sensory fibers terminate as complex, unencapsulated endings that are usually distinguished as either diffuse or compact (*Nonidez* 1939; *Miller* and *Kasahara* 1964).

It is still an unanswered question whether an "end-net" or "terminal reticulum" (*Meyling* 1953; *Mitchell* 1953; *Holmes* 1957a, b; *Khabarova* 1963; *Miller* and *Kasahara* 1964; *Williams* 1964; *Johnston* 1968) truly exists or is rather the result of structural artifacts of impregnation (*Botár* 1966; *Floyd* 1979). Some authors attributed a sensory function to such an end-net formation (*Miller* and *Kasahara* 1964; *Williams* 1964).

Practically all types of nerve endings have been described in the subendocardial tissues, but different nerve terminals likely to be sensory seem also to exist in the depth of the myocardium (*Khabarova* 1963) and around the coronary vessels (*Nettleship* 1936).

Concerning the contribution of vagal or sympathetic fibers to these sensory endings within the heart, *Wollard* (1926) concluded that a large proportion of cardiac sensory endings were of vagal origin: indeed he observed that an experimental bilateral stellectomy did not markedly modify what he considered to be the normal aspect of the sensory supply of the heart. *Nonidez* (1939) also believed that the majority of cardiac sensory fibers joined the vagi. The conclusions reached by *Nettleship* (1936) are more precise: the removal of the dorsal ganglia produced degeneration of fibers in the endocardial net at the apex of the ventricles and from the walls of the coronary vessels. More recently *Holmes* (1957a) observed survival of the "terminal nervous network" after vagotomy: if this structure were really sensory, the sympathetic afferent fibers are likely to be implicated.

Recent literature has not contributed further to a solution: the most valuable degeneration studies are still to be found in the earliest papers. As a working hypothesis, we may, however, accept *Khabarova*'s (1963) statement that "afferent fibers of spinal type innervate the same regions and layers of the heart as the vagal fibers, and their afferent fibers and endings frequently lie side by side with afferent fibers and endings of the vagus nerves". This opinion has the merit that it agrees with the electrophysiological findings which, so far, have suggested that vagal and sympathetic sensory endings are intermingled in all regions of the heart.

4 Methodology

Afferent sympathetic nerve fibers with receptor endings in the heart or in the great thoracic vessels can be isolated, for electrophysiological recordings, from three different points: a) the cardiac sympathetic nerves,

b) the rami communicantes, c) the spinal dorsal roots. For proper interpretation of these experimental findings one must be aware of the advantages and limitations of each approach.

a) The impulse activity that can be recorded from the cut peripheral end of a cardiac sympathetic nerve (*Brown* and *Malliani* 1971; *Armour* 1973) is largely afferent in nature although active efferent fibers may also be present. Moreover, as many vagal axons are present in the cardiac sympathetic nerves (*Nonidez* 1939) there is no way of ascertaining whether individual fibers are sympathetic or vagal. Therefore, this approach is likely to furnish equivocal data, unless each finding is corroborated by similar ones obtained by the other approaches (*Brown* and *Malliani* 1971).

b) A recording from the cut peripheral end of a ramus communicans (Fig. 1) can conclusively identify impulse activity directed to the spinal cord. However, the rami communicantes also contain a variable number of sympathetic postganglionic efferent fibers, largely predominant in the grey ramus, but also present in the white ramus (*Ranson* and *Billingsley*

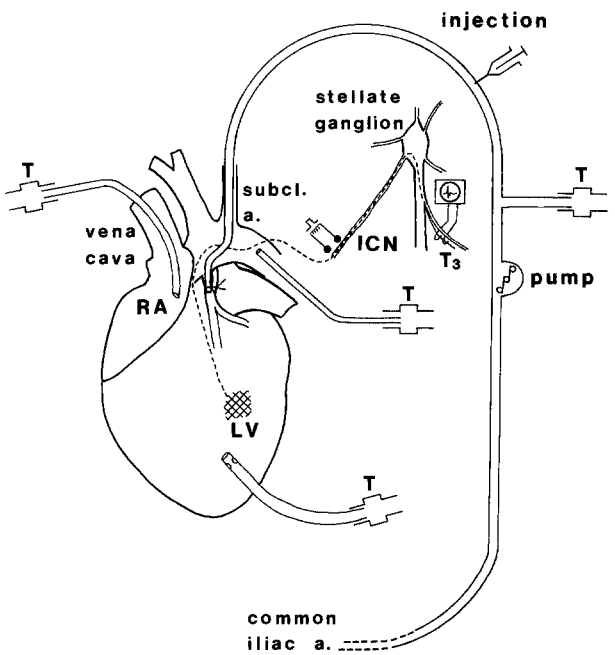

Fig. 1. Schema of the experimental model used in the cat for recording impulse activity of single afferent ventricular sympathetic nonmyelinated nerve fibers (*Lombardi* et al. 1981b). The left main coronary artery is perfused according to the method of *Brown* (1968). The conduction velocity of the recorded fiber is determined by stimulating the inferor cardiac nerve (*ICN*) or the surrounding tissues (*Malliani* et al. 1973b; *Malliani* and *Pagani* 1976; *Casati* et al. 1979). The extracorporeal perfusion circuit allows the interruption of the left main coronary artery flow or the intracoronary administration of chemical substances without direct manipulation of the heart (*Lombardi* et al. 1981b)

1918a, b). Somatic afferent fibers mainly from the neck muscles also run through the high thoracic rami communcantes (*Mizeres* 1955; *Holmes* and *Torrance* 1959). Therefore, recordings from the rami can be soundly interpreted only if functionally isolated afferent fibers are studied yielding action potentials constant for shape and amplitude, and if the sensory fields initiating the impulse activity can be located with appropriate maneuvers. In the case of cardiovascular mechanoreceptors the only location of the receptor endings that can be considered entirely sound is that obtained post mortem in the absence of circulation by using discrete mechanical probing (*Coleridge* et al. 1957). It is clear that the main danger implicit in the interpretation of recordings from the cut peripheral end of rami communicantes is to attribute to afferent sympathetic fibers action potentials which are derived from postganglionic efferent fibers running centripetally through the rami. An additional and important positive aspect of this approach is that only minor though skilled surgery is necessary to reach the rami, hence recordings can be obtained in animals under apparently normal hemodynamic conditions and, if necessary, also with a closed chest (*Malliani* et al. 1975a).

c) The isolation of sympathetic afferent fibers from the dorsal roots should not be affected by efferent impulse activity. However major surgery is needed and the afferent fibers possibly reaching the spinal cord through the ventral roots (*Coggeshall* et al. 1974; *Coggeshall* 1980) would be missed.

In conclusion, only afferent nerve fibers with cardiovascular receptor endings isolated from the rami communicantes or from the dorsal roots, but running through the sympathetic nerves, can be safely defined as cardiovascular sympathetic afferent fibers (*Malliani* 1979; *Malliani* et al. 1973b, 1975a).

As to identification, in the course of electrophysiological experiments, of afferent nerve fibers as myelinated or nonmyelinated, it must be recalled that the distinction is based on a purely functional criterion consisting of a nerve conduction velocity above or below the generally accepted frontier of 2 m/s (*Burgess* and *Perl* 1973). Obviously such a criterion should not be regarded as absolute: for instance, the conduction velocity of a fiber can be decreased by factors such as low temperature and various types of mechanical and chemical damage.

5 Functional Characteristics of the Various Types of Cardiovascular Sympathetic Afferent Fibers

In the anesthetized animal under resting hemodynamic conditions, the spontaneous impulse activity of sympathetic afferent fibers with endings in the heart or in the large thoracic vessels has one feature that seems independent of the location of the receptive field: it usually consists of, at most, one action potential per cardiac cycle, each cycle being not necessarily accompanied by a nervous impulse. If this observation, which we have repeatedly made (*Malliani* et al. 1972b, 1973b, 1975a; *Malliani* and *Pagani* 1976; *Casati* et al. 1979; *Malliani* 1979; *Lombardi* et al. 1981b), is accepted, it follows that when multiple impulses per cardiac cycle are present in the resting state they may belong to a multifiber recording, to other types of nerve fibers such as vagal afferent fibers (*Armour* 1973), or to a fiber whose endings have been damaged in the course of the experiment, e.g. by mechanical manipulations. However, changes in hemodynamic conditions induce repetitive firing during each cardiac cycle (see below).

The temporal relation between the action potentials and a particular hemodynamic event is likely to be determined by the location of the sensory endings. However, while such a temporal correlation is almost always detectable in the discharge of myelinated afferent fibers, it is rarely apparent in the background impulse activity of nonmyelinated afferent fibers (*Malliani* et al. 1973b; *Nishi* et al. 1974; *Uchida* et al. 1974; *Uchida* 1975a; *Malliani* and *Pagani* 1976; *Casati* et al. 1979).

To conclude these preliminary comments it is useful to recall the investigators who made the first observations.

Beccari (1934) obtained from the vertebral nerve a few recordings that possibly included the activity of sympathetic afferent fibers and that occasionally displayed a cardiac rhythm, a characteristic that, however, does not prove the cardiovascular location of the receptors. Those experiments remained, however, quite isolated. The favorable anatomical location of the vagi in the neck compared with the intrathoracic seclusion of the cardiac sympathetic nerves is likely to have influenced, for many years, the choice of vagal afferent fibers for the electrophysiological attempts to record impulses from cardiovascular receptors. In addition, the intensity of afferent impulse traffic present in cardiovascular vagal afferent fibers was obviously more rewarding compared with the sparse activity detected from the peripheral cut end of a sympathetic nerve. Yet, concepts more than facts probably represented the true obstacle: in particular the concept that cardiovascular sympathetic afferent fibers had no physiological regulatory function.

The first systematic attempt to investigate the properties of thoracic sympathetic afferent fibers can be found in the study by *Holmes* and *Torrance* (1959): a remarkable paper stimulated, however, more by an anatomical culture than by new physiological considerations. Most of the afferent fibers studied by these authors had no spontaneous discharge and innervated thoracic structures other than the heart and large vessels; an impulse activity phasic with cardiac rhythm was sporadically noticed and interpreted as coming from receptor endings located near the blood vessels.

Brown, in his Ph.D. thesis (1964) first reported recordings from cardiac sympathetic afferent fibers, most of which had no spontaneous discharge and which could be activated by mechanical or chemical stimuli. Subsequently (*Brown* 1967) this afferent sympathetic activity was interpreted as bearing only pathophysiological significance in the transmission of cardiac pain, as it was very low in baseline conditions and highly excited during myocardial ischemia. *Ueda* et al. (1969) carried out the first detailed electrophysiological study of the impulse activity of cardiovascular sympathetic afferent fibers. The fibers were found to be responsive both to mechanical probing and to hemodynamic stimuli: however, these findings were again interpreted only as an evidence that cardiac pain could be elicited mechanically.

The demonstration that in spinal vagotomized animals increases in arterial blood pressure, sometimes of moderate magnitude, could elicit sympatho-sympathetic reflexes (*Malliani* et al. 1970, 1971a) was crucial for the new hypothesis that cardiovascular sympathetic afferent fibers could be tonically involved in the neural regulation of the circulation and body fluids. Indeed, cardiovascular sympathetic afferent fibers were found to display a spontaneous impulse activity related to normal hemodynamic events (*Malliani* et al. 1972b, 1973b).

Location of the Receptors. This fundamental point can be explored only generally by electrophysiological experiments. In the case of mechanoreceptors, discrete mechanical probing is usually considered adequate although it has several important limitations. For instance, it produces a tissue deformation that bears little resemblance to the natural events which normally excite the receptors; thus the preterminal regions or even the fibers en passage (*Catton* 1970) may be activated. Hence, there is the possibility that mechanical probing may activate various regions simply possessed of an electrogenically reactive membrane (*Grundfest* 1966) without identifying the area normally responsible for triggering the action potentials.

At the time of our first experiments on cardiovascular sympathetic afferent fibers we preferred a "functional localization mainly because in

our hands a procedure such as probing the heart (most often performed while the heart was beating) never gave satisfactory results, since afferent fibres were often activated by probing more than one spot" (*Malliani* et al. 1971b). Indeed, mechanical probing of nearby regions, carried out in the presence of circulatory pulsations and respiratory movements, can activate from a distance a sensory field. This can be erroneously interpreted as evidence of a multiterminal afferent nerve fiber. Another common course of error arises from recordings of poorly distinguishable action potentials belonging to a multifiber preparation and erroneously said to be derived from a single axons. However, it has also been adequately demonstrated that both in the presence and absence of a circulation and following the methods described by *Coleridge* et al. (1957), cardiovascular sympathetic afferent fibers can be excited by probing several distinct spot-like areas (*Coleridge* et al. 1975, 1978; *Malliani* and *Pagani* 1976) (see below).

In all our subsequent experiments we have studied no more than one fiber per animal (with a few exceptions in which a recording was obtained containing two different types of action potentials of constant and clearly identifiable shape, as in Figs. 9 and 10): for each fiber the sensory field or fields were identified post mortem.

It should be pointed out that only very light preliminary probing should be used for locating receptive fields, after having identified functionally the location of the receptor and preferably after having already studied its functional characteristics. In fact, an abundant and blind probing may damage fibers or their endings, especially if they are nonmyelinated, and with possible consequences such as decreased sensitivity to the stimuli, an abnormal spontaneous discharge, bursting activity, etc.

It will become clear that the data from the various laboratories have not always been collected in comparable ways.

5.1 Atrial Receptors

Afferent sympathetic nerve fibers with their receptive endings located in the atrial walls have been described in numerous reports. The nerve fibers were myelinated (*Malliani* et al. 1973b; *Uchida* and *Murao* 1974c; *Uchida* 1975a) or nonmyelinated (*Uchida* and *Murao* 1974c; *Uchida* 1975a) as inferred from their conduction velocities. In the experience of one laboratory (*Malliani* et al. 1973b; *Malliani* 1979) all atrial mechanoreceptors had a spontaneous impulse activity, while a second laboratory (*Ueda* et al. 1969; *Uchida* and *Murao* 1974c; *Uchida* 1975a) rarely observed a spontaneous discharge. Nonmyelinated fibers were more frequently silent and could be activated by mechanical stimuli or chemical substances, such as

potassium chloride or bradykinin applied topically to the epicardial surface.

Within the spontaneous impulse activity there was a temporal relation between the action potential and a particular intra-atrial pressure wave (*Malliani* et al. 1973b, 1975a; *Uchida* and *Murao* 1974c; *Malliani* 1979) (Fig. 2). Fibers were found to discharge in phase with atrial systole (*a* wave of the atrial pressure) (Figs. 2a, 3a), with bulging of the atrio-ventricular valves (*c* wave) (Fig. 2b), and with atrial filling (*v* wave) (Fig. 2c). For some fibers a particular phasic pattern of spontaneous discharge was constant for periods of hours. However, such patterns could also change spontaneously (*Malliani* et al. 1973b; *Malliani* 1979) (Fig. 2d, e).

These observations were all obtained in artificially ventilated animals with the chest opened. However, a similar activity from atrial mechanoreceptors could also be recorded in animals with closed chest, breathing spontaneously. Opening the thorax and the pericardium did not grossly modify the firing of the fibers whose endings were found, post mortem, to be in the atria (*Malliani* et al. 1973b, 1975a).

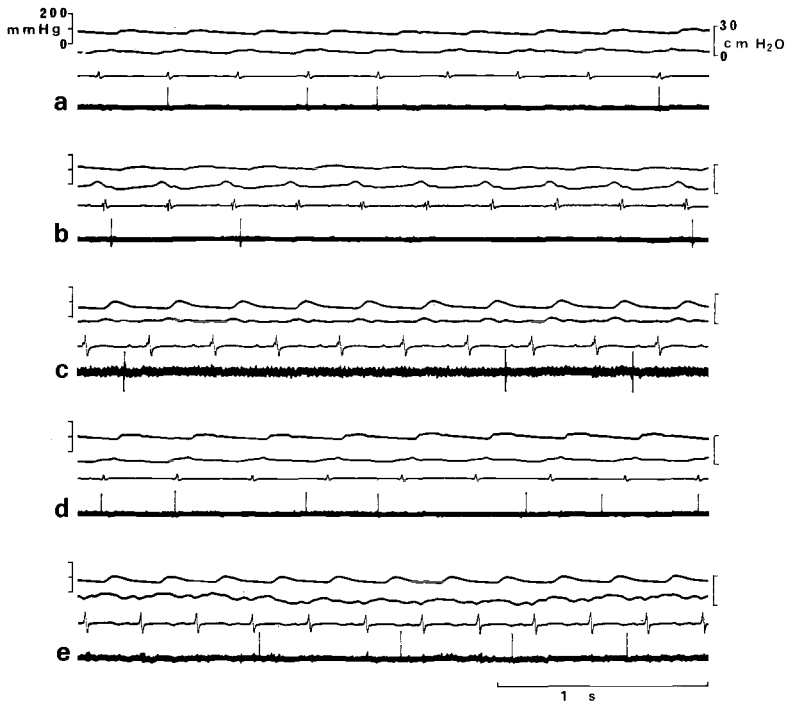

Fig. 2a–e. Spontaneous impulse activity of fibers with right atrial endings. Each record shows the activity of a different fiber, except *a* and *d*, which illustrate the discharge of the same fiber. Tracings, from top to bottom, represent the arterial blood pressure, the right atrial pressure, the ECG and the action potentials. (From *Malliani* et al. 1972b, unpublished work)

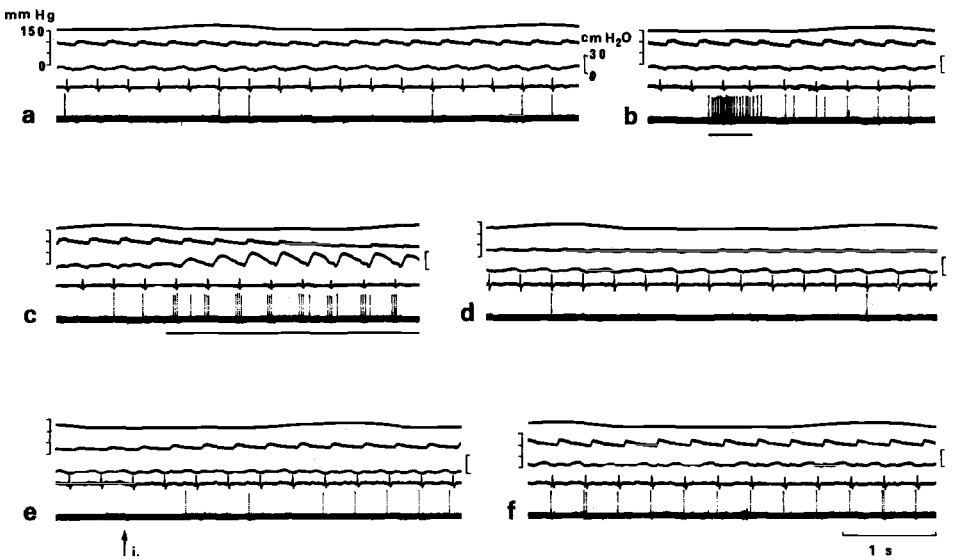

Fig. 3a–f. Activity of a fiber with right atrial endings during hemodynamic stimuli. The upper tracing represents the endotracheal pressure (inflation upwards); the other tracings as in Fig. 2. **a** Spontaneous impulse activity; **b** mechanical probing of an area of the right atrium, performed on the beating heart; **c** constriction of the pulmonary artery; **d** after rapid bleeding (30 ml in about 3 min); **e** reinjection of blood; **f** last part of the reinjection of blood. (From *Malliani* et al. 1975a)

The discharge of afferent cardiac sympathetic fibers with atrial endings was increased during rises in atrial pressure however obtained (*Malliani* et al. 1973b; *Uchida* and *Murao* 1974c; *Uchida* 1975a; *Kostreva* et al. 1975). Examples are shown in Fig. 3, illustrating the impulse activity of a right atrial receptor that spontaneously discharged in phase with atrial systole (Fig. 3a). A preliminary mechanical probing of an area of the right atrium, performed while the heart was beating, is illustrated in Fig. 3b. The fiber was excited during an increase in right atrial pressure obtained with the constriction of the pulmonary artery (Fig. 3c) or with reinjection of blood (Fig. 3e, f). Conversely, the impulse activity of atrial mechanoreceptors was always reduced or even abolished during reductions in atrial pressure as obtained while bleeding the animal (Fig. 3d) (*Malliani* et al. 1973b).

Atrial receptors can also be excited by chemical substances (*Uchida* and *Murao* 1974c; *Nishi* et al. 1977): this "polymodal" (*Burgess* and *Perl* 1973) sensitivity and the possible existence of purely chemosensitive endings will be discussed together with the more numerous data concerning left ventricular receptors (see below).

On the basis of our knowledge it seems impossible to identify the mechanical event that mainly regulates the activity of atrial mechanoreceptors. As their discharge can occur spontaneously during either atrial

systole or diastole, it seems likely that they can be excited by both muscular contraction and stretch. Comparison of the spontaneous activity of these afferent sympathetic fibers and that of the similarly myelinated afferent vagal fibers with atrial endings shows that the most obvious difference is that vagal fibers usually yield bursts of impulses during each cardiac cycle as opposed to a single impulse. This limits the possibilities of investigating the "static" and "dynamic" components of the transducing properties of the atrial sympathetic receptors that so far have not been studied with approaches similar to those used for atrial vagal receptors (*Recordati* et al. 1975, 1976).

5.2 Ventricular Receptors

With Myelinated Nerve Fibers. Different groups of researchers agree that ventricular sympathetic receptors with myelinated nerve fibers possess a mechanosensitivity which is the cause, in normal hemodynamic conditions, of their spontaneous impulse activity (*Malliani* et al. 1973b, 1975a; *Hess* et al. 1974; *Uchida* et al. 1974; *Uchida* 1975a). In the experience of one group of workers (*Malliani* et al. 1973b, 1975a) this background discharge consisted of, at most, one action potential per cardiac cycle, usually following the onset of the Q waves of the ECG by 40–120 ms (Figs. 4, 5a). For most fibers, not all cardiac cycles were accompanied by an action potential; therefore, the discharge was irregular although a cardiac periodicity was detectable. A regular discharge was infrequent (Fig. 4).

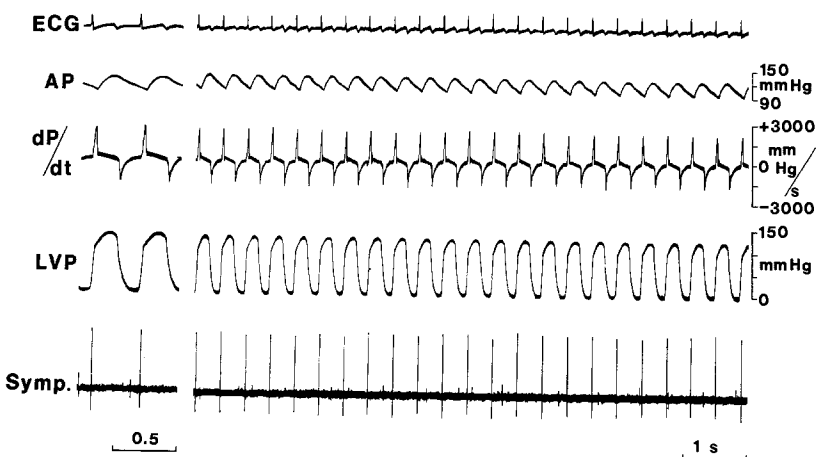

Fig. 4. Spontaneous impulse activity of a myelinated nerve fiber with left ventricular endings. Tracings, from top to bottom, represent the ECG, the arterial blood pressure, the left ventricular dP/dt, the left ventricular pressure, and action potentials

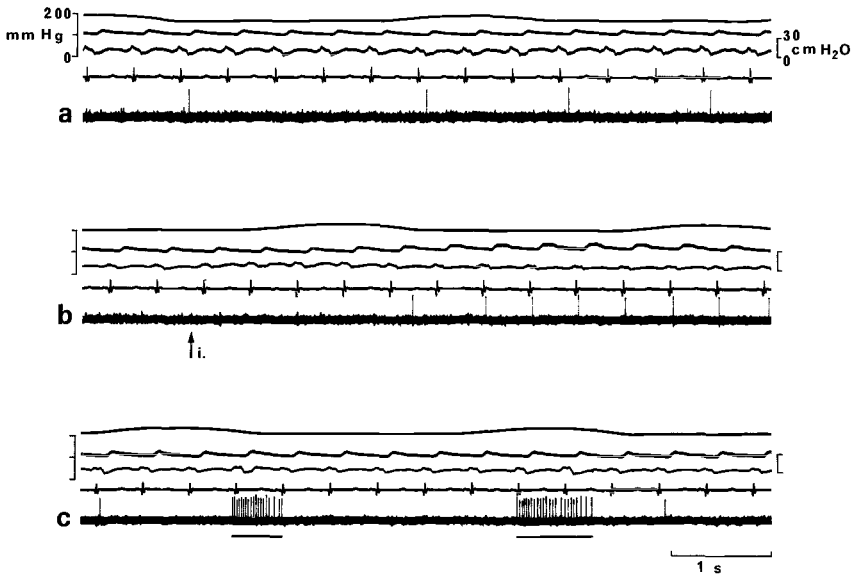

Fig. 5a–c. Impulse activity of a fiber with right ventricular endings. Tracings as in Fig. 3. **a** Spontaneous impulse activity; **b** after bleeding 10 ml blood, which abolished the discharge of the fiber, a fast reinjection of blood begins at the *arrow* (note that the first action potential occurs during a diastole); c mechanical probing of an area of the right ventricle, performed on the beating heart. (From *Malliani* et al. 1973b, unpublished work)

The coincidence between spontaneous action potentials and ventricular contractions is a general finding (*Ueda* et al. 1969; *Hess* et al. 1974; *Uchida* et al. 1974; *Nishi* et al. 1977); however, receptors firing spontaneously during ventricular diastole have also been noticed (*Ueda* et al. 1969; *Uchida* et al. 1974).

Ventricular receptor endings were excited during increases in ventricular pressure (*Ueda* et al. 1969; *Malliani* et al. 1973b; *Uchida* 1975a; *Nishi* et al. 1977) and, conversely, their discharge decreased during reductions in ventricular pressure (*Malliani* et al. 1973b; *Uchida* 1975a). Figure 5 illustrates the impulse activity of a right ventricular receptor: the discharge was abolished by a moderate bleeding of the animal, restored, and excited by fast restitution of blood (Fig. 5b).

These ventricular endings can also be excited by chemical substances such as bradykinin (*Uchida* and *Murao* 1974d; *Nishi* et al. 1977), veratridine (*Malliani* et al. 1973b, 1975a; *Nishi* et al. 1977), and acids (*Uchida* and *Murao* 1975). This responsiveness as well as the behavior of ventricular receptors during reductions in coronary flow will be discussed together with the response of ventricular nonmyelinated afferent fibers.

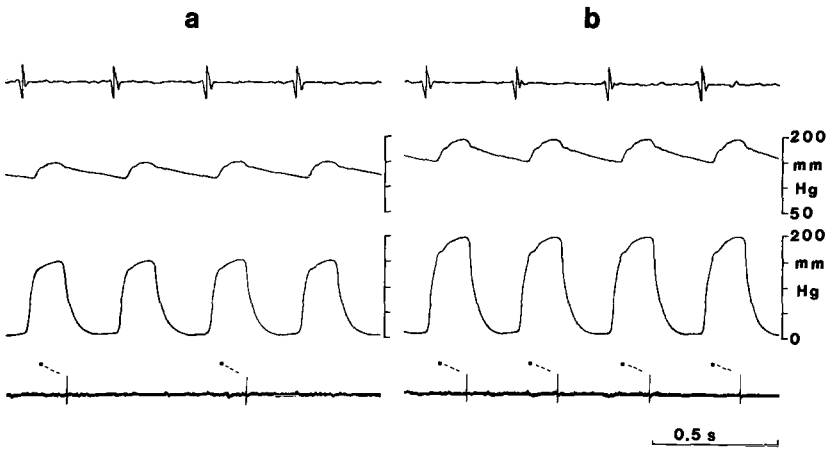

Fig. 6a, b. Impulse activity of an afferent sympathetic nonmyelinated nerve fiber with its receptive field in the left ventricle. Tracings represent from top to bottom, the ECG, the systemic arterial pressure, the left ventricular pressure and neural activity. **a** Spontaneous activity; **b** during occlusion of the aorta. The fiber conduction velocity was 0.87 m/s; the measured conduction distance from the receptive field to the recording electrode was 9.6 cm. Dots indicate the approximate relation between impulses and cardiac cycles, taking into account a conduction time of 110 ms. (From *Casati* et al. 1979)

With Nonmyelinated Nerve Fibers. A fixed temporal correlation between receptor impulses and ventricular dynamics is most often not detectable (*Uchida* et al. 1974; *Uchida* 1975a; *Casati* et al. 1979; *Lombardi* et al. 1981b); a clear difference from the discharge of myelinated sympathetic ventricular afferent fibers. However, in some cases, after taking into account the conduction time within the fiber, most of the spontaneous impulses appear to occur during ventricular systole (Fig. 6) (*Casati* et al. 1979). In a recent study (*Casati* et al. 1979) several hemodynamic stimuli were used in order to determine the functional properties of these receptors.

As shown in Fig. 7, the impulse activity of all tested fibers was significantly increased when ventricular pressure was elevated by mechanical obstructions of the thoracic aorta, during positive inotropic interventions induced by i.v. injection of isoprenaline (0.2 μg/kg) or during rises of left ventricular end-diastolic pressure produced by i.v. infusion of isotonic NaCl. Conversely, acute reductions in venous return produced by the occlusion of the inferior vena cava decreased the receptor firing that was unmodified during bleeding of the animal. In short, these sympathetic receptors would be responsive to both ventricular contraction and distension. Some examples of these responses are illustrated in Fig. 8.

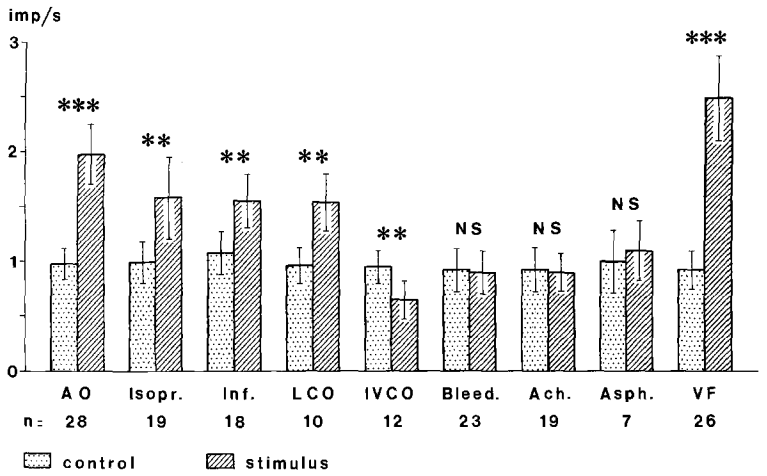

Fig. 7. Responses of ventricular sympathetic nonmyelinated afferent fibers to the interventions. *AO* aortic occlusion; *Isopr.* i.v. injection of isoprenaline; *Inf* i.v. infusion of isotonic solution; *LCO* left coronary occlusion; *IVCO* inferior vena cava occlusion; *Bleed* bleeding; *ACh* i.v. injection of acetylcholine; *Asph.* asphyxia; *VF* ventricular fibrillation; *n* number of fibers studied; $***P < 0.001$; $**P < 0.02$; *n.s.* not statistically significant. (From *Casati* et al. 1979)

During the excitation elicited by aortic occlusion (Fig. 8a), the impulses, if one considered the conduction time, occurred 60–70 ms after the beginning of the ventricular complex of the electrocardiogram: it should also be noticed that the impulse frequency of the fiber was higher during the rising phase of the stimulus than during its plateau. This would indicate a "dynamic" and "static" component in the response of the receptor (*Burgess* and *Perl* 1973).

It is interesting that all ventricular sympathetic receptors with nonmyelinated fibers were excited during ventricular fibrillation. Various patterns were noticed. In some cases, the ventricular receptors were immediately and strongly excited; for example, frequency of discharge increased in the bursts up to 47 imp/s (Fig. 9c) at the beginning of the fibrillation episode. More frequently, excitation was continuous during the whole fibrillation episode, however without bursts of high frequency discharges (Fig. 10c, d). The excitation appeared after a mean latency of about 10 s.

This excitation of ventricular receptors during ventricular fibrillation was likely to reflect a mechanical stimulation in those cases in which a precise temporal correlation existed between onset of fibrillatory movements and sudden enhancement of the frequency of the impulses (Fig. 9c). However, this does not rule out that in the course of the episode some chemical substance may contribute to the depolarization of the endings. Such as mechanism would be compatible with those cases in which some

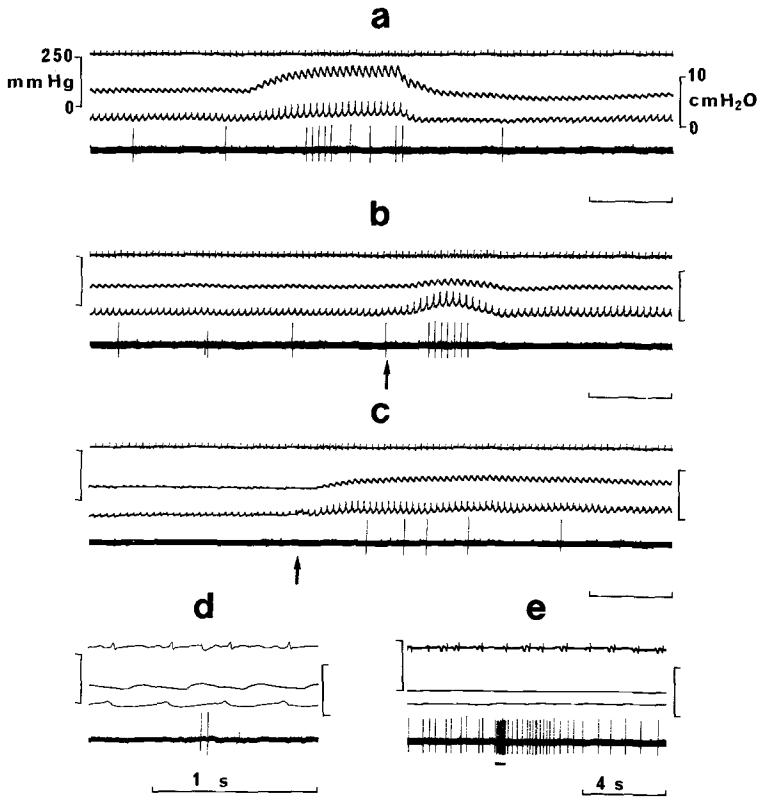

Fig. 8a–e. Activity of an afferent sympathetic nonmyelinated nerve fiber with its receptive field located in the left ventricle. Tracings represented from top to bottom, the ECG, the systemic arterial pressure, the right atrial pressure, the nervous activity (all tracings are cathode-ray oscilloscope recordings). **a** Occlusion of the descending thoracic aorta (indicated by the rise in arterial pressure); **b** i.v. injection of 5 ml warm saline, beginning at the *arrow;* **c** occlusion of the inferior vena cava released at the *arrow;* **d** electrical stimulation of the left inferior cardiac nerve activating the afferent fiber; the biphasic first deflexion is the artifact of the stimulus, detectable also on the ECG trace, while the second biphasic deflexion is the action potential of the fiber. The approximate length of the fiber was 3.8 cm. The conduction velocity calculated for this fiber was 0.92 m/s; **e** mechanical probing of an area of the external surface of the left ventricle, performed on the non-beating heart, after bleeding the animal to death; notice the after-discharge which is typical of group C fibers. (From *Casati* et al. 1979)

seconds elapsed before normal firing was restored after the fibrillation had subsided (Fig. 9d).

In five instances, the activity of one nonmyelinated and one myelinated nerve fiber with left ventricular endings were recorded simultaneously from the same nerve strand during episodes of ventricular fibrillation: three myelinated ventricular afferent fibers were excited (Fig. 10c, d), while the other two seemed to be unaffected. Although these data are

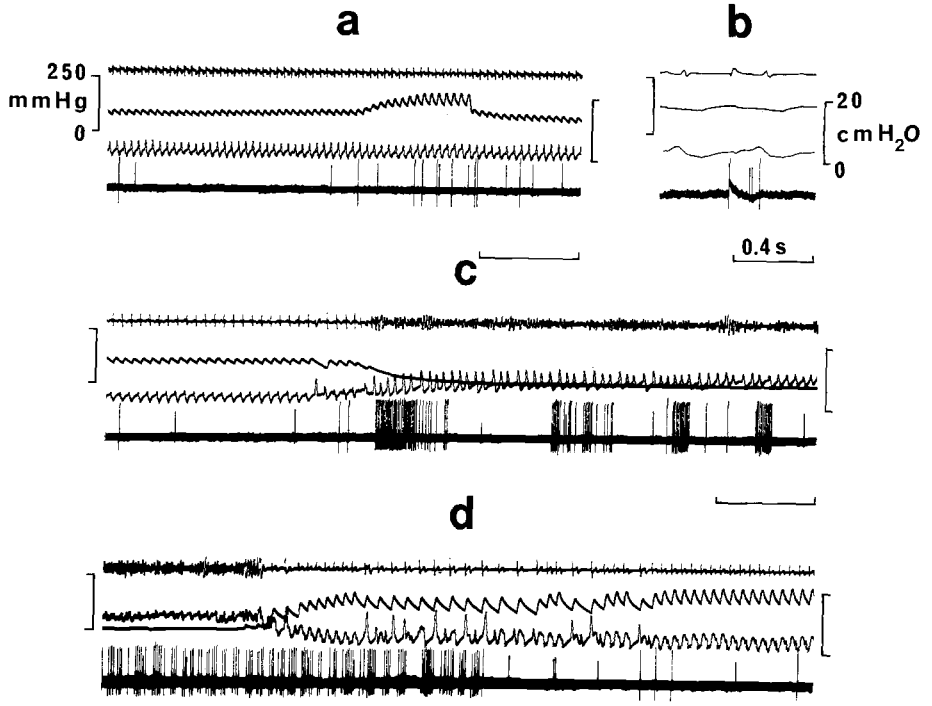

Fig. 9a–d. Activity of a nerve filament containing impulses of two different nonmyelinated fibers: the fiber yielding biphasic action potentials had its receptive field in the depth of the left ventricle, while the receptive field of the fiber with monophasic potentials was in the left atrium. Tracings as in Fig. 8. **a** Occlusion of the descending thoracic aorta; **b** electrical stimulation of the left inferior cardiac nerve activating both afferent fibers; the biphasic first deflection is the artifact of the stimulus, followed by a double activation of the atrial fiber and by the potential of the ventricular fiber. The approximate length of the fiber was 4.8 cm. The conduction velocity calculated for the ventricular and atrial fibers was respectively 0.32 m/s and 0.53 m/s; **c** an episode of ventricular fibrillation is induced by gentle mechanical stimulation of the right ventricle, corresponding to the ectopic beat preceding the episode itself by a few cardiac cycles; **d** the ventricles spontaneously return to a normal action after about 80 s. (From *Casati* et al. 1979; in part unpublished work)

insufficient to draw any quantitative conclusion on the behavior of myelinated ventricular afferent fibers during ventricular fibrillation, these results indicate that there are circumstances in which the endings of myelinated and nonmyelinated fibers appear to be influenced in a different manner by the same local event.

In their responses to acute bleeding, myelinated and nonmyelinated ventricular afferent fibers also behaved differently. The latter did not reduce their discharge (Fig. 7): more abrupt reductions in venous return were needed, such as those obtained with the occlusion of the inferior vena cava (Figs. 7, 8c), in order to reduce activity.

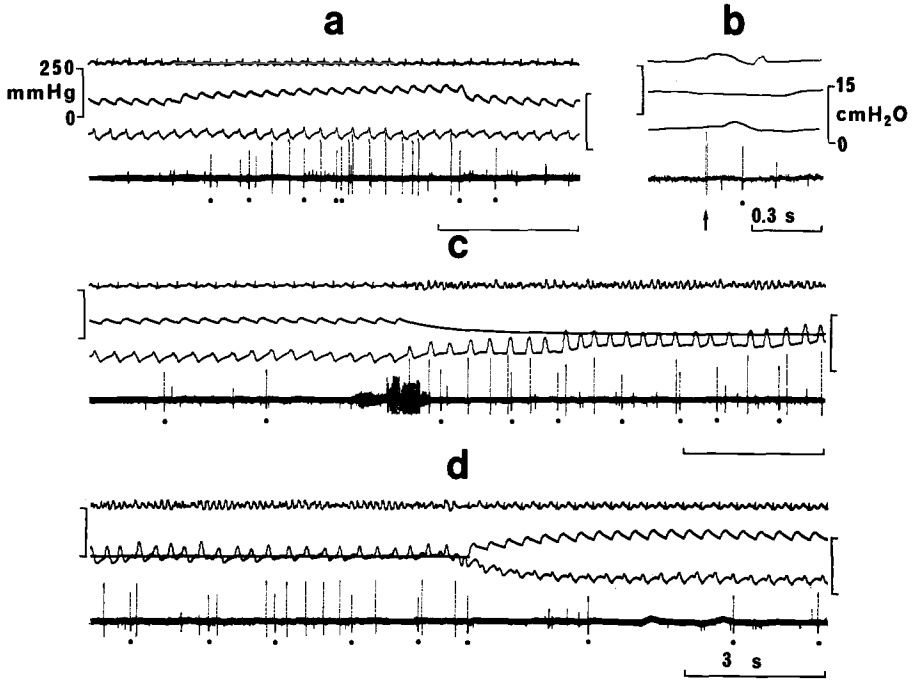

Fig. 10a–d. Sympathetic nerve filament containing a nonmyelinated and a myelinated afferent fiber, both with their receptive field in the left ventricle. The action potentials of the nonmyelinated fibers are marked with dots; the largest potentials were produced by the myelinated fiber. Tracings as in Fig. 8. **a** Occlusion of the descending thoracic aorta; **b** electrical stimulation of the inferior cardiac nerve; the stimulus artifact corresponds to the first deflexion indicated by the *arrow;* the large action potential of the myelinated fiber is barely distinguishable from the artifact, followed after a long latency by the potential of the nonmyelinated fiber. The approximate length of the nerve was 5.6 cm. The calculated conduction velocity was 0.36 m/s for the nonmyelinated and 7.23 m/s for the myelinated fiber. **c** Ventricular fibrillation is induced by a high-frequency electrical stimulation of the right ventricle; **d** spontaneous interruption of the fibrillation episode after 68 s. (From *Casati* et al. 1979; in part unpublished work)

For most atrial and ventricular afferent fibers only one sensory field was found on probing the heart, post mortem. However, in a few cases, afferent fibers were excited equally from two distinct but nearby areas (*Malliani* et al. 1973b; *Nishi* et al. 1977). The finding of multiple sensory cardiac fields was more frequent in the experiments by *Coleridge* and associates (*Coleridge* et al. 1975, 1978; *Baker* et al. 1980). I can provide no explanation for this quantitative difference as the mechanical probing was also often performed post mortem by these authors (however, they did not study only one fiber per experiment). A similar observation of multiple sensory fields was first made on afferent vagal fibers with epicardial receptors by *Sleight* and *Widdicombe* (1965).

Finally, it should be stressed that some ventricular endings could only be excited by a probing performed against the internal surface of the opened ventricle or by mechanical stimuli deforming the depth of the ventricular muscle, e.g. punctures with penetrating needles (*Malliani* et al.

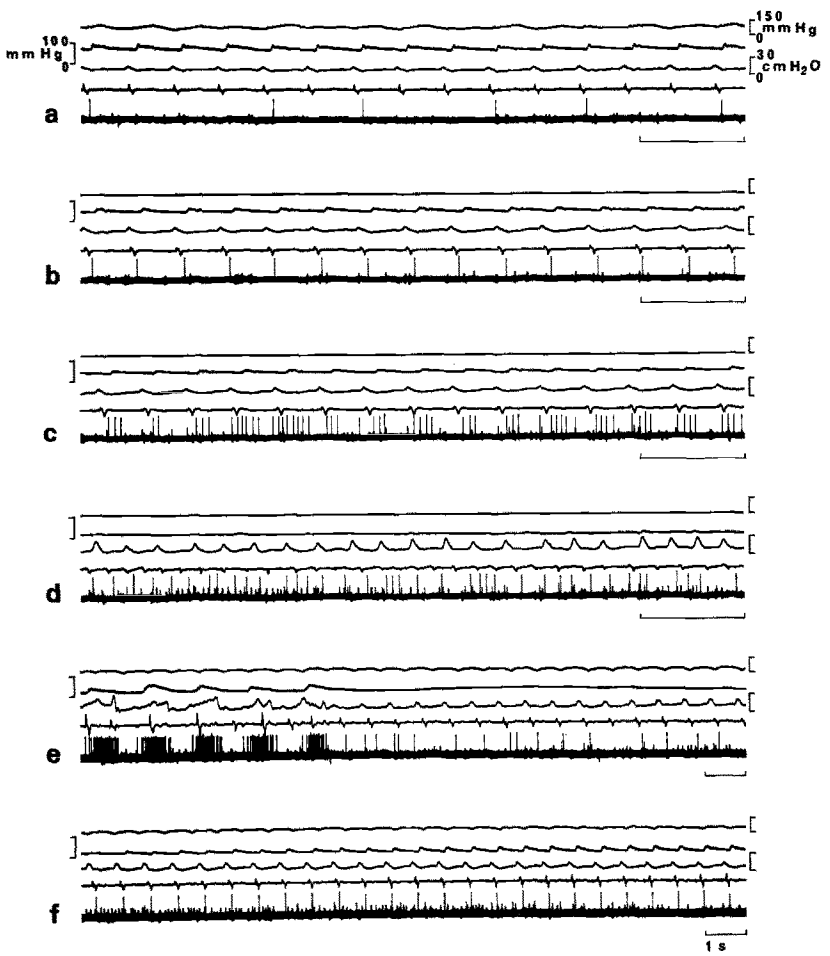

Fig. 11a–f. Effects of a prolonged interruption of left coronary arterial flow. Fiber with right ventricular endings. Tracings represent, from top to bottom, the coronary inflow pressure, the arterial blood pressure, the right atrial pressure, the ECG, the nervous recording (cathode-ray oscilloscope recordings). **a** Control (the flow is set at 11 ml/min); **b** the record starts 70 s after the coronary perfusion has been interrupted; **c** starts 39 s after the end of the preceding record; **d** after additional 67 s; a coarse ventricular fibrillation is present. Fifteen seconds after the end of **d** the coronary perfusion is instituted again, however, the ventricles do not contract; **e** 10 s later cardiac massages are performed (markedly exciting, mechanically, the endings of the fiber); **f** progressively the heart recovers (**e** and **f** are continuous tracings). (From *Malliani* et al. 1973b)

1973b; *Casati* et al. 1979). In these cases a probing performed on the beating heart would be ineffective in identifying the mechanosensitive endings.

Effects of Reduction in Coronary Flow. In order to interpret correctly the effects of reduction in coronary flow on the activity of cardiac receptors, it is crucial to avoid undue direct mechanical stimulation of the fibers en passage or of their receptor endings. To this purpose, coronary perfusion can be used (Fig. 1) and myocardial ischemia can be produced by interrupting the action of the perfusion pump without manipulation of the heart (*Brown* and *Malliani* 1971; *Malliani* et al. 1973b; *Lombardi* et al. 1981b). Alternatively, the pericoronary nerves can be surgically isolated

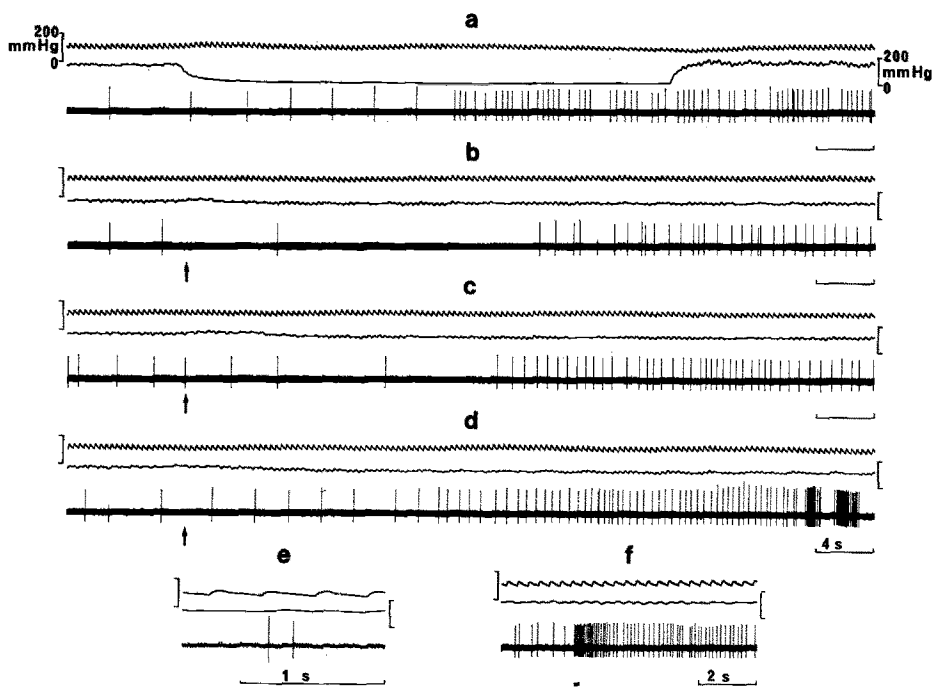

Fig. 12a–f. Activity of an afferent sympathetic nonmyelinated nerve fiber with a left ventricular sensory field. Tracings represent, from top to bottom, systemic arterial pressure, coronary perfusion pressure, nerve impulse activity (cathode-ray oscilloscope recordings). **a** Interruption of the left main coronary artery perfusion; **b** intracoronary administration, beginning at the *arrow*, of bradykinin, 5 ng/kg; **c** intracoronary administration of bradykinin, 10 ng/kg; **d** intracoronary administration of bradykinin, 30 ng/kg; **e** electrical stimulation of the left inferior cardiac nerve activating the afferent fiber; the biphasic first deflection is the artifact of the stimulus, and the second biphasic deflection is the action potential of the fiber. The approximate length of the nerve was 8 cm. The conduction velocity calculated for this fiber was 0.45 m/s. **f** Mechanical probing, marked by a bar, of an area of the external surface of the left ventricle: notice the after-discharge which is typical of nonmyelinated afferent fibers. (From *Lombardi* et al. 1981b)

from the coronary arteries: in the cat, a satisfactory isolation of the pericoronary nerve from the left main coronary artery is possible (*Brown* 1967; *Casati* et al. 1979).

Both myelinated (*Brown* 1967; *Malliani* et al. 1973b; *Uchida* and *Murao* 1974b; *Bosnjak* et al. 1979) and nonmyelinated (*Uchida* and *Murao* 1974b; *Casati* et al. 1979) ventricular sympathetic afferent fibers are excited during interruptions of coronary flow. Following coronary artery occlusion, excitation of myelinated fibers began after a mean of 80 s (Fig. 11), whereas only approximately 15 s elapsed before nonmyelinated fibers were activated (Fig. 12) (*Malliani* et al. 1973b; *Casati* et al. 1979; *Lombardi* et al. 1981b). The excitation of the myelinated ventricular afferent fibers occurred only when the heart was markedly dilated and thus had a long latency: moreover, when cardiac massage was performed, because of ventricular fibrillation, the consequent reduction in cardiac size was clearly accompanied by a decreased receptor discharge (Fig. 11e). All these facts point to a predominant mechanosensitivity for the myelinated ventricular afferent fibers, a conclusion also reached by *Uchida* and *Murao* (1974b) and *Bosnjak* et al. (1979).

It is interesting to note that afferent cardiac vagal fibers were excited after interruption of left coronary artery perfusion after a mean latency of 42 s (*Recordati* et al. 1971).

The shorter latency for excitation of nonmyelinated ventricular afferent fibers may indicate either a different level of mechanosensitivity or a greater responsiveness to chemical factors. On the other hand, *Uchida* and *Murao* (1974b) observed in the dog shorter latencies for the excitation of myelinated afferent fibers (about 21 s) than for nonmyelinated fibers (about 35 s). The discrepancy with the preceding data is likely to depend on the technique used, since the Japanese authors occluded the anterior descending branch of the left coronary artery: it is possible that the mechanical stimulus of occlusion directly affected nearby nerve fibers or receptive fields. A similar explanation may also apply to the short latencies for excitation of ventricular myelinated afferent fibers found by *Bosnjak* et al. (1979).

The different latencies for the activation of myelinated and nonmyelinated afferent fibers may be relevant to the onset of reflex effects and pain (*Casati* et al. 1979; *Malliani* and *Lombardi* 1982).

Effects of Chemical Substances. Sympathetic ventricular receptors with nonmyelinated fibers display a marked responsiveness to chemical substances such as bradykinin, potassium, acids, veratridine. These substances have been applied topically to the epicardial surface (*Uchida* and *Murao* 1974a, c, d, 1975; *Nishi* et al. 1977; *Baker* et al. 1980; *Coleridge* and *Coleridge* 1980), injected i.v. (*Nishi* et al. 1977), or administered by the

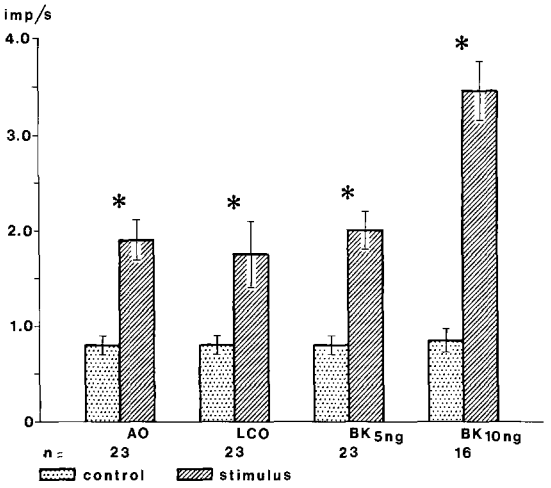

Fig. 13. Responses of afferent sympathetic nonmyelinated fiber with left ventricular endings to various experimental interventions. *AO* aortic occlusion; *LCO* interruption of the perfusion of the left main coronary artery; *BK 5 ng* and *BK 10 ng*, intracoronary administration of bradykinin, 5 ng/kg and 10 ng/kg; *n* number of fibers studied; $*P < 0.001$. (From *Lombardi* et al. 1981b)

intracoronary route (*Brown* and *Malliani* 1971; *Malliani* et al. 1973; *Lombardi* et al. 1981b) (Figs. 12b–d, 13). On the basis of the experimental findings two different general conclusions have been reached.

Some authors found that all the left ventricular sympathetic receptors with nonmyelinated fibers (*Lombardi* et al. 1981b) and a large proportion of cardiac sympathetic receptors with myelinated fibers (*Nishi* et al. 1977) displayed properties of low-threshold "polymodal" receptors. This term (*Burgess* and *Perl* 1973) indicates that the receptor zone is considered sensitive to mechanical and chemical stimuli, although a transducer mechanism that can account for such dual responsiveness has not yet been found (*Leek* 1977). In fact, due to their mechanosensitivity, all these receptors have a spontaneous impulse activity in the presence of adequate hemodynamic conditions. Low doses of chemical substances often appear capable of increasing such a mechanosensitivity, suggesting a phenomenon of "sensitization" (*Nishi* et al. 1977; *Lombardi* et al. 1981b). On the other hand, *Uchida* and *Murao* (1974a, c, d, 1975) found silent ventricular sympathetic nonmyelinated afferent fibers that became active only after the administration of chemical substances: hence they concluded that a large proportion of these ventricular receptors are purely chemosensitive.

This discrepancy deserves some comments. If the analysis is restricted to nonmyelinated ventricular sympathetic afferent fibers, the claim for purely chemosensitive endings is based on the appearance of action potentials from previously silent ventricular afferent fibers elicited by the epicardial application of chemical substances. However, the same authors (*Ueda* et al. 1969; *Uchida* et al. 1974) report a significant number of fibers that display mechanosensitivity to probing and yet are devoid of spontaneous activity. In all such cases, it is possible that the hemodynamic conditions in the heart were below threshold for some mechanosensitive

endings, thus causing their fibers to remain without background discharge. In addition, it should be noted that topical application of chemical substances to the epicardial surface in the concentrations used might directly excite the fibers en passage (*Khayutin* et al. 1976), while a superficial probing of the beating heart (*Uchida* et al. 1974; *Uchida* and *Murao* 1974a, d, 1975) was probably not adequate to assess the existence of mechanosensitive fields if they were located deeply in the ventricular mass (*Casati* et al. 1979).

Finally, *Baker* et al. (1980) claimed to have identified ten ventricular receptors that were "primarily" chemosensitive. In fact, the receptors said to have such specific transducing properties had a spontaneous impulse activity of 0.3 ± 0.3 imp/s that increased to 0.8 ± 0.3 imp/s during a 50 mmHg rise in mean aortic pressure, i.e. they increased almost three times their firing during a physiological increase in aortic pressure. A similar change was reported for these ventricular mechanoreceptors (*Casati* et al. 1979). Other differentiating criteria were considered to be their unresponsiveness to light superficial probing and their afterdischarge following strong mechanical stimulation: again these are typical properties of deeply located ventricular mechanoreceptors (*Casati* et al. 1979). In short, this population of so-called primarily chemosensitive receptors appears indistinguishable from other polymodal receptors.

Cardiac Nociception. It is generally accepted that the sympathetic nerves are essential to the perception of cardiac pain (*Jonnesco* 1921; *Leriche* and *Fontaine* 1927; *Sutton* and *Lueth* 1930; *Lindgren* and *Olivecrona* 1947; *White* 1957; *Brown* 1967). However, this notion does not solve the more analytical problem of whether noxious events, likely to be algesic, induce only an intensification in the tonic discharge of the sympathetic sensory endings or recruit instead silent fibers which possess a specific nociceptive function. This problem is part of a more general question concerning the peripheral mechanisms for nociception, for which two main hypotheses have been considered: they are the "intensity" or "specificity" theories (*Perl* 1971). The "intensity" hypothesis assumes that pain results from an excessive stimulation of receptive structures normally stimulated at lower levels. Alternatively, pain may be conceived as a "specific" sensation; that is, the product of the excitation of a well-defined nociceptive apparatus, the functional characteristics of which make it responsive only to a limited class of events, "noxious" stimuli that threaten the integrity of a tissue (*Sherrington* 1906). "In absence of previous insults . . . sensory units fitting the criteria for nociceptors do not have background activity" (*Burgess* and Perl 1973).

The "specificity" hypothesis would be consistent with the findings of *Uchida* and co-workers who have repeatedly reported the existence of a

large population of afferent sympathetic fibers with ventricular endings, normally silent and excited during coronary occlusion or by chemical substances (*Uchida* and *Murao* 1974b, d, 1975). This hypothesis has also been recently privileged by *Coleridge* and co-workers (*Baker* et al. 1980; *Coleridge* and *Coleridge* 1980); however, their cardiac nociceptors all had a background activity.

On the other hand, in our studies, we never observed a recruitment of silent afferent sympathetic cardiac fibers either following stimulation of the cardiac nerves or coronary occlusion (*Malliani* et al. 1973b; *Casati* et al. 1979). More recently, the intracoronary injection of bradykinin, a natural algesic substance (*Guzman* et al. 1962), suspected to take part in the genesis of cardiac pain (*Burch* and *De Pasquale* 1963), was adopted as a tool for exciting silent chemosensitive ventricular receptors (*Lombardi* et al. 1981b). However, intracoronary administration of bradykinin never recruited silent afferent fibers, a result which confirmed a previous study in which the drug was applied topically to the epicardium and the effects on active myelinated sympathetic afferent fibers were studied (*Nishi* et al. 1977).

The conclusion seems inescapable that sympathetic cardiac receptors possess some degree of mechanosensitivity and have a spontaneous firing if the hemodynamic conditions are in the normal range. Accordingly, the "intensity" hypothesis seems to be the most appropriate to account for the functional properties of the neural substratum subserving cardiac nociception (*Lombardi* et al. 1981b; *Malliani* and *Lombardi* 1982).

5.3 Coronary Receptors

Brown and *Malliani* recorded impulse activity of afferent cardiac sympathetic nerve fibers that were excited by increases in coronary flow and pressure and by occlusion of the coronary sinus (*Malliani* and *Brown* 1970; *Brown* and *Malliani* 1971). Some of the fibers were also activated by interruption of left coronary artery flow leading to myocardial ischemia and by chemical substances (veratridine, acids). In these experiments, light mechanical stimuli were applied to the beating heart in order to localize the receptive fields that appeared to be in close proximity to the left main coronary artery. In my opinion these coronary receptors cannot be distinguished from other ventricular receptors that are also excited by increases in coronary flow and pressure (*Malliani* et al. 1973b, 1975a).

With regard to the problem of cardiac nociception discussed earlier, *Brown* and *Malliani* (1971) observed a few silent fibers that became active during interruption of the coronary artery perfusion (Fig. 14). Such

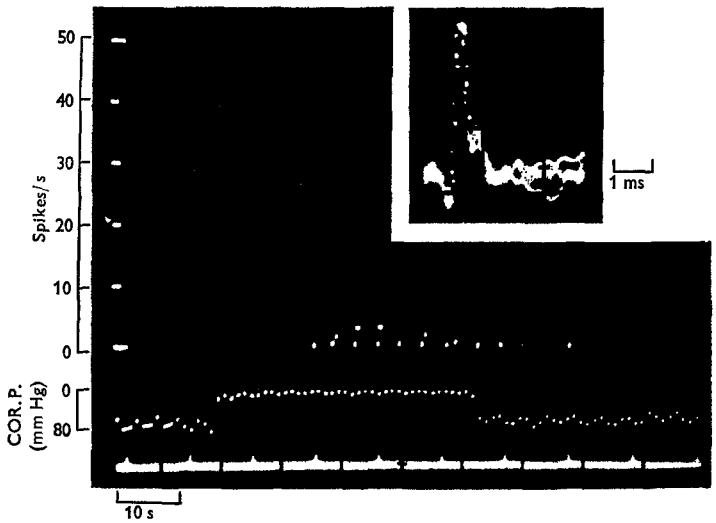

Fig. 14. Effect of myocardial ischemia on an afferent cardiac sympathetic nerve fiber. Computer analysis. Fall in coronary pressure shown as an upward deflexion of bottom tracing. The fiber had no background activity. After 15–18 s a discharge appeared and persisted for some 20 s after flow was recommenced. Each action potential gave a point on the frequency histogram; all spikes were superimposed for the inset. (From *Brown* and *Malliani* 1971)

recruitment was interpreted as suggesting the existence of "specific" cardiac nociceptors excited by myocardial ischemia. It should however be pointed out that those recordings were obtained in spinal animals with a lower than normal arterial pressure, a fact that might have resulted in the lack of spontaneous firing of cardiac mechanoreceptors.

5.4 Receptors in the Large Thoracic Vessels

The endings of myelinated nerves on blood vessels were described at the end of the nineteenth century (*Dogiel* 1898). Usually they were regarded as subserving a sensory function (*Woollard* 1926). Some of the afferent nerve fibers from receptors in the large thoracic vessels were traced to the stellate ganglia (*Muratori* 1934).

Electrophysiological experiments have recently provided convincing evidence on the existence of afferent sympathetic fibers, myelinated and nonmyelinated, innervating these vascular areas.

5.4.1 Aorta. Aortic mechanoreceptors with sympathetic nerve fibers were studied by *Coleridge* et al. (1975), *Pagani* (1975), *Uchida* (1975b), *Malliani* and *Pagani* (1976).

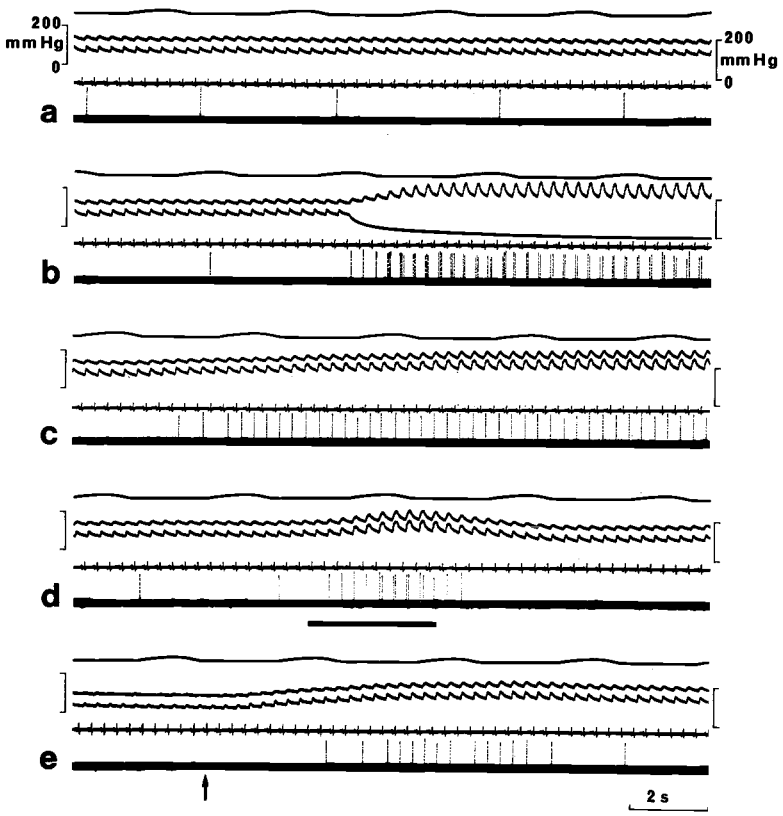

Fig. 15a–e. Activity of an afferent sympathetic myelinated nerve fiber with receptive field located in the proximal third of the descending thoracic aorta. Calculated conduction velocity 5 m/s. Tracings in **a**, **b**, **c**, **d** and **e** represent, from top to bottom, the endotracheal pressure (inflations upwards), the aortic and femoral arterial pressure, the ECG, and the nervous recordings. **a** Control; **b** occlusion of the descending thoracic aorta (indicated by the diverging blood pressure traces); **c** effects of an i.v. injection of 2 μg angiotensin, performed just before the beginning of the record; **d** effect of a reflex blood pressure rise produced by occluding the right carotid artery (occlusion indicated by the bar); **e** effect of an abrupt increase in venous return produced by releasing, at the *arrow*, an occlusion of the inferior vena cava. (From *Malliani* and *Pagani* 1976)

In the experiments by *Malliani* and *Pagani* (1976) all myelinated afferent fibers were active at a mean systolic pressure of 139 mmHg, in phase with the aortic pressure pulses (Fig. 15a). Whenever aortic pressure was elevated by mechanical occlusion of the thoracic aorta (Fig. 15b), by injection of pressor drugs (Fig. 15c), by carotid sinus reflex (Fig. 15d), or by increasing the venous return (Fig. 15e), the impulse activity of all fibers studied increased markedly. Some myelinated fibers displayed repetitive discharges at high frequency with each pressure pulse (Fig. 15b). Maximal activity was attained while arterial pressure was rising and was

related to the extent and rate of such a rise. Conversely hypotension always caused a decrease or suppression of the impulse activity that ceased when systolic blood pressure was lower than 102 mmHg. Myelinated aortic afferent fibers often had no spontaneous discharge in *Uchida*'s experiments (1975b) and this is in conflict with our results.

The nonmyelinated afferent fibers displayed functional properties similar to those observed for the myelinated fibers (*Malliani* and *Pagani* 1976). Thus, they had a spontaneous impulse activity at a mean systolic blood pressure of 132 mmHg (Fig. 16a). Although the spontaneous discharge appeared more erratic, if the slow conduction velocity was taken into account, most of the impulses corresponded to the aortic pressure pulses. All nonmyelinated fibers ceased to fire when systolic blood pressure was below 100 mmHg or when the animal was bled to death. Asphyxia never increased their discharge, provided that it was not accompanied by an arterial pressure rise.

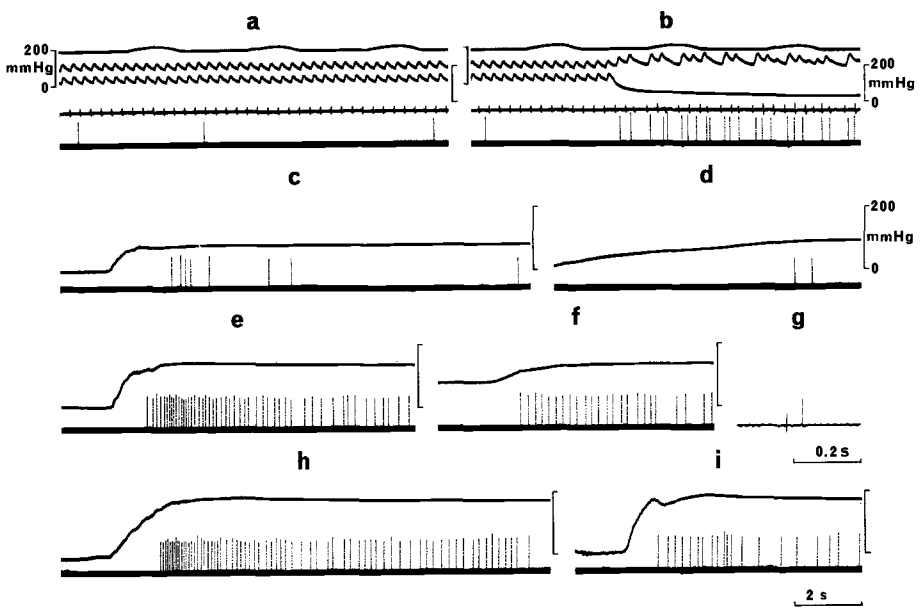

Fig. 16a–i. Activity of an afferent sympathetic nonmyelinated nerve fiber with receptive field located in the distal third of the aortic arch. **a** Control; **b** occlusion of the descending aorta; c, **d**, **e**, **f**, **h**, and **i**, effects of stretching aortic wall by distending a latex balloon located in the distal part of the aortic arch after the animal had been killed by bleeding; g electrical stimulation of the left inferior cardiac nerve activating the fiber. Approximate length of the fiber, 5 cm. Calculated conduction velocity 1 m/s. Tracings in **a** and **b** as in Fig. 15. c, **d**, **e**, **f**, **h**, and **i** top tracing: pressure applied to the distending balloon; bottom tracing; nervous activity. (From *Malliani* and *Pagani* 1976)

It is impossible to reconcile these data with those reported by *Uchida* (1975b): in his experiments nonmyelinated aortic afferent fibers had an activity mainly related to respiration and excited by asphyxia. This fact deserves some comment as it would have important pathophysiological implications. It may be that nonmyelinated aortic afferent fibers responsive to asphyxia exist in the dog (*Uchida* 1975b) but not in the cat (*Malliani* and *Pagani* 1976). However, from *Uchida*'s data it is not possible to ascertain whether asphyxia was accompanied by an arterial pressure rise. Usually, in acute experimental conditions, some bleeding is necessary to maintain constant arterial pressure during asphyxia. It is also possible that the multifiber preparations from which the records were obtained included some postganglionic efferent activity, although details of the surgical preparations as described suggest that the preganglionic input to the stellate ganglion was interrupted.

In five experiments, *Malliani* and *Pagani* (1976) studied, post mortem, the functional properties of myelinated and nonmyelinated aortic afferent fibers. Figure 16 shows an example of one of these experiments while recording from a nonmyelinated fiber. The fiber was strongly excited in vivo by increases in aortic pressure but with an irregular rhythm, due to cardiac arrhythmias accompanying the abrupt pressure load (Fig. 16b). When an aortic balloon was inflated (Fig. 16c–i), the highest impulse frequencies were attained during the rising phase of the pressor stimulus, followed thereafter by an adapted discharge (Fig. 16e, h). A dynamic component of the stimulus was also demonstrated by reaching the same level of absolute pressure at different speeds (Fig. 16c, d) or from different initial pressure (Fig. 16e, f). Finally, a response was observed which might be attributed to receptor fatigue and/or mechanical alteration of the vascular wall: in Fig. 16h a pressure rise produced a much higher activation of the impulse activity than that illustrated in Fig. 16i where the same pressure step was applied after the stimulus had been sustained for 100 s and just released for a few seconds.

In the study by *Malliani* and *Pagani* (1976), 35 out of 24 aortic sympathetic fibers were found, post mortem, to have a single spotlike receptive field, while 11 had multiple receptive fields (from two to four): these were usually located in nearby aortic areas and, in addition, in other proximal portions of the arterial tree originating from the aorta (intercostal arteries, left subclavian artery, innominate artery, coronary artery), or in the adjacent pleura and connective tissue.

Earlier anatomical observations (*Wollard* 1926) had in fact indicated that vascular sensory fibers could terminate in the adventitia of an artery by means of one branch and in the adjacent connective tissue by means of another branch.

Coleridge and co-workers (1975) were the first to report afferent sympathetic fibers with multiple endings supplying distant cardiovascular areas. Out of 85 single afferent fibers, 48 fibers each had a single ending and 37 had 2–9 endings (average 4). Of the fibers with multiple endings, 26 innervated single organs (left ventricle, left atrium, pericardium, aorta, pulmonary artery, lung, trachea, esophagus and pleura). Eleven fibers innervated two or more structures, e.g., on fiber supplied endings in aorta, pleura, bronchus, and esophagus. In the opinion of *Coleridge* and co-workers these findings suggest that these sympathetic afferent fibers are unlikely to provide the central nervous system with specific information on events in a particular organ (*Coleridge* et al. 1975, 1978). This may perhaps hold true for those fibers, first described by *Holmes* and *Torrance* (1959), that most often have no spontaneous discharge and that seem only indirectly influenced by hemodynamic events as they innervate large portions of the pleura and the connective tissue surrounding the various thoracic organs. On the other hand, multiple but nearby cardiac sensory fields (*Malliani* et al. 1973; *Nishi* et al. 1977) are likely to signal similar local events. As for the aortic sympathetic mechanoreceptors, even with their possible satellite endings in the perivascular structures, they appear sensitive to hemodynamic stimuli and, for instance, quite well suited for signalling pulsatile aortic stretch. Indeed, were this to be their function, I do not think that a less specific message would reach the nervous centers if the receptor areas were not only located on the aorta but on the intercostal arteries as well, since aorta and nearby arterial rami do not usually have a different hemodynamic regimen. It should also be appreciated that mechanical probing, even if performed in the most appropriate conditions, indicates only a possibility for a normal receptor transduction but surely cannot determine, in the presence of multiple sensitive areas, whether action potentials originate only from one site or whether all of them participate randomly in this function. Thus the answer to the question of specificity must be defined from a study of the behavior of the receptors rather than from what we assume may be their potentials.

5.4.2 Pulmonary Artery. Nishi et al. (1974) provided a very careful study of the afferent sympathetic myelinated fibers innervating the wall of the pulmonary artery. The receptor fields were localized, post mortem, and most of them were in the distal part of the extrapulmonary tract of the pulmonary artery. These mechanoreceptors had spontaneous impulse activity that did not occur with each pressure pulse, but when they did appear the impulses were in phase with the upstroke of the arterial pressure pulse. When mean pulmonary arterial pressure was raised, impulses occurred during each cardiac cycle.

Acetylcholine also excited the receptor discharge but this was interpreted as the result of a simultaneous rise in pulmonary arterial pressure. As expected, a reduction in pulmonary arterial pressure obtained by bleeding the animal caused a reduction in the impulse firing.

5.4.3 Pulmonary Veins. *Nonidez* (1941) observed that the pulmonary veins of previously sympathectomized cats contained no receptor endings. In his opinion this indicated that the sensory fibers innervating these vessels might run in the sympathetic nerves.

Using electrophysiological techniques *Lombardi* and co-workers (1976) identified afferent sympathetic myelinated nerve fibers which had their endings on the pulmonary veins, thus confirming Nonidez's deduction.

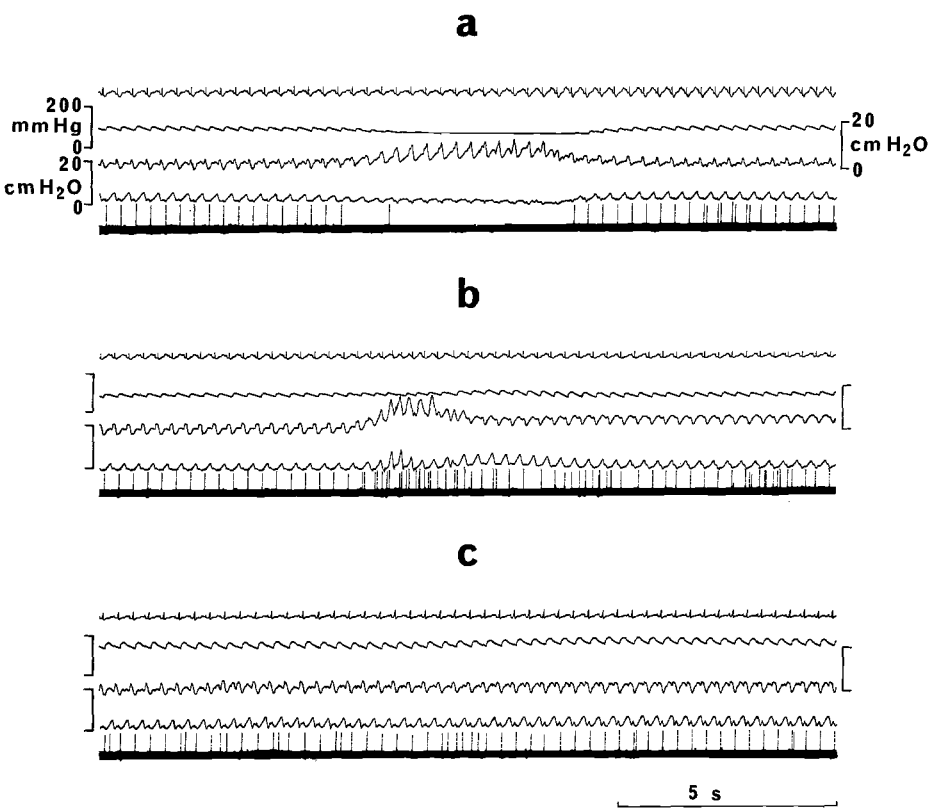

Fig. 17a–c. Nervous activity of a single afferent sympathetic fiber innervating the left superior pulmonary vein. In each display recordings are, from top to bottom: ECG, systemic blood pressure, right atrial pressure, left atrial pressure, and nervous activity. **a** Constriction of the pulmonary artery; **b** i.v. injection of 5 ml warm saline; **c** progressive rising of arterial blood pressure induced by the i.v. injection of 5 μg noradrenaline. (From *Lombardi* et al. 1976)

The receptive fields were relatively small (restricted to a few millimeters) when compared with other receptive fields observed by the same workers in other sites of the cardiovascular system. Moreover, each fiber had a single field and all were restricted to the pulmonary veins although they extended to the atrial junctions. However, there is some disagreement on this point as *Coleridge* and co-workers stated (1978) that in their experience the pulmonary veins seem to receive as large a proportion of fibers with multiple endings as do other cardiovascular regions. Future work will probably clarify this discrepancy.

All fibers had spontaneous impulse activity that was mainly in phase with atrial systole (*Lombardi* et al. 1976). The discharge was increased whenever pressure in the left atrium and, consequently, in the pulmonary veins was increased, e.g. i.v. injection of warm saline (Fig. 17b), pressor drugs (Fig. 17c), or mechanical constrictions of the thoracic aorta. All fibers were also excited during forced inflation of the lungs. Conversely, impulse activity decreased during reductions in pulmonary venous pressure, however produced (Fig. 17a). In general, these sympathetic receptors appear particularly suitable to sense pulmonary congestion.

6 Reflexes Mediated by Sympathetic Afferent Fibers

The study of the reflex effects elicited by the stimulation of cardiovascular sympathetic afferent fibers has probably contributed more to the appreciation of the importance of this afferent pathway than the detailed analysis of the functional characteristics of its receptors. In fact, it has become progressively clearer that these afferent fibers constitute by no means a kind of redundant and less sophisticated channel of information, but that instead they mediate reflexes which are quite different from those subserved by the supraspinal cardiovascular afferent fibers.

Much work on this topic has been carried out in various laboratories during the last 15 years (*Malliani* et al. 1975a; *Brown* 1979) and a brief summary of the approaches that can be used will provide an appropriate frame to a concise description of the results.

1. More or less restricted hemodynamic stimuli, capable of modifying the activity of cardiovascular receptors, can be applied while the reflex effects are detected by monitoring the impulse activity of efferent nerve fibers. A shortcoming of this approach is that the exact function of the recorded efferent fibers, isolated as they may be from a well-defined outflow, remains unknown. However, this type of experiment is likely to provide information on the complexity of neural mechanisms participating even in the simplest reflexes elicited with natural stimuli.

2. The afferent sympathetic fibers can be stimulated electrically or their endings chemically and the reflex effects can be measured either by recording the impulse activity of efferent visceral nerve fibers or by measuring cardiovascular target functions. Although the electrical stimulation can be performed with graded currents and various frequencies, these experiments are likely to suffer from the artificiality of activating simultaneously and at the same frequency fibers that in normal conditions would never fire synchronously. Thus the interneuronal modulations are likely to be severely distorted. On the other hand, a discrete chemical stimulation of the endings has the advantage of respecting the impulse generating capabilities of the "polymodal" receptor (*Burgess* and *Perl* 1973). However, if larger doses are used, it becomes progressively more likely that the preterminal regions of the fibers may also be excited, and thus the stimulus bypasses the function of the generator potential. Not all chemical substances can be considered in the same category, for instance a natural substance like bradykinin should surely be preferred to a drug like veratridine. Finally, a chemical substance can be administered locally at doses incapable of producing direct general cardiovascular effects, thus any possible reflex would be easily detectable.

3. A hemodynamic disturbance can be simulated by an appropriate mechanical stimulus that does not alter, per se, the general hemodynamic conditions, and the reflex effects can be studied as hemodynamic or nervous responses.

6.1 Acute Experiments

Our experiments on reflexes mediated by cardiovascular sympathetic afferent fibers began with the observation that coronary occlusion could reflexly alter the firing frequency, most often toward excitation, of preganglionic sympathetic fibers (*Malliani* et al. 1969a, b). Recordings were obtained from single fibers isolated from the left third thoracic ramus communicans (T3), which is known to contribute to the innervation of the heart (*Bronk* et al. 1936; *Pannier* 1946; *Randall* et al. 1957). As the reflex response was present in animals with the vagi and spinal cord cut, a cardiocardiac spinal sympathetic reflex was proposed, the afferent and efferent pathways of which were both in the sympathetic nerves. However, the reflex was also present in animals with intact neuraxes and in unanesthetized decerebrate preparations: in cases where the baroreflex could be operative, the increased sympathetic discharge occurred in absence of any decrease in arterial pressure. In the section on human pathophysiology (p. 63–65), the potential importance of this reflex will be discussed.

From a historical point of view, there was little in the literature to indicate that an excitory reflex could be elicited from the heart through an afferent sympathetic limb.

In 1940, *De Waele* and *Van De Velde* (1940) claimed that cardiac receptors, activated by reduced venous return, could mediate a hypertensive reflex. Although their analysis of the mechanical or chemical stimuli capable of inducing the phenomenon was largely inadequate, they still made the remarkable observation that a mechanical manipulation of the heart could produce a hypertensive response which was probably reflex in nature as its afferent limb could be interrupted by sectioning the higher thoracic dorsal roots. Subsequently, *Taquini* and *Aviado* (1961) found that a partial occlusion of the pulmonary artery could increase pulmonary blood flow. The increased flow was present after vagotomy and in spinal animals and appeared to depend on intact sympathetic innervation.

To the best of my knowledge this was the scanty experimental evidence, before our own observations, on the possibility of eliciting excitatory reflexes from the heart, through afferent sympathetic fibers. Recently, however, *Felder* and *Thames* (1979, 1981) questioned the existence of the reflex described by *Malliani* et al. (1969a, b), which, in their opinion, is present only in animals submitted to a spinal section. These findings are worth detailed analysis in view of their overall relevance to the reflexes mediated by sympathetic afferent fibers and because of more general methodological implications.

In the first paper by *Felder* and *Thames* (1979) the specific search for an excitatory reflex mediated by cardiac sympathetic afferent fibers was carried out on dogs after acute sino-aortic denervation and vagotomy: this procedure was likely to have increased sympathetic activity near to a maximal level (the heart rate was 220 beats/min) a point accepted and discussed in the paper. Nevertheless in 1980 I suggested that these high baseline levels of sympathetic efferent activity prevented the observation of an excitatory reflex: indeed, careful analysis of their published data makes it clear that they sometimes observed an excitatory response after sino-aortic denervation and vagotomy (*Felder* and *Thames* 1979, Fig. 3). In those animals in which an excitatory response was detectable, the heart rate was lower and it is possible therefore that their baseline conditions had a less abnormally enhanced level of sympathetic activity. However, the authors were concerned about the level of the baseline sympathetic activity and accordingly performed a new series of experiments (*Felder* and *Thames* 1981). The influence of the cardiac sympathetic afferent fibers on changes in sympathetic discharge to the heart during coronary occlusion was studied in dogs with an intact or interrupted neuraxis. In experiments on dogs with an intact neuraxis, basal activity in the cardiac sympathetic nerves was maintained at moderate or low levels by increas-

ing the perfusion pressure in both carotid sinuses. It was concluded that an excitatory cardiocardiac sympathetic reflex can be demonstrated in dogs with the spinal cord sectioned but not with spinal cord intact. More explicitly it was suggested that cardiac sympathetic afferent fibers are not likely to mediate reflexes during myocardial ischemia in humans and therefore a classical and exclusive nociceptive function was the most appropriate role for sympathetic afferent fibers.

However, the following comments should be considered:

1. An increased carotid sinus pressure could not only decrease the control sympathetic efferent discharge but severely depress the mediation of the reflexes either at a presynaptic or interneuronal level, similar to that known to be exerted on somatic reflexes when inhibitory supraspinal structures are activated (*Carpenter* et al. 1966; *Engberg* et al. 1968a, b).

2. Recordings from the whole ventrolateral cardiac nerve may not be a sensitive method of detecting excitation of sympathetic fibers as the cardiac sympathetic outflow is not excited as a whole (*Malliani* et al. 1969a, b).

Moreover, the recent additional experimental findings are relevant. *Weaver* and her co-workers (1981) have recently published a study carried out on anesthetized cats using a carefully controlled protocol. Sympathetic and/or vagal cardiac afferent fibers remained intact while arterial baroreceptors were either left intact or denervated; a multifiber efferent sympathetic activity was recorded from the renal nerves. It was clearly shown that cardiac sympathetic afferent fibers can have excitatory influences on renal sympathetic efferent nerve activity and on arterial blood pressure during myocardial ischemia, and that this excitatory influences opposed the inhibitory respones mediated by cardiac vagal afferent fibers.

Quite independently *Lombardi* et al. (1981a) studied cats on which a sino-aortic denervation had been performed 1 week before the experiment: the sympathetic efferent activity was recorded from fibers isolated from T3 (Fig. 18) with a nearly normal discharge under baseline conditions. In all cats occlusion of the left anterior descending coronary artery produced a significant increase in sympathetic cardiac efferent impulse activity; after vagotomy a similar coronary occlusion produced, in addition, a significant increase in left ventricular pressure, LVdP/dt, and mean arterial pressure (Fig. 18a). These responses were abolished by interruption of cardiac sympathetic afferent fibers (Fig. 18b). Such positive findings cannot be ignored.

The finding of a cardiocardiac sympathetic reflex (*Malliani* et al. 1969a, b) raised the more general problem of whether the natural hemodynamic events could also elicit sympathetic reflexes in spinal animals.

Numerous reports, starting with *Sherrington*'s observations (1906), indicated the existence of vasomotor and sympathetic responses in experimental spinal animals (*Langley* 1924; *Brooks* 1933, 1935; *Heymans* et al.

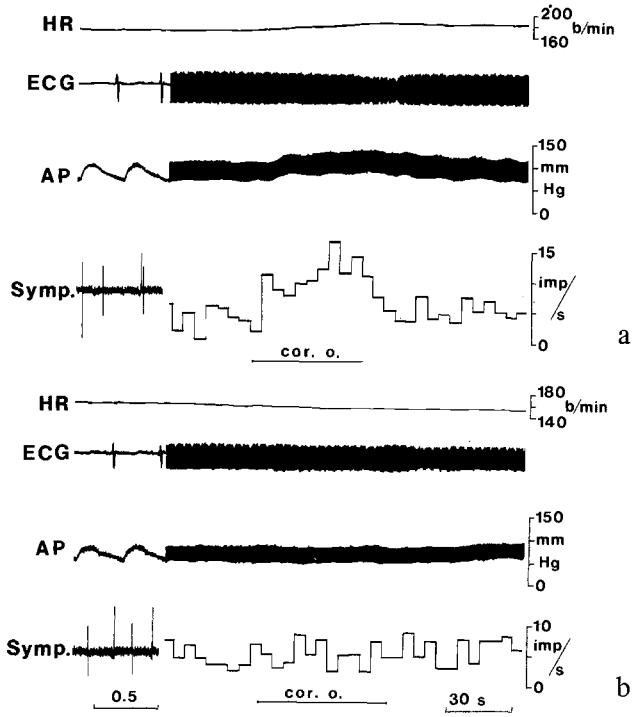

Fig. 18a,b. Effects of occluding the left anterior descending coronary artery in a vagotomized cat. Sino-aortic denervation had been performed 1 week before. Between **a** and **b** the left stellate ganglion and the left thoracic sympathetic chain were removed down to T4, thus producing a partial "sympathetic deafferentation" that, however, was sufficient for the interruption of the afferent limb of the reflex. Tracings from top to bottom are the heart rate, the ECG, the arterial pressure, the impulse activity recorded from a multifiber preparation obtained from the left T3. (From *Lombardi* et al. 1981a, unpublished work)

1936; *Alexander* 1945; *Kuntz* 1945; *Downman* and *McSwiney* 1946; *Richins* and *Brizzee* 1949; *Murkherjee* 1957; *Beacham* and *Perl* 1964; *Franz* et al. 1966; *Beacham* and *Kunze* 1969) and in paraplegic men (*Guttmann* and *Whitteridge* 1947). However, in spite of these descriptions it was not generally appreciated that spinal sympathetic centers may react reflexly in response to natural hemodynamic events, such as changes in blood pressure. The only suggestions for the existence of spinal vasomotor and sympathetic reflexes elicited by arterial pressure changes were to be found in accounts by *Heymans* et al. (1936) and, more recently, by *Fernandez de Molina* and *Perl* (1965); however, in both studies the reflex nature of these responses was not properly defined.

In our experience (*Malliani* et al. 1971a) we found that when increases in systemic arterial pressure were produced in spinal vagotomized cats, the impulse activity of single preganglionic sympathetic fibers in T3 was either

excited or decreased. The type of response was consistent for each individual fiber and was always reflex in nature. When, however, the increases in pressure were restricted to the coronary circulation, by changing the flow of a perfusing pump (Fig. 1) the preganglionic and postganglionic sympathetic discharge to the heart was always excited (*Malliani* and *Brown* 1970; *Brown* and *Malliani* 1971).

We subsequently designed a series of experiments (*Pagani* et al. 1974) in order to analyze specifically the excitatory and inhibitory components of spinal reflexes: the activity of preganglionic sympathetic fibers isolated from T3 was tested during various hemodynamic and mechanical events in spinal vagotomized cats. Small rubber balloons mounted on catheters were inserted into the thoracic portions of the inferior vena cava and of the aorta, in the infundibular region of the left ventricle: these balloons could be inflated to obstruct blood flow. In addition, the pulmonary artery or

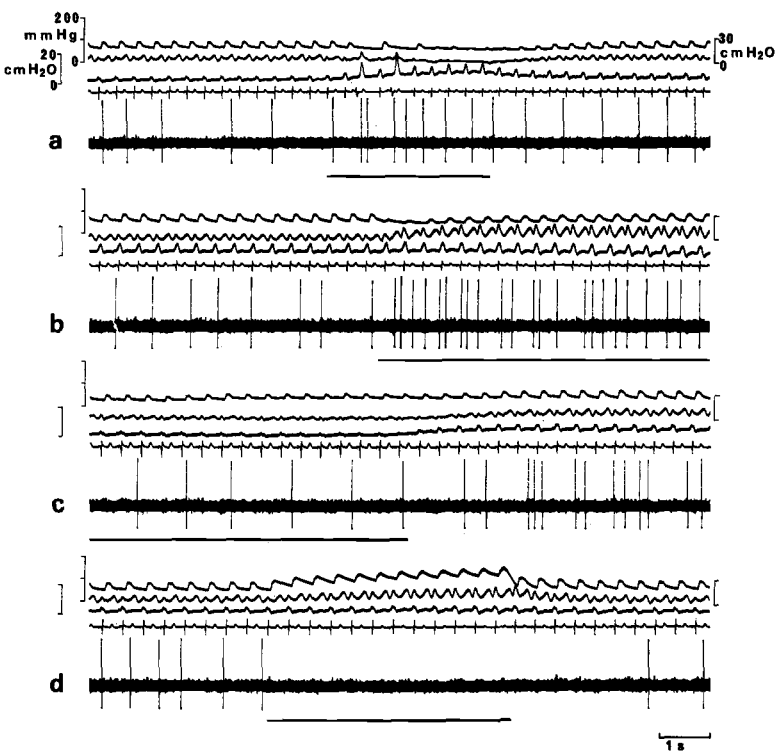

Fig. 19a–d. Increases or decreases in the discharge of the same sympathetic preganglionic neuron obtained with different stimuli. Tracings represent, from top to bottom, the carotid arterial blood pressure, the left atrial pressure, the right atrial pressure, the ECG and the nervous recording. a Stenosis of the pulmonary artery by a snare; **b** obstruction of the left ventricular outflow by inflating a balloon in the root of the aorta; c release of a transient occlusion of the inferior vena cava; **d** obstruction of the midthoracic aorta by a snare. Spinal vagotomized cat. (From *Pagani* et al. 1974)

the aorta could be constricted by using snares. In these experiments it was found that when the stimuli were applied to the heart, thus eliciting possible cardiocardiac reflexes, an excitatory response was the rule (Figs. 19a–c, 22). Conversely, when the stimuli simultaneously affected cardiac and vascular receptors (rises in arterial pressure), the discharge of the same fibers was either increased or decreased (Fig. 19d). A cannula consisting of a stainless steel tube surrounded by an inflatable rubber cylinder was used to stretch the walls of the thoracic aorta without interfering with aortic blood flow (Fig. 20). In this manner it was possible to excite selectively aortic mechanoreceptors with a physical stimulus whose effect on

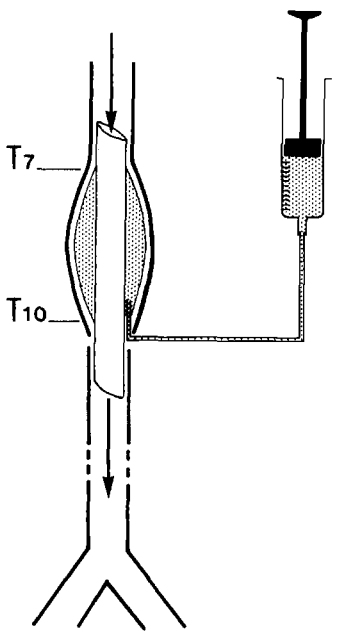

Fig. 20. Schema of a cannula, consisting of a stainless steel tube surrounded by an inflatable rubber cylinder, used to stretch the walls of the thoracic aorta without interfering with aortic blood flow

aortic walls was the same as an increase in mean aortic pressure. The reflex responses of each preganglionic sympathetic neuron were either excitatory or inhibitory (Fig. 21), and they were consistent and in the same direction as observed during the increases in systemic arterial pressure. It was thus obvious that receptors located in various cardiovascular sites could exert different reflex effects on the same sympathetic preganglionic neuron.

We therefore advanced the hypothesis that a prevalence of excitatory mechanisms existed in sympatho-sympathetic reflexes in which input and output were circumscribed to a few spinal segments, e.g., cardiocardiac reflexes, while inhibitory mechanisms were present in the reflexes involving more spinal segments, e.g., aorto-cardiac reflexes (Fig. 22). It is also possible that the specific activation of a population of afferent sympathetic

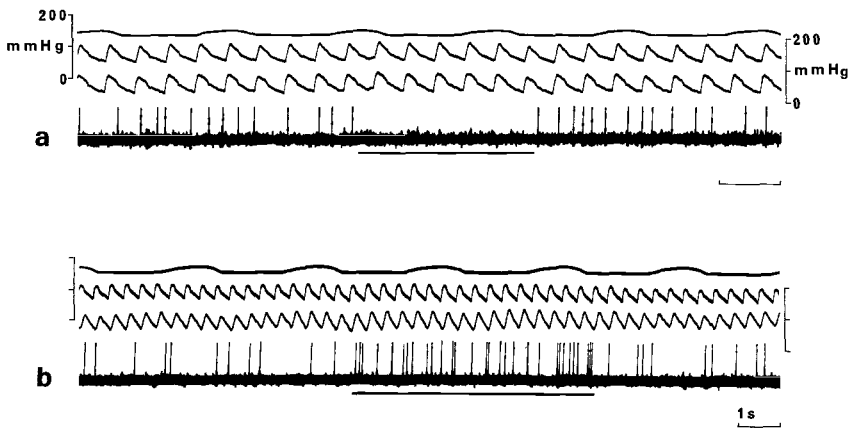

Fig. 21a, b. Effects of stretching the aortic walls (with the aortic cannula) on the discharge of two different (a and b) sympathetic preganglionic neurons. Tracings represent, from top to bottom, the endotracheal pressure (inflations upwards), the carotid and femoral arterial blood pressure, and the nervous recordings. Spinal vagotomized cat. (From *Pagani* et al. 1974)

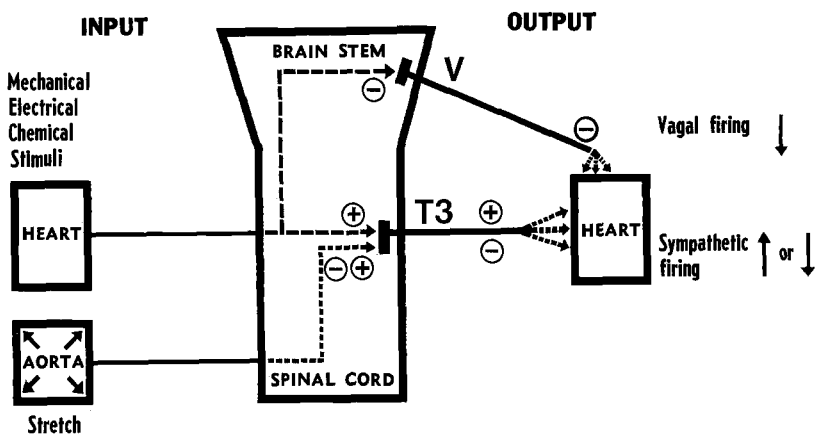

Fig. 22. Reflex responses of sympathetic and vagal efferent neurons elicited by the stimulation of afferent sympathetic fibers. Scheme derived from electrophysiological experiments. (From *Malliani* et al. 1975a)

fibers, i.e., the myelinated or the nonmyelinated ones, may also modulate the excitatory and inhibitory reflex components.

Electrical or chemical stimulation of afferent cardiac sympathetic fibers was found to elicit a simultaneous inhibition of vagal efferent fibers and an excitation of sympathetic efferent fibers, both directed to the heart and isolated from the same cardiac nerve at its junction with the right atrium (*Schwartz* et al. 1973). This sympathovagal reflex (Fig. 22) represented a total overturning of the classic vagosympathetic circuitry. More-

over, these electrophysiological experiments suggested a synergistic excitatory effect on cardiac function mediated through an excitatory sympathetic reflex and a reduction in vagal restraint.

Peterson and *Brown* (1971) were the first to assess the functional significance of reflexes mediated by sympathetic afferent fibers: they found a reflex increase in arterial pressure elicited by electrical stimulation of afferent cardiac sympathetic fibers. Subsequently it was found that similar electrical stimulations reflexly induced an increase in myocardial contractility (*Malliani* et al. 1972a), heart rate (*Malliani* et al. 1973a), and aortic smooth muscle tone (*Pagani* et al. 1975). In particular, when the increases in myocardial contractility could be induced with intracoronary injections of veratridine (*Malliani* et al. 1972a), conclusive evidence was obtained on the existence of cardiocardiac sympathosympathetic reflexes. *Staszewska-Barczak* et al. (1976), on the other hand, were able to demonstrate clearly the existence of excitatory cardiovascular reflexes elicited by the epicardial application of bradykinin and mediated by cardiac sympathetic afferent fibers.

However, it still had to be proved that cardiovascular reflex responses could be elicited by natural stimulation of sympathetic mechanoreceptors. The observation that numerous sympathetic sensory endings could be identified in the walls of the thoracic aorta by their function and that a stretch localized to a segment of it could reflexly modify the activity of sympathetic preganglionic neurons (*Pagani* et al. 1974) seemed to offer a possible solution to this problem. A similar aortic cannula (Fig. 20) was used: in spinal vagotomized cats or in cats with an intact central nervous system but with sino-aortic denervation, stretch of the thoracic aorta, which did not interfere with aortic blood flow, induced significant increases in arterial blood pressure, heart rate, and maximum rate of increase in left ventricular pressure (Fig. 23a) (*Lioy* et al. 1974). These responses were eliminated by infiltrating the wall of the thoracic aorta with xylocaine. In the adrenalectomized cats with intact central nervous system, reflex responses were reduced but were still statistically significant. Phenoxybenzamine abolished the pressor response but not the increases in heart rate and dP/dt max. Propranolol drastically reduced the increases in heart rate and dP/dt max but not the pressor response (Fig. 23b). Thus, aortic stretch induced an increase in sympathetic nerve efferent activity affecting the heart, the peripheral vessels, and probably the adrenal glands through a reflex present in animals with intact central nervous system and with a spinal section.

Several other reports have defined responses which are mediated by sympathetic afferent fibers. *Weaver* (1977) found that low-frequency electrical stimulation of cardiopulmonary sympathetic afferent fibers could reflexly decrease the arterial blood pressure and efferent impulse

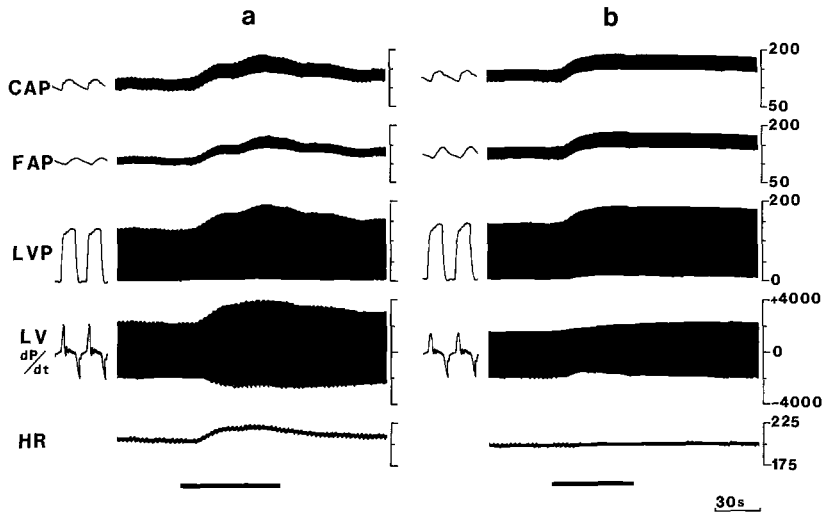

Fig. 23a, b. Effects of stretching the thoracic aorta in a vagotomized cat with an intact central nervous system and both common carotid arteries occluded. *CAP* carotid artery pressure (recorded proximal to the point of occlusion). *FAP* femoral artery pressure. *LVP* ventricular pressure (all in mmHg). *LV dP/dt* rate of change of left ventricular pressure (mmHg/s). *HR* heart rate (beats/min). On the left of each section are fast-speed records of each variable. The aortic stretch is indicated by a bar. **a** Control; **b** after administration of propranolol (1 mg/kg, i.v.). (From *Lioy* et al. 1974)

activity in renal nerves; both effects were reversed to an excitation by increasing the frequency of the stimulating pulses. *Purtock* et al. (1977) similarly found that low-frequency stimulation of thoracic sympathetic afferent fibers induced renal vasodilation, while high-frequency stimulation induced renal vasoconstriction. Hence these reports confirm that it is also possible to elicit reflex inhibitory effects which are mediated by sympathetic afferent fibers.

The experiments summarized above demonstrate that afferent sympathetic nerve fibers can mediate cardiovascular reflexes. However, as to their physiological significance, we realized that most responses were obtained in anesthetized animals in which the buffering influences exerted by vagal and carotid sinus afferent fibers no longer existed. It was totally unproven whether such reflexes could exist in the fully innervated animal and whether a substantial activation of the cardiovascular sympathetic afferent fibers could occur in the conscious state in the absence of pain.

6.2 Chronic Experiments

In order to achieve some perspective on the natural role of excitatory reflexes there was a need for models that could reveal, in the unanesthetized

state and possibly in the presence of an intact innervation, functioning cardiovascular reflexes mediated by sympathetic afferent fibers.

The first model (*Malliani* et al. 1975a; *Bishop* et al. 1976) consisted of cats with a chronic spinal section performed at the level of the eighth cervical segment (Fig. 24), breathing spontaneously, and with normal arterial pressure. In these animals the cardiac innervation consisted of two independent loops, one vagovagal and one sympathosympathetic. Atropine (0.5–0.7 mg/kg) was administered i.v. to block the outflow of the vagal loop. Due to the chronic spinal section, the sympathetic efferent tonic activity was presumably low as suggested by the mean baseline heart rate (109 beats/min) and, after atropine, 127 beats min. Under these conditions, i.v. infusion of saline (50–150 ml) over a period of 2–5 min resulted in a significant tachycardia (Fig. 25a): the maximal increase observed was 22 beats/min, while the average was 10 beats/min. A section of thoracic dorsal roots T 1–6 and of the spinal cord between T6 and T7 abolished the response (Fig. 25b), thus proving that it was reflexly mediated through sympathetic afferent fibers.

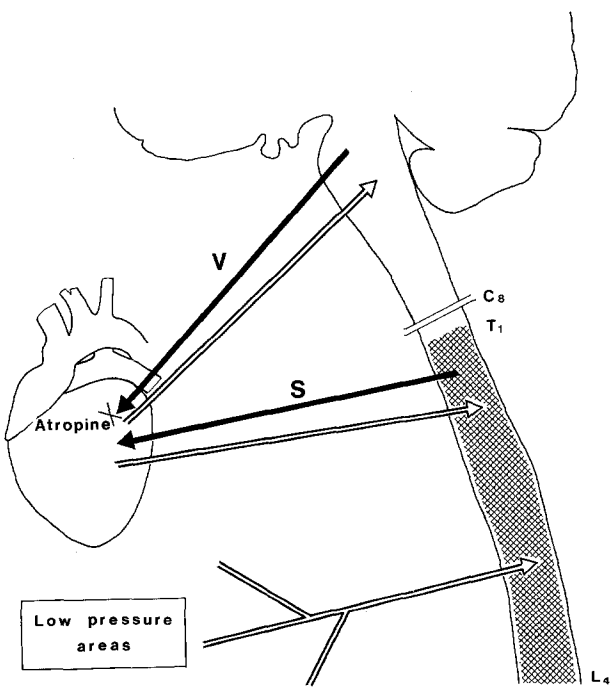

Fig. 24. Schema of the animal model used in the experiments by *Malliani* et al. (1975a) and *Bishop* et al. (1976). A chronic spinal section was performed at the level of the eighth cervical segment; atropine was administered to block the vagal outflow. The cardiac innervation with a possible reflex function was thus restricted to a sympathosympathetic loop

A tachycardia evoked by i.v. infusions and thought to be reflexly mediated by sympathetic afferent fibers was also described in anesthetized dogs (*Gupta* 1975; *Gupta* and *Singh* 1977). Thus the increase in heart rate following infusions first described by *Bainbridge* (1915) appears to be mediated at least in part by afferent sympathetic fibers. Such a reflex mechanism may play an important role in the course of congestive heart failure.

Intravenous infusion could activate many different cardiovascular sympathetic mechanoreceptors although those innervating the atria (Fig. 3) and the pulmonary veins (Fig. 17), i.e., low pressure areas, were likely to be involved. On the other hand, it is also clear that in intact animals an i.v. infusion may reflexly modify the cardiac frequency, through sympathosympathetic, sympathovagal, vagosympathetic (*Linden* 1979), and

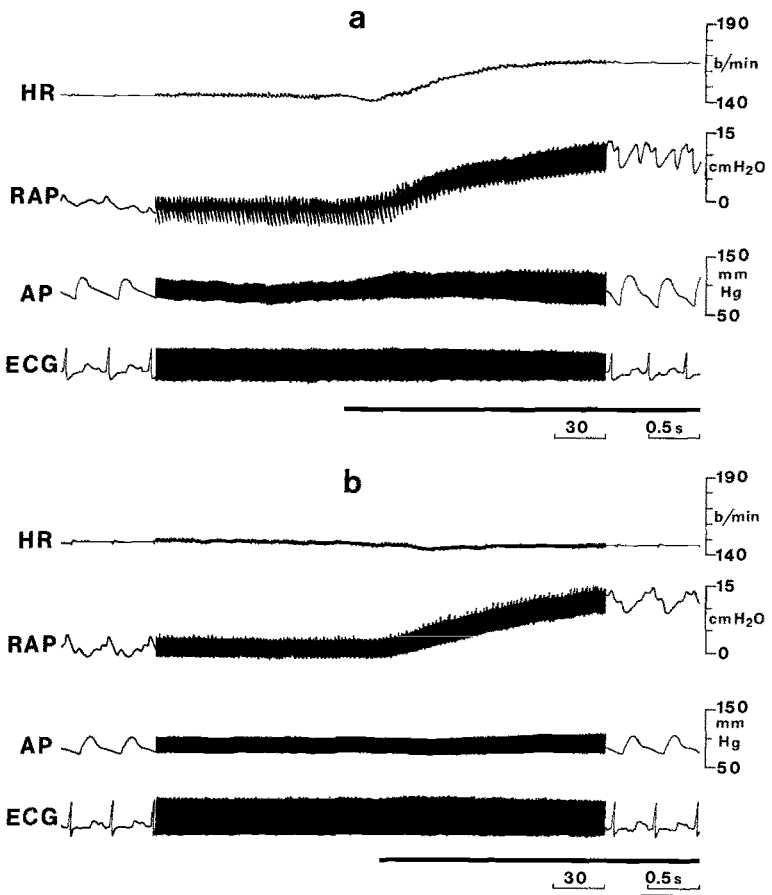

Fig. 25a, b. Analogue recording of heart rate (*HR*), right atrial pressure (*RAP*), arterial pressure (*AP*), and electrocardiogram (*ECG*) in chronic spinal cat in control conditions and during i.v. infusions. **a** Sham preparation (dorsal roots T_1–T_6 isolated but not cut); **b** after section of dorsal roots T_1–T_6 and of spinal cord between T_6 and T_7. Recordings in **b** were obtained 36 h after those shown in **a**. Infusions indicated by bars. (From *Bishop* et al. 1976)

vagovagal circuits. This complexity is easily illustrated by the effects of anesthesia on the reflex heart rate response: from a consistent tachycardia response in unanesthetized animals (*Horwitz* and *Bishop* 1972) one may observe either tachycardia or bradycardia depending on the initial heart rate (*Coleridge* and *Linden* 1955; *Jones* 1962) during anesthesia.

Apart from these considerations, the experiments described above (*Bishop* et al. 1976) were the first to demonstrate that a natural hemodynamic stimulus could elicit a reflex cardiovascular response through a sympathosympathetic circuit in the unanesthetized animal. However, the presence of a chronic spinal section was an important disadvantage when evaluating the significance of this reflex and its interplay with other regulatory mechanisms.

A second model has also been used and consisted of stretching a short segment of the thoracic aorta, without obstructing the aortic flow, in a conscious dog with an intact cardiovascular innervation. In the initial experiments (*Malliani* et al. 1979) a metal cannula covered by a rubber cylinder, similar to that used in acute experiments (Fig. 20) was implanted. Subsequently (*Pagani* et al. 1980, 1982) a Teflon stiff core was employed for the cannula which allowed the use of an ultrasound technique using piezoelectric crystals to measure external aortic diameter during control conditions and during the stretch. Catheters for pressure recordings, piezoelectric crystals, and the aortic cannula were all implanted under general anesthesia and aseptic conditions.

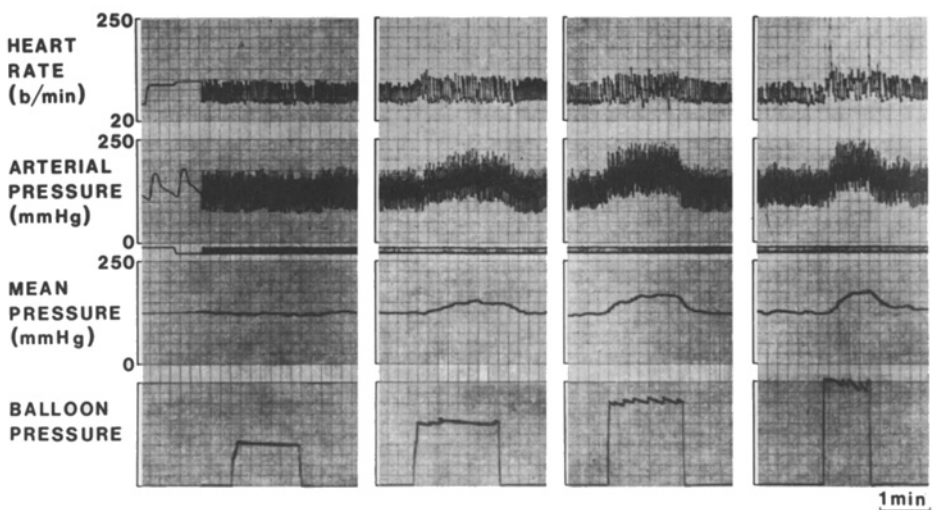

Fig. 26. Effects of a progressively increasing aortic stretch on arterial pressure and heart rate in a conscious dog. The distending balloon pressure, which obviously does not correspond to the pressure effectively applied to the aortic walls, is displayed in the bottom tracing as an index of the progressive stretch. (From *Malliani* et al. 1979)

After recovery from surgery, aortic diameter was increased 9.6% ± 0.4% from 16 ± 1 mm by inflating the implanted cannula. This stretch, which did not evoke behavioral changes or any overt pain reaction, produced a rise in mean aortic pressure of 31% ± 3% from 100 ± 3 mmHg and an increase in heart rate of 20% ± 3% from 91 ± 3 beats/min ($P < 0.01$) (*Pagani* et al. 1982).

An example of these pressor reflexes is shown in Fig. 26; once a threshold level was exceeded, progressive increases in arterial blood pressure were obtained by augmenting distension. Alpha-adrenergic receptor blockade (phentolamine, 0.5–1 mg/kg body weight i.v.) abolished the arterial pressure response (Fig. 27). The reflex tachycardia was prevented by combined muscarinic and β-adrenergic receptor blockade (atropine 0.2–0.3 mg/kg and propranolol 1 mg/kg, i.v.). The reflex nature of the response was, therefore, proven.

The possibility that this sympathetic reflex might interact with baroreceptor mechanisms was also investigated, because such an interplay was

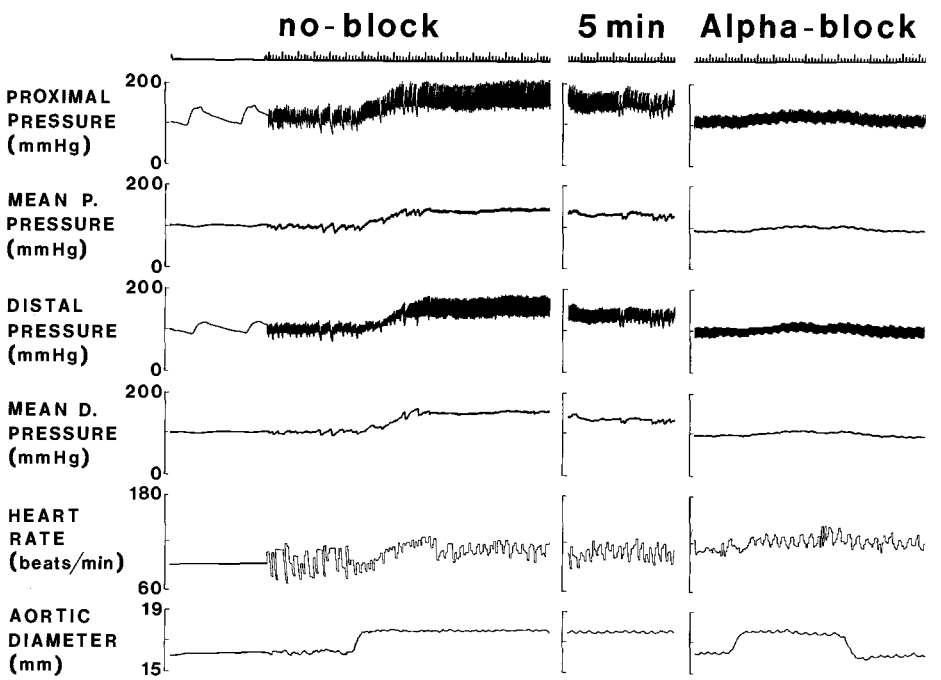

Fig. 27. Pressor and heart rate responses to stretch of the descending thoracic aorta in a conscious dog. The initiation of aortic stretch (*left panel*) is indicated by the increase in aortic diameter. Notice the similar increase in both proximal and distal pressures, indicating the lack of direct mechanical obstruction to blood flow by aortic distension. After 5 min (*middle panel*), the pressor and heart rate responses were still maintained. Alfa-adrenergic blockade (phentolamine 1 mg/kg) (*right panel*) virtually abolishes the pressor response to aortic stretch, while an increase in heart rate is still present. (From *Pagani* et al. 1982).

suggested by a previous electrophysiological study (*Schwartz* et al. 1973). The slope of the regression of the electrocardiographic R-R interval on the systolic pressure increase induced by phenylephrine (50 μg/kg i.v.) was used as an index of baroreceptor sensitivity (*Smyth* et al. 1969).

Aortic stretch produced a significant reduction in baroreflex sensitivity (57% ± 7% from 18 ± 2 ms/mmHg, $P < 0{,}01$). Additionally, the arterial pressure response increased after carotid nerve section and vagotomy to 49% ± 8% (*Pagani* et al. 1982). This observation not only confirmed that the afferent limb of the reflex was in the sympathetic nerves but also indicated that the baroreceptive and vagal afferent fibers were likely to play a restraining role. In Sect. 7, the possible significance of this pressor reflex will be analyzed further.

In the third model (*Pagani* et al. 1981), we resorted to the intracoronary administration of bradykinin in the conscious dog. As described above, bradykinin produces marked activation of cardiac sympathetic afferent fibers (*Uchida* and *Murao* 1974d; *Nishi* et al. 1977; *Coleridge* et al. 1978; *Baker* et al. 1980; *Lombardi* et al. 1981b) and in addition it substantially excites afferent cardiac vagal nonmyelinated fibers (*Kaufman* et al. 1980). Catheters were inserted in the aorta and either the left circumflex or anterior descending coronary artery. A Doppler flow probe was also inserted around the same coronary artery for blood flow determinations and a solid state pressure gauge into the left ventricle (*Pagani* et al. 1981). Preliminary data indicated that bradykinin (100 ng/kg) injected into the cannulated coronary artery 1–2 weeks after surgery induced in the conscious animals a significant ($P < 0.01$) increase in mean arterial pressure (31% ±. 3% from 85 ± 2 mmHg), in heart rate (34% ± 3% from 84 ± 9 beats/min), as well as in left ventricular pressure, left ventricular dP/dt max (33%), and coronary blood flow. These changes were obtained in the absence of overt pain reactions and were also present after pretreatment with morphine (1 mg/kg, i.v.). The reflex nature of the blood pressure change was shown by its disappearance after α-adrenergic receptor blockade with phentolamine (1 mg/kg, i.v.). Thus a pressor sympathetic reflex can be obtained in the conscious state from a fully innervated heart.

In other studies on anesthetized animals, the intracoronary administration of bradykinin produced depressor reflexes (*Neto* et al. 1974) or either pressor or depressor reflexes (*Reimann* and *Weaver* 1980; *Lombardi* et al. 1982): the depressor component is mediated by vagal afferent fibers. These facts clearly indicate the fundamental role played by anesthesia, when several neural circuits are simultaneously activated, in determining the final response.

In general it also appears that the concept, derived from experiments using veratridine in anesthetized animals (*Von Bezold* and *Hirt* 1867), that a chemical stimulus applied to the neurally intact heart always elicits a

vagally mediated depressor response and that vagotomy is necessary (*Coleridge* and *Coleridge* 1979) to reveal pressor sympathetic reflexes is no longer tenable (*Pagani* et al. 1981). In the conscious state, it can be concluded that excitatory reflexes evoked by bradykinin and mediated by sympathetic afferent fibers usually predominate.

In investigations into the algogenic action of bradykinin, larger doses (300–600 ng/kg) were injected into the cannulated coronary artery without eliciting pain reactions (*Pagani* et al. 1981). It is possible that some recent surgical injury, absent in our experimental conditions, may greatly facilitate the algogenic action of bradykinin (*Guzman* et al. 1962). However, the absence of pain reactions in our chronic experiments was surprising. I would suggest that visceral pain is more likely to result from the extreme activation of a spatially very restricted population of afferent sympathetic fibers (as it may occur during the localized mechanical abnormalities accompanying acute myocardial ischemia). Conversely, when activation of the sympathetic afferent fibers is widely distributed, some central inhibitory modulation (*Wall* 1976) may prevent pain mechanisms. Indeed, a systemic increase in arterial blood pressure produces a very substantial and widespread increase in the activity of cardiovascular sympathetic afferent fibers. Yet, in humans a marked increase in systemic arterial pressure is not painful, although it is often accompanied by some discomfort. In short, the intracoronary injection of bradykinin would produce a widespread activation of the cardiac sympathetic afferent fibers and thus not elicit pain. This hypothesis can be tested experimentally, although pain is a conscious experience which can be explored only indirectly with our laboratory animals.

Thus we have obtained substantial evidence that excitatory cardiovascular reflexes can take place in animals with an intact innervation and that a significant activation of cardiovascular sympathetic afferent fibers can occur, in the conscious state, in the absence of pain.

Finally it should be noted that the experiments on coronary occlusion in unanesthetized animals have not yet provided a clear answer on the possible role played by reflexes mediated by sympathetic afferent fibers. This uncertainty probably reflects the complexity of the experimental situation created by coronary occlusion: apart from the striking alterations in ventricular function (*Pagani* et al. 1978), myocardial ischemia can excite both sympathetic and vagal (*Recordati* et al. 1971; *Thoren* 1979) receptors. Thus, pressor and depressor reflexes could be activated from the heart simultaneously and, to a variable extent, both could interact with baroreflexes. In practice it was found that brief occlusion of the left circumflex coronary artery produced a rise in heart rate, a modest but significant fall in arterial pressure, and a slight increase in peripheral resistance (*Peterson* et al. 1973; *Peterson* and *Bishop* 1974). It was shown

that the tachycardia was due both to an arterial baroreflex and to a reflex from the heart: however, the afferent pathway from the heart was not investigated directly. In another study (*Bishop* and *Petersen* 1978), it was demonstrated that cardiac vagal afferent fibers mediate depressor reflexes from the heart during coronary occlusion. On the other hand, in the unanesthetized monkey, the occlusion of the distal part of the left anterior descending coronary artery elicited an increase in arterial pressure, heart rate, and LVdP/dt (*Randall* et al. 1978).

It is clear that much more work is needed to unravel the complex interactions of the various reflex mechanisms accompanying acute myocardial ischemia in the conscious fully innervated animal.

7 The Positive Feedback Hypothesis

The common observation that arterial blood pressure in a resting man or in anesthetized animals is relatively constant and that powerful reflexes tend to counteract changes in pressure, provided the most factual basis to the teleologic concept of circulatory homeostasis. Accordingly, the sinoaortic negative feedback control system has been regarded for decades as the indisputable leader of this homeostasis. It was not until 1959 that an authoritative academic voice, that of *Bard* (1960), asserted in the opening lecture of an international symposium that suprabulbar influences must inhibit baroreceptor function when an organism has to maintain an elevated heart rate in the face of an increased arterial pressure, as happens during periods of stress or exercise. *Moruzzi* (1940) had already shown that carotid sinus reflexes could be inhibited by stimulation of anterior vermis of the cerebellum. It was, however, only the subsequent progressive exploration into the hemodynamic conditions occurring during exercise or emotion (*Rushmer* et al. 1960; *Bergamaschi* and *Longoni* 1973; *Vatner* and *Pagani* 1976) that revealed that the negative feedback baroreflexes could change to such an extent (*Bristow* et al. 1971; *Coote* et al. 1971; *Smith* 1974; *Vatner* and *Pagani* 1976) that they become sometimes quite permissive by standers in those circulatory "storms" (*Lewis* 1931).

As for the mechanisms through which baroreflexes could be attenuated, early attention was paid to the suprabulbar structures (*Hilton* 1966; *Smith* 1974). Subsequently it was realized that the mechanisms inhibiting the baroreflexes could be activated also from the periphery, through vagal (*Vatner* et al. 1975) or somatic (*Kumada* et al. 1975) afferent nerve fibers. These mechanisms could provide an explanation for the variable efficacy

of baroreflexes; however, the strategy of regulation through neural circuits would still be based exclusively on negative feedback operational systems.

Our experimental data suggest an additional possibility. In an open loop model (Fig. 28, upper part) a stimulus likely to mimic the effects of an increase in mean aortic pressure on aortic mechanoreceptors, i.e., an aortic stretch, elicited an increase in systemic arterial pressure (and heart rate) through a sympathosympathetic reflex. This is indicated by the positive sign for this feedback mechanism, as opposed to the negative feedback characteristics of the baroreflexes (Fig. 28, lower part).

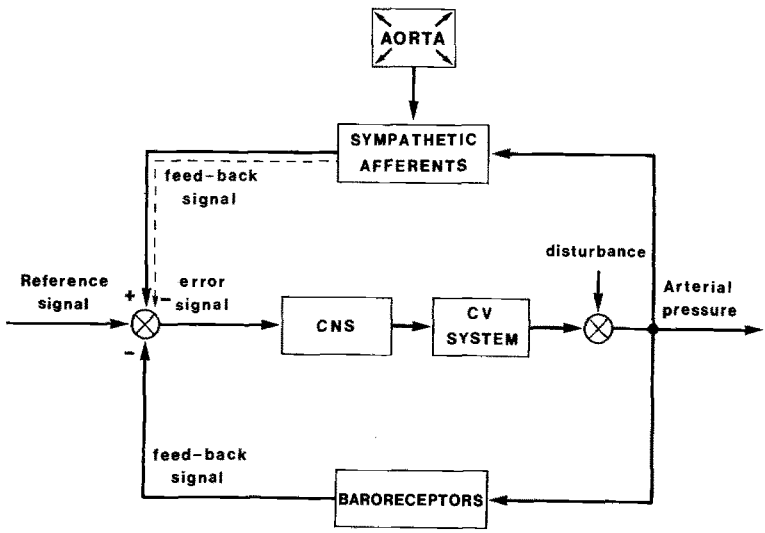

Fig. 28. Schema of suggested mechanisms underlying nervous control of arterial blood pressure regulation. Baroreceptors are indicated as the example of receptors that activate negative feedback mechanisms. The coexistence of inhibitory components in reflexes mediated by sympathetic afferent fibers is represented by the broken line. *CNS* central nervous system; *CV* cardiovascular. (From *Malliani* et al. 1979)

We hypothesize that these positive feedback reflexes are tonically operative for two reasons: firstly, aortic sympathetic mechanoreceptors have a spontaneous impulse activity at normal arterial pressures (*Malliani* and *Pagani* 1976); secondly, the amount of aortic stretch necessary to initiate a pressor reflex produces an increase in aortic diameter that is comparable to that which accompanies rises in arterial pressure within the physiological range (*Pagani* et al. 1980, 1982). One consequence of this is the problem of the normal function of these excitatory reflexes. By the Darwinian hypothesis, of no less value in physiology than in morphology, every reflex must be purposive. But the assignment of a particular purpose

to a particular reflex is often difficult and hazardous (*Woodworth* and *Sherrington* 1904).

The positive feedback reflexes (*Malliani* et al. 1975b, 1979) should be considered as one component of those complex regulatory mechanisms which result from the interplay of multiple and independent peripheral loops and of multifarious possibilities of central integration. In the resting or anesthetized state, the supraspinal structures are likely to exert a restraining influence on these reflexes (*Lioy* and *Szeto* 1975; *Pagani* et al. 1982). It should also be kept in mind that reflexes mediated by sympathetic afferent fibers possess inhibitory components as well (*Pagani* et al. 1974) (Fig. 28). In brief, the negative feedback mechanisms frequently seem to act as the effective controllers of the overall cardiovascular regulation. However, even in these cases, positive feedback mechanisms could play a regulatory role in modulating the range of operation and stability of supraspinal cardiovascular reflexes. In this regard, it should be recalled that the sensitivity of negative feedback baroreceptive control of heart rate could be markedly reduced during aortic stretch (*Malliani* et al. 1979; *Pagani* et al. 1982). Similarly, baroreflex control of heart rate was decreased during coronary occlusion (*Takeshita* et al. 1980). Thus, excitation of cardiovascular sympathetic afferent fibers is likely to modulate the activity of the structures that integrate baroreflexes through ascending pathways.

In conclusion, in resting conditions positive feedback reflexes may behave discreetly while participating in the fine tuning of homeostasis. On the other hand, there are physiological conditions, such as exercise or emotion, in which the efferent sympathetic activity seems to be unrestricted. If a reflex must be purposive, an animal running away from a predator would find positive feedback mechanisms quite well suited for its goal. Conversely, pathophysiological states often suggest an involvement of mechanisms that are purposeless or even detrimental when their physiological function is removed: thus teleologic reasoning is not productive. Arterial hypertension as a disturbance of regulation could, especially in its early phases, partly be the result of an increased sympathetic efferent activity. This increase, according to our hypothesis, may depend not only on an augmented central command but also on the peripheral action of sympathosympathetic loops exhibiting positive feedback characteristics. In fact, the mechanisms producing a sustained increase in sympathetic efferent activity may be similar to those in the decerebrate animal that are responsible for spasticity: *Sherrington* (1906) found that spasticity is removed by deafferentation. It was thus shown that an augmented central command was incapable in itself of causing a sustained increase in the postural tone but that a peripheral loop was necessary for its maintenance.

In brief, we suggest that negative and positive feedback mechanisms may interact continuously to achieve the most adequate regulation for the

various cardiovascular performances: if this is the case each specific hemodynamic condition, even those corresponding to the most stable resting states, would reflect some degree of interaction of opposite tendencies, a biological example of a true dialectic process.

In paraplegic patients, cardiovascular sympathetic reflexes seem often to possess a savage power (*Corbett* et al. 1971a–c), which perhaps indicates the full potential of the system.

"The phenomena of disease are thought to be purely adventitious; they are spoken of as 'pathological', and are supposed to bear no relation, even remotely, to any mode of response which has previously existed in the individual or the race". "Normally. . . (the more primitive responses) are suppressed because they would disturb the more discriminative response of higher centres; but they still remain capable of revival under conditions demanding urgent and impulsive action" (*Head* 1921).

8 General Properties of Cardiovascular Sympathetic Afferent Fibers: A Summary

Afferent sympathetic nerve fibers with cardiovascular receptive endings display a tonic impulse activity in relation to normal and specific hemodynamic events. Their sensitivity to natural stimuli can be extreme: as in the case of atrial receptors that seem capable of detecting minimal alterations in atrial dynamics, even before these may be reflected by changes in atrial pressure (*Malliani* et al. 1972b). The spontaneous low firing rates of sympathetic afferent fibers was attributed, as a working hypothesis (*Malliani* et al. 1973b), to a special type of transducer, different from that of the vagal endings, possibly an end-net formation. *Coleridge* et al. (1978) emphasized, quite appropriately, "the curious discrepancy between the relative low rate of firing that is evoked when the ending is stimulated physiologically by an increase in transmural pressure and the high frequency response to even the lightest touch". There is no explanation for this common finding: one may simply suggest that even the lightest touch produces a generator potential that differs from those occurring normally and that is capable of a more efficient coupling with the electrically excitable conductile membrane (*Grundfest* 1966). Moreover, it cannot be excluded that probing may also directly excite the terminal parts of the conductile membrane. However, the basic low impulse activity of sympathetic afferent fibers should perhaps be considered in relation to the positive feedback mechanisms that they are capable of activating and, although unexplained, this low activity may then appear desirable.

Coleridge et al. (1978) also wrote that "when one compares the brief and relatively modest response to even marked increases in pressure or volume with the dramatic effects of bradykinin and prostaglandin, one cannot help but feel that it is in their response to endogenous chemicals that afferent sympathetic endings find their true expression". I cannot agree with this statement for two reasons: high doses of bradykinin could directly excite the preterminal fibers (*Khayutin* et al. 1976) and in our experience, ventricular fibrillation could sometimes abruptly excite non-myelinated ventricular afferent fibers even more than bradykinin (Figs. 9, 12). Yet, I do not think that the true expression of this afferent pathway is signalling ventricular fibrillation.

The well-recognized nociceptive function of these afferent nerve fibers is likely to depend on their intense activation rather than the recruitment of a specific population of nociceptive units. This afferent neural channel, connecting the cardiovascular system to the spinal cord (Fig. 29), seems to subserve a tonic reflex function contributing to the complexity of the neural regulation of hemodynamic events. The excitation of this spinal input produces cardiovascular reflexes that are mainly excitatory in nature, although inhibitory components are also present.

The reflexes mediated by sympathetic afferent fibers, when they only involve the sympathetic outflow, can be present in spinal preparations and therefore spinal structures appear sufficient to integrate them. However,

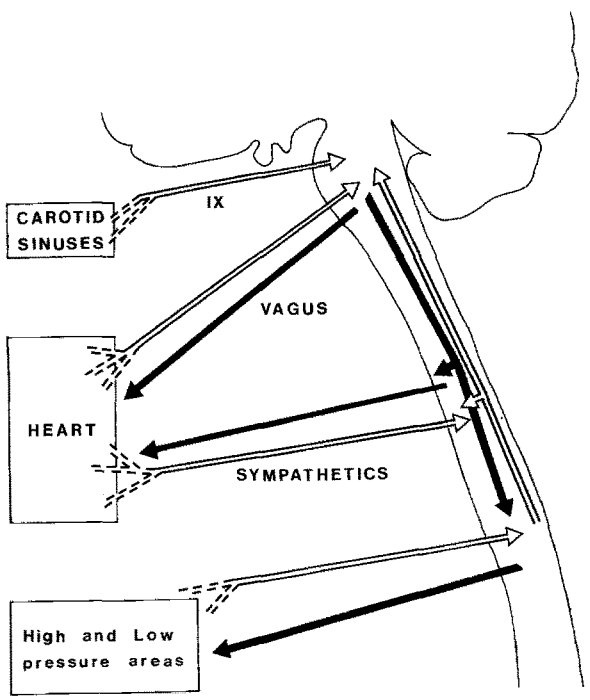

Fig. 29. Schema of the cardiovascular sympathetic innervation conceived as an input-output system interacting with supraspinal nervous mechanisms. (From *Malliani* 1981)

this does not mean that supraspinal structures cannot be involved when the neuraxis is intact. In fact, it was proven that in anesthetized and unanesthetized animals the excitation of sympathetic afferent fibers could also modulate the sensitivity of supraspinal reflexes.

As to the effect of spinal section on the magnitude of these reflexes, we never observed an increase but, if anything, a small decrease in their entity. Therefore, I would agree with *Peterson* and *Brown* (1971) and with *Staszewska-Barczak* and *Dusting* (1977), who stated that, after spinal section, the reflex responses to the stimulation of cardiac sympathetic afferent fibers are reduced, rather than with *Felder* and *Thames* (1981), who stated that a reflex mediated by cardiac sympathetic afferent fibers can only be present after spinal section. The acute effect of a spinal transection is quite different from the "release of function in the nervous system" (*Head* 1921), a phenomenon that should require time. "If the fall of general blood-pressure be regarded as part, and a severe part, of the 'spinal' shock which ensures on spinal transection in the cervical region" (*Sherrington* 1906), one would suggest that this is the most frequent consequence of such an intervention, especially when not properly performed in terms of anesthesia and surgery.

In the conscious state, potent pressor reflexes can be elicited in the absence of pain.

9 Human Pathophysiology

This section concentrates on the neural mechanisms likely to participate in the pathophysiological complexity of acute myocardial ischemia. Various laboratories have been accumulating, over the years, a great deal of pertinent data which largely anticipated clinical understanding.

The experiments by *Von Bezold* and *Hirt* (1867) introduced the notion of vagally mediated depressor reflexes from the heart, which supported the intuition of *Cyon* and *Ludwig* (1866). Much time, however, had to elapse before depressor reflexes were found to be associated with experimental coronary occlusion (*Costantin* 1963; *Dokukin* 1964; *Thorén* 1979). An erroneous extension of finalistic interpretations from physiology to pathophysiology probably enabled the establishment of the opinion that all reflexes arising from the diseased heart had to subserve a function of decreasing its load.

When we described the sympathetic excitatory reflex elicited by coronary occlusion (*Malliani* et al. 1969a, b) we hypothesized that the reflex might have two opposite consequences in the course of human disease. On the one hand, increased cardiac sympathetic activity could signify increased myocardial oxygen consumption and facilitated arrythmias; on the other

hand, a reflex increase in contractility might be an important mechanism to oppose ventricular dilatation and cardiogenic shock (*Aviado* and *Schmidt* 1955; *Salisbury* et al. 1960). Obviously, the hypothesis was not based on teleologic reasoning for the benefit of the patient but on the factual results of an increased sympathetic activity.

Subsequently it was proved that the presence of a cardiac sympatho-sympathetic loop plays an important role in the arrhythmias associated with coronary occlusion (*Schwartz* et al. 1976) and that cardiac sympathetic afferent fibers can mediate a reflex increase in myocardial contractility (*Malliani* et al. 1972a). However, the link with human disease was almost nonexistent.

The clinical work by Pantridge's group offered a new perspective and represented a milestone (*Webb* et al. 1972; *Pantridge* 1978). By showing that a majority of patients had signs of "autonomic disturbance" at the onset of an acute myocardial infarction and that excessive sympathetic activity (as revealed by tachycardia and/or hypertension) was more frequent in cases of anterior infarctions, whereas a vagal overactivity (as revealed by bradycardia and/or hypotension) was more frequent in inferior infarctions, they suggested the existence of specific mechanisms independent of pain and emotion or of a pure pump failure. Hence, pressor and depressor reflexes arising from the jeopardized myocardium were suggested. Some link, though fragile, now existed between the laboratory and the complexitiy of human disease. I think that this link may be further substantiated if the hemodynamic alterations that can accompany acute and reversible electrocardiographic changes typical of ischemic episodes of the myocardium are analyzed properly. It is possible to observe: (1) decreases in arterial pressure and heart rate (*Guazzi* et al. 1971); (2) a decrease in arterial pressure and a rise in heart rate (*Guazzi* et al. 1971, 1975; *Maseri* et al. 1978); (3) increases in arterial pressure and heart rate (*Lewis* 1931; *Roughgarden* 1966; *Littler* et al. 1973; *Guazzi* et al. 1975; *Maseri* et al. 1978). In some cases, it was clearly shown (*Guazzi* et al. 1971, 1975; *Maseri* et al. 1978; *Figueras* et al. 1979; *Chierchia* et al. 1980; *Figueras* and *Cinca* 1981) that hemodynamic and electrocardiographic alterations could precede pain or occur in the absence of it.

Thus, the participation of vagally mediated depressor reflexes and of sympathetically mediated excitatory reflexes appears extremely likely (Fig. 30). More specifically, hypertension and tachycardia preceding or independent of pain would be the result of a reflex from the heart and not of a primary and undetermined "vasomotor storm" as hypothesized by *Lewis* (1931).

It is obvious that a black box of fundamental importance embraces the fact that an increased sympathetic afferent activity can induce reflexes

without pain or, less likely, pain without reflexes. The careful studies of Foreman and associates (*Foreman* et al. 1978; *Foreman* and *Ohata* 1980) attempt to face this problem. Yet, "it must be remembered that there is a critical and still mysterious step between input of sensory origin to the higher central nervous system and conscious perception" (*Perl* 1971).

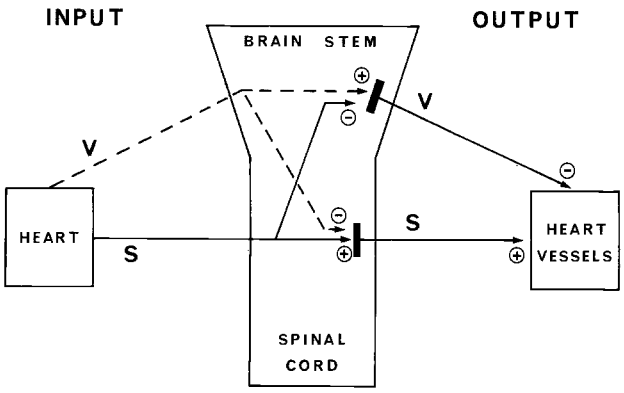

Fig. 30. Schema of the neural pathways mediating reflexes from the heart during myocardial ischemia. (From *Malliani* 1978)

Moreover, a pathophysiological event could also be that of an increased vagal and sympathetic efferent activity as the result of an excitation of both vagovagal and sympathosympathetic reflexes (*Malliani* et al. 1980). Such an event would weaken the old concept of vagal and sympathetic outflows working only in a sort of reciprocal arrangement.

These neural mechanisms are likely to play a crucial role in life-threatening arrhythmias which may be associated with myocardial ischemia (*Schwartz* et al. 1975, 1978; *Malliani* and *Lombardi* 1978; *Lown* 1979; *Malliani* et al. 1980).

A peculiar clinical example of an excitatory cardiovascular reflex mediated by sympathetic afferent fibers could be that of hypertension after coronary bypass surgery (*Tarazi* et al. 1978; *Estefanous* and *Tarazi* 1980; *Wallach* et al. 1980) that was rapidly controlled with lidocaine block of one stellate ganglion (*Tarazi* et al. 1978).

In brief, old and recent experimental studies on cardiovascular innervation have often opened new ways of interpreting the complexity of clinical reality. On the other hand, the recognition of this complexity should prevent any wish to generalize too much from any particular experimental model.

However, these are only notes from the initial pages of a travelogue. A conclusion should not even be attempted: "there will be time" (T.S. Eliot).

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The Functions of the Renal Nerves

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Contents

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1 Introduction

The structure and function of the intrinsic innervation of the kidney have been investigated for over 100 years. Until recently, there has been no agreement concerning the precise anatomical distribution or neurotransmitter specificity of the renal nerves. Recently, combination electron microscopic, histochemical, and fluorescent methods have more precisely localized the distribution and neurotransmitter specificity of the nerves within the kidney.

Up until the time of these anatomical studies, the physiological role of the renal nerves was a subject of much controversy. Much of the controversy existed because previous experiments involved stressful anesthesia and/or surgery, the comparison of an innervated kidney with a possibly incompletely denervated kidney, or the use of high levels of direct electrical renal nerve stimulation as opposed to physiological reflex alterations in efferent renal nerve activity. To summarize the views of one authority, adamant in his view that the renal nerves were unimportant in the regulation of renal excretory function under normal conditions, "For the moment it may be said that substantial evidence of the neural control of either the tubular excretion or reabsorption of any urinary constituent is lacking." (*Smith* 1937).

Since these early observations our understanding of the physiological role of the intrinsic renal innervation has advanced to a more sophisticated level. It is the purpose of this survey to critically review and summarize the current state of information concerning the functions of the renal nerves. In view of several recently published reviews (*Gill* 1969; *Pogglitsch* 1973; *Schrier* 1974; *Hillemand* et al. 1976; *DiBona* 1977, 1978, 1981; *Gottschalk* et al. 1978; *Linden* 1978; *Gottschalk* 1979; *Gill* 1979; *Kim* et al. 1979) which address many portions of this topic, only selected aspects will be discussed.

2 Renal Neuroanatomy

The innervation of the kidney has been a subject of intense study since Pappenheim's early observation that nerve fibers enter the kidney together with the main renal artery and run along it down to its finest branches (*Pappenheim* 1840).

2.1 Gross Innervation

Relative to its size, the kidney has a richer innervation than almost any other organ (*Mitchell* 1950). The status of knowledge in this area is represented by the work of *Mitchell* (1950), *DeMuylder* (1952), and *Shvalev* (1966). The renal nerves are described as being composed of fibers derived from the celiac plexus, the thoracic and lumbar branches of the splanchnic nerves, the superior and inferior mesenteric plexus, the intermesenteric nerves, and the superior hypogastric plexus (*Mitchell* 1950). Based on spinal cord stimulation studies (*Takeuchi* et al. 1964) these fibers derive from spinal cord segments T_5 to L_3. All of these nerve fibers and their interconnections make up the renal plexus which lies in rather constant association with the aorticorenal ganglion. The aorticorenal ganglion is the largest ganglion associated with the renal plexus and lies near the junction of the aorta and the renal artery (*Norvell* 1968). The renal nerve fibers that enter the kidney derive from the renal plexus and course along the renal artery and vein to enter the hilus.

2.2 Intrinsic Innervation

The introduction of specific histochemical and fluorescent techniques for the identification of adrenergic and cholinergic neurons and the application of electron microscopy has greatly clarified the details of the distribution and neurotransmitter specificity of the intrinsic renal innervation. The conclusions of the older literature (*Mitchell* 1950; *DeMuylder* 1952) were that the renal nerves, both adrenergic and cholinergic, were distributed to the blood vessels of the kidney but did not innervate renal tubular structures.

However, the elegant series of studies by *Barajas* and colleagues provides clear evidence that these conclusions must be revised. Using a combination of catecholamine fluorescent histochemistry and autoradiography for localization of exogenous tritiated norepinephrine for demonstration of adrenergic nerves, the thiocholine histochemical method for demonstration of acetylcholinesterase-containing nerves, and electron microscopy, *Barajas* and colleagues (reviewed in 1978) have studied the intrinsic renal innervation in the rat and monkey. In both the rat and monkey, prominent adrenergic nerve bundles are associated with the arterioles in the cortex, characteristically appearing in the space between the afferent and efferent glomerular arterioles and the surrounding tubules. Nerve bundles are seen adjacent to the tubules, often filling the space between it and the arteriole. The tubules receive a distinct tubular innervation with the finding of nerve bundels closely following the contour of both proximal and distal tubules;

these tubular branches arise from the periarteriolar nerves. This pattern of distribution is similar in the monkey and the rat but the nerve bundles are thinner and the density of innervation is less in the rat than in the monkey. Electron microscopy discloses in both rat and monkey that the nerves are composed of variable numbers of axons partially or totally surrounded by a Schwann cell. The axons display dilated segments (varicosities) which contain mitochondria and the characteristic vesicles observed in autonomic nerves (small dense-cored vesicles, neurosecretory granules). The varicosities establish contact with both arteriolar walls and tubular epithelial cells. At the site of contact the basement membranes of the nerve and arteriolar wall or tubular epithelial cell fuse and this site is referred to as a nerve terminal (neuroeffector junction). In both proximal and distal tubules, varicosities containing small dense-cored vesicles are seen in direct contact with the tubular epithelial cell basement membrane.

In the rat, light and electron microscopic autoradiography was used for localization of exogenous tritiated norepinephrine (*Barajas* and *Wang* 1979). Accumulation of grains were noted in axonal varicosities packed with small, dense-cored vesicles, which were in direct contact with afferent and efferent arterioles, juxtaglomerular granular cells, and proximal and distal tubules. Neuroeffector junctions were characterized by a space of 150–250 nm in width separating the plasma membrane of the effector cell from that of the axolemma; basement membrane material was present in this space.

Using similar techniques in the dog, *DiBona* (1977) has shown that proximal and distal tubular epithelial cells are directly innervated by catecholamine-containing adrenergic nerve terminals. Using electron microscopy alone, *Zimmerman* (1972) observed in 13–16 week old human fetuses that the distal convoluted tubule was innervated; he demonstrated nerve terminals containing small dense-cored vesicles in direct contact with the basement membranes of distal tubular epithelial cells.

Neural innervation of renal tubules has been demonstrated in non-mammalian species. *Pang* et al. (1982) have demonstrated nerve terminals in contact with renal tubular epithelial cells of the bullfrog, *Rana catesbeiana.*

With regard to cholinergic nerves. the studies of *Barajas* and colleagues (1974, 1975, 1976) have led to a revised understanding of this matter. Acetylcholinesterase-containing nerve bundles are associated with the afferent and efferent glomerular arterioles and both proximal and distal tubules. Since the specific histochemical precipitate reflecting acetylcholinesterase, copper ferrocyanide, is electron opaque, the light microscopic histochemical findings can be verified with the electron microscope. In both monkey and rat, acetylcholinesterase deposits are located extracellularly around axons and varicosities in the perivascular and peritubular

nerves. However, little or no acetylcholinesterase deposit is seen at the neuroeffector junctions. The histochemical demonstration of acetylcholinesterase in renal nerves has long been considered to indicate the existence of a distinct cholinergic innervation. Such a view was supported by the presence of residual acetylcholinesterase innervation after the disappearance of adrenergic fluorescence following renal transplantation (*Weitsen* and *Norvell* 1969; *Norvell* et al. 1970). However, two observations suggested that the acetylcholinesterase-positive nerves might really be adrenergic and contain the enzyme. First, in the rat, serial section electron microscopy showed small dense-cored vesicles characteristic of adrenergic nerves in all axon segments present in the juxtaglomerular region, an area where acetylcholinesterase-positive nerves are abundant. Second, in the monkey, electron microscopy shows that all nerve bundles around the glomerular arterioles have acetylcholinesterase deposits while, by catecholamine fluorescence histochemistry, a dense adrenergic innervation is characteristic of that region. To test this hypothesis further, *Barajas* and *Wang* (1975) used the agent 6-hydroxydopamine which selectively destroys adrenergic nerves. If the acetylcholinesterase-positive nerves are adrenergic but contain the enzyme, administration of 6-hydroxydopamine should result in the disappearance of both acetylcholinesterase and catecholamine fluorescence from the nerves. In the rat, administration of 6-hydroxydopamine resulted in the disappearance of acetylcholinesterase and catecholamine fluorescence from virtually all nerves associated with the glomerular arterioles and the adjacent tubules. However, there was slight residual acetylcholinesterase and catecholamine fluorescence seen in association with small arteries and larger blood vessels elsewhere in the kidney. Electron microscopy disclosed degeneration of the nerves associated with the glomerular arterioles and the adjacent tubules. These studies support the presence of an exclusive adrenergic innervation of the glomerular arterioles and the adjacent tubules with the presence of acetylcholinesterase in adrenergic nerves being in accord with the hypothesis of *Burn* and *Rand* (1965).

It is known that the overwhelming majority of spinal viscerosensory fibers are myelinated fibers of large (over 7 μm) and medium (4–7 μm) diameter and that the kidney of dog and man contains the smallest number of such sensory fibers in comparison (ascending order) to small intestine, liver, lungs, and heart. *Zimmerman* (1975) and *Barajas* and *Wang* (1978) demonstrated that the rat kidney contains myelinated and unmyelinated nerve fibers. They observed nerve bundles with myelinated and unmyelinated axons in three areas of the kidney: the corticomedullary region at the outer stripe of the outer zone of the medulla, the periarterial loose connective tissue, and the subepithelial connective tissue of the calyces. The diameter of 17 myelinated axons averaged 2.8 μm (range, 2.1–3.9

μm) and the diameter of 180 unmyelinated axons averaged 0.5 μm (range, 0.1–1.3 μm). The results of light and electron microscopic autoradiography for the localization of exogenous tritiated norepinephrine indicated that the unmyelinated nerve fibers are adrenergic. *Niijima* (1975) has shown that the rabbit renal nerve trunk contains myelinated nerve fibers with an average diameter of 4.3 μm (range, 2.0–8.0 μm, 166 fibers); parallel physiological studies indicated that these myelinated nerve fibers were afferent. Thus, these observations suggest that there is a close functional relationship in the kidney between the afferent myelinated and the efferent adrenergic unmyelinated nerve fibers.

The innervation of the juxtaglomerular apparatus (rat) has been recently reviewed by *Gorgas* (1978a, b) and *Barajas* (1979, 1981). Fluorescent histochemistry for biogenic amines demonstrates a plexus of catecholaminergic nerves associated with the glomerular arterioles extending from the afferent to the efferent arteriole and the adjacent tubules. Electron microscopy discloses the presence in the nerves of small dense-cored vesicles thought to contain norepinephrine and believed to be characteristic of adrenergic nerves. Their disappearance after the injection of reserpine correlates with the depletion of catecholamines from the renal tissue and the abolition of catecholamine fluorescence. Serial section electron microscopy indicates that about one-fourth of the cells of the vascular component and about one-third of the cells of the afferent and efferent arterioles are innervated. Only one-tenth of the cells in the extraglomerular mesangial region were innervated while about half of the granular cells in the glomerular arterioles and one-sixth of the granular cells (lacis and smooth muscle cells) of the vascular component were innervated. Although based on evaluation of a single juxtaglomerular apparatus, it would appear that a large proportion of the cells of the vascular component are non-innervated. Of particular importance is the observation that axons can be in contact with both vascular and tubular cells; thus, the same axon can innervate granular cells, smooth muscle cells in the glomerular arterioles, and cells of the distal tubule. This ultrastructural finding makes plausible the suggestion that the activity of a single axon could affect the function of the juxtaglomerular apparatus by having a direct effect on renin secretion from the juxtaglomerular granular cells, by changing the diameter of the arterioles through a direct action on vascular smooth muscle cells, and by a direct action on epithelial cells of the distal tubule near the macula densa. The serial section technique disclosed that all axons contained small dense-cored vesicles which are characteristic of adrenergic nerves. Thus, this observation suggests that the innervation of the juxtaglomerular region is exclusively adrenergic.

Further support for the exclusive adrenergic innervation of the juxtaglomerular apparatus is derived from the studies with 6-hydroxy-dop-

amine (vide supra). Treatment with 6-hydroxydopamine resulted in almost total disappearance of both catecholamine fluorescence and acetylcholinesterase activity from the juxtaglomerular apparatus. Electron microscopy showed degenerating axons. Since 6-hydroxydopamine destroys only adrenergic nerve endings, this finding supports the hypothesis that the majority of the nerves in the juxtaglomerular apparatus are adrenergic nerves which contain acetylcholinesterase. Additional evidence for sole adrenergic innervation of the juxtaglomerular apparatus comes from studies using the uptake of tritiated norepinephrine as a specific functional marker for adrenergic nerves (*Barajas* and *Wang* 1979). Light and electron microscopic autoradiography showed accumulations of grains in association with afferent and efferent arterioles as well as adjacent proximal and distal tubules. The grains were also noted to be in contact with juxtaglomerular granular cells. Virtually all of the grains were on axons in varicosities packed with vesicles, some of which were of the small dense-cored variety. Thus, these findings support the hypothesis that the juxtaglomerular apparatus is innervated mainly by adrenergic nerves.

2.3 Catecholamine Receptors

The subject of renal catecholamine receptors has recently been reviewed by *Insel* and *Snavely* (1981). Using a fluorescent β-adrenoceptor antagonist, 9-amino-acridine-propranolol, *Atlas* et al. (1977) demonstrated localization in the epithelium of proximal and distal convoluted tubules and collecting ducts as well as the efferent arterioles of the glomerular vascular pole and the juxtaglomerular apparatus. Further detailed localization was not possible and the blockade of fluorescence with propranolol was equivocal.

Young and *Kuhar* (1980) reported that α-2 adrenoceptors are located predominantly on the proximal tubules of the guinea pig kidney. They used an in vivo labeling autoradiographic technique to examine the distribution of specific [^{3}H] clonidine binding sites with the light microscope. However, the process of identification of the proximal tubule was not rigorous and depended entirely on poorly defined anatomical criteria. Binding of [^{3}H] WB-4101, an α-1 adrenoceptor antagonist, was not observed.

Radioligand binding techniques have been used to identify renal adrenoceptors in partially purified renal tubular plasma membrane preparations. For α-adrenoceptors, radioligand binding has been used to identify α-2 adrenoceptors in the guinea pig kidney (*Jarrott* et al. 1979) and both α-1 and α-2 adrenoceptors in the rat kidney (*Rouot* and *Snyder* 1979; *U'Prichard* and *Snyder* 1979). In addition, *Graham* et al. (1978, 1980) have reported that renal α-adrenoceptors are increased in spontaneously

hypertensive rats and stroke-prone spontaneously hypertensive rats as compared to normotensive Wistar-Kyoto control rats. *Felder* et al. (1980a) found renal tubular α-adrenoceptors in the rat but not the dog kidney. *Pettinger* et al. (1981) showed that total α-adrenoceptor number was higher in renal membranes from kidneys of Dahl sodium-sensitive rats than Dahl sodium-resistant rats and increased further with a high sodium diet. Increased α-2 adrenoceptor binding accounted for most of the increment, although α-1 adrenoceptor binding was also increased. High sodium diet did not affect α-1 or α-2 adrenoceptor binding in Dahl sodium-reistant rats. Binding affinities were not affected. Information on the effect of alterations in dietary sodium intake on adrenoceptors in normal rat renal membranes is required in order to interpret these changes in a mixed genetic-environmental form of experimental hypertension.

For β-adrenoceptors, radioligand binding has been used to identify renal β-adrenoceptors in the rat kidney (*Woodcock* et al. 1978; *Eliahou* et al. 1980; *Gavendo* et al. 1980; *Snavely* and *Insel* 1980). *Gavendo* et al. (1980) demonstrated that the order of potency for inhibition of radioligand binding of β-adrenoceptor antagonists was isoproterenol > epinephrine ⩾ norepinephrine, thus being consistent with a β-1 adrenoceptor (*Hoffman* and *Lefkowitz* 1980). *Felder* et al. (1980a) found renal tubular β-adrenoceptors in both the rat and dog kidney. With respect to the classification and quantitation of β-adrenoceptor subtypes (*Minneman* et al. 1981), the hypothesis of *Carlsson* et al. (1972) must be considered. This hypothesis suggests that both β-1 and β-2 adrenoceptors could coexist in the same organ and be involved in many β-adrenoceptor-mediated responses. The relative involvement of the two β-adrenoceptor subtypes will vary depending on the agonist involved and the relative amounts of the two β-adrenoceptor subtypes existing in the effector organ under study. For dopaminergic receptors, *Dinerstein* et al. (1979) used histofluorescence techniques to demonstrate neuronal elements at the glomerular vascular poles of dog renal cortex containing predominantly dopamine. A preliminery report indicates the existence of dopamine receptors in dog (*Scott* and *Vanderwende* 1980) and rat (*Felder* et al. 1980b, 1981) renal cortex (*Adam* 1980).

Glomerular adrenoceptors have been sought in dogs and rats. α- and β-adrenoceptors have been found in the glomeruli of the dog and rat (*Felder* et al. 1980a). Dopamine receptors have been found in the glomeruli and tubules of the rat kidney (*Felder* et al. 1980b, 1981).

Although these represent important initial investigations, the ability of these studies to provide precise anatomical localization of these receptors is limited since the preparations employed contain material from multiple cell types and different tubular segments. Further work will be necessary before it will be possible to completely define renal tubular epithelial cell

catecholamine receptor anatomy, e.g., luminal versus peritubular membrane, proximal convoluted versus proximal straight segments, superficial versus juxtamedullary, and cortex versus medulla.

2.4 Catecholamine Metabolism

The renal metabolism of catecholamines in relation to activation of efferent renal sympathetic nerves and urinary sodium excretion has been studied extensively by *Baines, Morgunov,* and colleagues (*Morgunov* 1980). Using microinjection techniques, it was demonstrated that after rat proximal tubular injection of norepinephrine, dopamine, normetanephrine, or methoxytyramine, 87%–94% was recovered in the urine of the injected kidney. Less than 10% was chemically altered during passage through the nephron. After peritubular capillary injection, first passage tubular secretion was 25% for dopamine, 47% for methoxytyramine, 13% for norepinephrine, and 4% for normetanephrine. After peritubular capillary injections of dopamine, urinary excretion of methoxytyramine and dopamine was greater from the microinjected than the contralateral kidneys, whereas after peritubular capillary injection of norepinephrine, urinary excretion of norepinephrine and normetanephrine was similar from the two kidneys. Thus, dopamine and norepinephrine released into peritubular capillaries are methylated by catechol-*O*-methyl-transferase and both amines and their methylated derivates are secreted into the tubular lumen with nearly complete delivery into the final urine (*Baines* et al. 1979). The fate of catecholamines which diffuse into peritubular cortical interstitial space has been examined using subcapsular microinjection of radioactive catecholamines. Fractional secretion rates were 20% for norepinephrine, 47% for epinephrine, and 66% for dopamine, and were not affected by prior chronic renal denervation. Increasing circulating plasma dopamine concentrations inhibited the tubular secretion of norepinephrine and dopamine (*Baines* and *Morgunov* 1980). Urinary catecholamine excretion may derive from several sources: filtration, reabsorption, and secretion of catecholamines entering the kidney in renal artery blood; release from renal nerve endings; and production by nonneuronal sources in the kidney. Measuring catecholamine concentrations in arterial blood, renal vein blood, lymph, and urine from innervated and denervated kidneys in the same rat, *Baines* and colleagues have derived several important quantitative conclusions. For urinary norepinephrine excretion, approximately 30% derives from circulating norepinephrine with the remainder derived from the renal nerves since renal denervation reduced the renal component of urinary norepinephrine excretion to zero. For urinary epinephrine excretion, approximately 70% derives from circulating epinephrine with the

remainder derived from the renal nerves, since renal denervation reduced the renal component of urinary epinephrine excretion to zero. For urinary dopamine excretion, none is derived from circulating dopamine and all is derived approximately equally from the renal nerves and nonneuronal sources in the kidney (*Stephenson* et al. 1982). In general, renal denervation decreases renal venous concentrations of norepinephrine, epinephrine, and dopamine to levels below those observed in arterial blood. Under control conditions, renal lymph concentrations of all three catecholamines are in the range of arterial and renal venous catecholamine concentrations. Following activation of efferent renal sympathetic nerves, renal lymph concentrations are higher for norepinephrine, lower for epinephrine, and approximately the same for dopamine in comparison to paired arterial blood samples (*Baines* and *Morgunov* 1980). Since the low circulating arterial concentration of free dopamine cannot explain the rate of urinary dopamine excretion, *Baines* and *Chan* (1980) demonstrated that as much as 30% of urinary dopamine excretion could derive from the metabolism by renal nonneuronal tissue of circulating free L-dihydroxyphenylalanine (L-dopa). It is known that both innervated and denervated kidneys contain L-dopa decarboxylase, the enzyme responsible for conversion of L-dopa to dopamine, presumably in nonneuronal tissue such as renal tubular epithelial cells (*Nagatsu* et al. 1969).

Using bilateral common carotid artery occlusion to reflexly increase efferent renal sympathetic nerve activity (RSNA), *Morgunov* and *Baines* (1981a) have shown that the increase in urinary norepinephrine excretion derives from both systemic extrarenal sources and the renal nerves. The increase in urinary epinephrine excretion derives from systemic extrarenal sources with little contribution from the renal nerves and the increase in urinary dopamine excretion derives exclusively from the renal nerves with no systemic extrarenal contribution. In the rabbit *Lappe* et al. (1980a) and *Willis* et al. (1980) reported that norepinephrine released from nerve terminals by renal nerve stimulation and ^{3}H-norepinephrine (renal cortical application) released from postglomerular nerve terminals by tyramine administration were exreted into the urine by a cationic tubular secretory process which was inhibited by cyanine but not by probenecid.

In regard to the relationship between the renal regulation of extracellular fluid volume and urinary catecholamine excretion, it is known that increases in dietary sodium intake lead to duration-dependent increases in extracellular fluid volume with a constant plasma sodium concentration (*Reinhardt* and *Behrenbeck* 1967; *Kaczmarczyk* et al. 1979). A direct correlation between sodium intake and urinary dopamine excretion and an inverse one with urinary norepinephrine excretion have been described (*Alexander* et al. 1974; *Oates* et al. 1979). However, *Baines* and *Morgunov*

(1980) have shown that increased dietary sodium intake increases the urinary excretion of both norepinephrine and dopamine in rats. Comparison studies studies with isotonic glucose or sodium bicarbonate solution as drinking fluid indicate that urinary flow rate, urinary pH (*Reynolds* et al. 1978), and dietary carbohydrate intake (*DeHaven* et al. 1980) as well as sodium intake modify urinary catecholamine excretion.

In the bilateral common carotid artery occlusion studies of *Morgunov* and *Baines* (1981), referred to earlier, a low dietary sodium intake reduced the systemic extrarenal contribution but not the renal nerve contribution to a lowered urinary excretion of norepinephrine, enhanced the systemic extrarenal contribution but not the renal nerve contribution to an increased urinary excretion of epinephrine, and reduced the systemic extrarenal contribution but not the renal contribution to a decreased urinary excretion of dopamine. A high dietary sodium intake reduced the systemic extrarenal contribution and abolished the renal contribution to a reduced urinary excretion of norepinephrine and abolished both the systemic extrarenal and renal release of epinephrine and dopamine. Thus, the urinary excretion of catecholamines derived from renal nerves was markedly influenced by dietary sodium intake. Angiotensin II, known to be elevated during dietary sodium deprivation (*Fray* et al. 1977), potentiates the release of catecholamines from nerve endings (*Zimmerman* 1978; *Westfall* 1980). However, dietary sodium deprivation also results in loss of catecholamines from peripheral nerve endings with a resultant decreased ability to respond to acute stimulation (*Ljungqvist* 1975; *Rocchini* et al. 1977). Dietary sodium excess may decrease catecholamine release from nerve endings via decreases in circulating angiotensin II concentrations. Additionally, volume expansion may modulate baroreceptor reflex responses through interaction via cardiopulmonary receptors (*Clement* et al. 1972). Also, baroreceptors are known to possess ionic (sodium) sensitivity (*Brown* 1980). Thus, multiple mechanisms activated by changes in dietary sodium intake may be involved in the observed alterations in renal catecholamine metabolism.

In acute renal denervation experiments, the ipsilateral natriuresis was associated with a decrease in the urinary excretion of norepinephrine and and increase in the urinary excretion of dopamine. The contralateral antinatriuresis was associated with an increase in the urinary excretion of norepinephrine and a decrease in the urinary excretion of dopamine (*Morgunov* and *Baines* 1981a). Using direct electrical stimulation of the afferent vagus nerve, it was shown that the observed natriuresis was associated with an increase in the renal nerve-mediated release of dopamine but not norepinephrine; neither arterial pressure nor glomerular filtration rate were changed (*Morgunov* and *Baines* 1981b). As discussed later (see Sect. 4.2), the relationship between endogenous dopamine and renal tubular sodium reabsorption remains unclear.

The effect of direct electrical renal nerve stimulation on the release of catecholamines from the kidney into the renal venous blood or urine has been studied. *Lappe* et al. (1980b), using a level of renal nerve stimulation that reduced glomerular filtration rate by 30% in anesthetized rabbits, observed that the urinary excretion of norepinephrine but not epinephrine increased when factored for glomerular filtration rate. Since plasma norepinephrine concentration did not change, the urinary clearance ratio for norepinephrine was also increased by renal nerve stimulation. *Kopp* et al. (1980b) showed that the renal release rates of norepinephrine, epinephrine, and dopamine were negative in the acutely denervated kidney of the anesthetized dog. Stimulation of the renal nerves sufficient to reduce renal blood flow by 5% increased the renal release rate of norepinephrine from -0.89 ± 0.49 to 1.92 ± 0.72 pmol/min per gram without any change in the renal release rate of epinephrine or dopamine. Stimulation of the renal nerves sufficient to reduce renal blood flow by 50% increased the renal release rate of norepinephrine from -0.86 ± 0.17 to 8.68 ± 0.10 pmol/min per gram, and that of dopamine from -0.15 ± 0.04 to 0.33 ± 0.04 pmol/min per gram; it did not affect the renal release rate of epinephrine. Phenoxybenzamine increased the renal release rates of both norepinephrine and dopamine during strong renal nerve stimulation, whereas both metoprolol and indomethacin had no effect. *Oliver* and colleagues (1980a) have shown that the renal release rate of norepinephrine is positive in the innervated kidney of both anesthetized and conscious dogs. There was a linear relationship between the frequency of renal nerve stimulation and the renal release rate of norepinephrine over the range of 0.5–18.0 Hz; however, the maximum reduction in renal blood flow occurred at 6.0 Hz.

2.5 Summary

Morphological studies indicate that the mammalian kidney receives a predominant adrenergic innervation which involves the vessels, tubules, and juxtaglomerular apparatus. There is no evidence for a significant cholinergic innervation. Initial observations support the existence of dopaminergic neurons. Efferent unmyelinated nerve fibers predominate over afferent myelinated nerve fibers. Radioligand binding studies indicate that both glomeruli and tubules possess α- and β-adrenoceptors as well as dopamine receptors. Direct or reflex-induced increases in efferent RSNA increase the release of norepinephrine and dopamine, but not epinephrine, into renal venous blood and urine. These responses are modified by alterations in dietary sodium intake. The kidney is able to synthesize dopamine from precursors in nonneuronal tissue.

3 Electrical Characteristics of the Renal Nerves

This section will emphasize those investigations which have employed neurophysiological recording techniques to measure renal nerve activity directly. Those investigations in which alterations in renal nerve activity have been inferred from renal functional measurements are considered in Sect. 4.

3.1 Efferent Renal Nerves

Adrian, Bronk, and *Phillips* (1932) first demonstrated in the rabbit and cat that efferent renal sympathetic nerve activity (RSNA) occurred in pulse-synchronous rhythmic bursts with respiratory-dependent periodic variations of the nerve impulse frequency. A similar stiuation is known to exist in several other mammalian species, including the rat (*Judy* et al. 1971; *Thoren* and *Ricksten* 1979; *Ricksten* et al. 1979), cat (*Engelhorn* 1957), rabbit (*Aars* and *Akre* 1968), and dog (*Takeuchi* et al. 1965). In addition to these observations made in unconscious anesthetized animals, similar findings have been made in conscious unanesthetized animals (*Judy* et al. 1976; *Ricksten* et al. 1981; *Weidinger* and *Kirchner* 1967; *Schad* and *Seller* 1975; *Kirchheim* and *Gross* 1978; *Gross* and *Kirchheim* 1980).

Efferent RSNA is influenced by several reflex mechanisms. Carotid baroreceptor stimulation, i.e., increased carotid sinus pressure, inhibits both spontaneous and reflex efferent RSNA, while the reverse, i.e., decreased carotid sinus pressure, increases efferent RSNA (*Kezdi* and *Geller* 1968; *Kirchheim* and *Gross* 1978; *Gross* and *Kirchheim* 1980).

There are multiple types and locations of cardiac mechanoreceptors and chemosensitive receptors, some of which have been shown to influence efferent RSNA (*Thoren* 1979; *Coleridge* and *Coleridge* 1980; *Donald* and *Shepherd* 1980). All four cardiac chambers contain receptors with myelinated vagal afferents, receptors with unmyelinated vagal afferents, and receptors with sympathetic (myelinated and unmyelinated) afferents. It would appear that receptors with myelinated vagal afferents are more numerous in the atria than in the ventricles, while the ventricular receptors with unmyelinated vagal afferents are more numerous in the left ventricle than in the right ventricle. Receptors with sympathetic afferents appear to be more numerous in the ventricles than in the atria.

Investigations concerning the role of these various receptor groups in reflexly modulating efferent RSNA have employed various techniques to stimulate the receptors. They range from discrete stimulation (e.g., direct

probing, small balloon inflation) to more widespread but local stimulation (e.g., left atrial balloon inflation, coronary artery occlusion, epicardial application of pharmacological agents) to more diffuse circulatory stimuli (e.g., volume expansion, hemorrhage, water immersion). In addition, the degree to which afferent input from other receptor areas influences the response of the receptor area under study is quite variable. Furthermore, the variety of efferent renal nerve recording techniques ranging from single fiber to few multifiber to whole nerve is an additional variable. Thus, these multiple considerations make it difficult to give an unambiguous description of these various control systems.

Karim et al. (1972) demonstrated that relatively discrete activation of canine left atrial receptors by distension of balloons at the left pulmonary vein-atrial junction produced a mean decrease in impulse frequency of 27% in efferent RSNA; the response was abolished by cooling or section of both cervical vagi. This response was specific for the kidney since simultaneously measured cardiac sympathetic nerve activity increased while there was no change in lumbar or splenic sympathetic nerve activity. This response was not influenced by alterations in carotid sinus pressure (*Linden* et al. 1979) and was shown to be dependent only on atrial receptors discharging into myelinated vagal fibers (*Linden* et al. 1980). *Prosnitz* and *DiBona* (1978) showed that more widespread activation of canine left

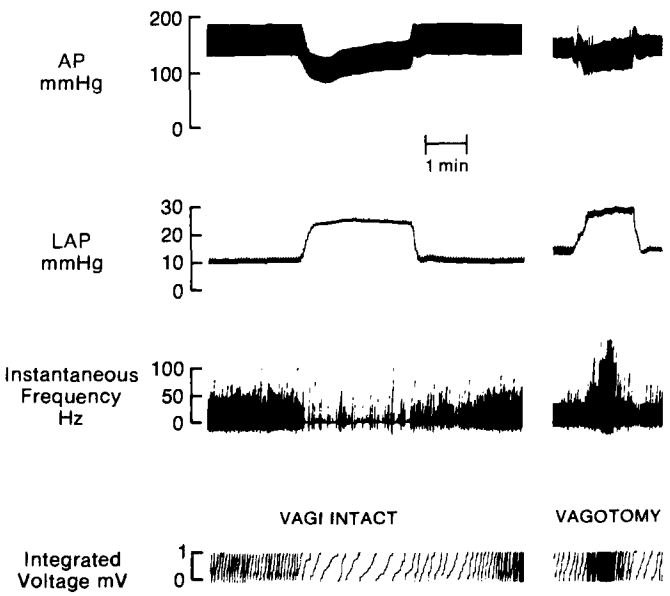

Fig. 1. Effect of left atrial balloon inflation on efferent renal sympathetic nerve activity in the anesthetized dog. *AP*, arterial pressure; *LAP*, left atrial pressure. (*Prosnitz* and *DiBona* 1978)

atrial receptors by left atrial balloon inflation produced a mean decrease in impulse frequency of 40% in efferent RSNA; this response was abolished by section of both cervical vagi (Fig. 1). Thus, these several studies indicate that left atrial receptor stimulation, independent of afferent input from carotid sinus baroreceptors, reflexly decreases efferent RSNA via an afferent pathway consisting of myelinated vagal fibers.

Other workers have measured efferent RSNA following more nonspecific stimulation of receptors in the cardiopulmonary region subserved by vagal afferents. *Clement* et al. (1972) showed that 10% expansion of the blood volume in sinoaortic denervated rabbits reduced efferent RSNA by 41%; withdrawal of the blood volume returned efferent RSNA to the control level. A similar decrease in blood volume increased efferent RSNA by 33%; restoration of the blood volume returned efferent RSNA to the control level. These changes were unaffected by cutting the vagi at the diaphragm but were abolished by cutting the vagi in the neck. Interruption of vagal afferents resulted in an increase in efferent RSNA, indicating that vagal afferents exert a tonic inhibition on the sympathetic outflow to the kidney. These experiments demonstrate a role for the low pressure cardiopulmonary receptors (precise location indeterminate) in the control of efferent RSNA in response to changes in blood volume. *Mancia* et al. (1973), in dogs with aortic nerves cut and input from the carotid baroreceptors minimized by vascular isolation and perfusion of the carotid sinuses at 40 mmHg, demonstrated that cold block or section of the cervical vagi increased efferent RSNA by 28%. Cooling of the cervical vagi with carotid sinus pressure at 200 mmHg resulted in no change in efferent RSNA. In anesthetized sinoaortic denervated dogs *Thames* et al. (1980b) have shown that blood volume expansion produces a dose-dependent increase in left atrial pressure and a decrease in efferent RSNA which show a significant inverse linear correlation; the inhibition of efferent RSNA was enhanced by circumflex coronary artery injection of acetylstrophanthidin and abolished by vagotomy. Thus, cardiopulmonary receptors (precise location indeterminate) with afferent vagal fibers exert a tonic restraint on efferent RSNA, especially when input from the carotid and aortic baroreceptors is decreased or eliminated.

In consideration of the interaction between low and high pressure baroreceptor reflexes in the control of efferent RSNA and the regulation of blood volume, several studies have been performed in which the major intervention is an acute change in blood volume, *Echtenkamp* et al. (1980), in the anesthetized nonhuman primate *Macaca fascicularis,* demonstrated that bolus intravenous volume expansion increased left atrial pressure and decreased efferent RSNA. The inhibition of efferent RSNA was partially abolished by vagotomy and totally abolished by a combination of vagotomy and sinoaortic denervation. Similar results were obtained

in the anesthetized cat (*Echtenkamp* and *Gilmore* 1980). In both the monkey and the cat, following vagotomy and sinoaortic denervation, there was no change in efferent RSNA following the administration of norepinephrine, intravascular volume expansion, or veratrine to stimulate intravascular mechanoreceptors. Similar results have been observed in the dog (*Zucker* et al. 1981). Thus, these observations indicate that there are no afferent pathways mediating intravascular mechanoreceptor modulation of efferent RSNA outside the carotid sinus, aortic and vagus nerves. These findings, which agree with those of *Clement* et al. (1972) in the rabbit, exclude a role for sympathetic afferent fibers and thus do not agree with the studies of *Weaver* et al. (1977, 1979) in the cat. *Weaver* (1977), in the anesthetized cat subjected to baroreceptor denervation and vagotomy, found that blood volume expansion produced a decrease in efferent RSNA which was correlated with the increase in central venous pressure. This response was abolished by thoracic sympathectomy. This difference in results was postulated to be time dependent in that it is possible that sympathetic afferent pathways may eventually compensate for lost baroreceptor and vagal pathways; however, their physiological role in the intact animal would be small. *Ricksten* et al. (1979), in sinoaortic denervated rats, showed that plasma volume expansion produced a decrease in efferent RSNA that was correlated with the increase in mean left atrial pressure. Bilateral vagotomy restored renal nerve activity to pre-plasma volume expansion levels. Aortic constriction produced a rise in mean left atrial pressure in association with a decrease in mean arterial pressure and efferent RSNA; bilateral vagotomy prevented decrease in efferent RSNA. These several studies indicate that low pressure cardiopulmonary receptors, located in the left side of the heart, with vagal afferent fibers participate in the control of efferent RSNA in response to changes in intravascular volume.

The role of cardiopulmonary sympathetic afferents in reflexly influencing efferent RSNA has been studied in some detail. *Weaver* (1977), in the sinoaortic denervated and vagotomized cat, showed that electrical activation of cardiopulmonary sympathetic afferent nerves decreased (low frequency, 1–3 Hz) or increased (high frequency, 5–20 Hz) efferent RSNA. *Purtock* et al. (1977) further demonstrated that sympathetic afferent fibers from cardiopulmonary receptors can modulate efferent RSNA during hypotension. Dogs were subjected to a constant pressure hemorrhage technique to lower mean arterial pressure to 50 mmHg; this produced stimulation of efferent RSNA via constant stimulation to the arterial baroreceptors. In agreement with the findings of *Weaver* (1977), low frequency (3 Hz) stimulation of cardiopulmonary sympathetic afferents decreased efferent RSNA, while high frequency (30 Hz) stimulation increased it. In a subsequent study, *Weaver* et al. (1979) explored further

the ability of the cardiopulmonary sympathetic afferent nerves to both excite and inhibit efferent RSNA. The hypothesis that this was due to opposite responses of individual renal neurons to afferent stimulation was rejected because virtually all single postganglionic renal fibers responded to electrical cardiopulmonary sympathetic afferent stimulation with excitation followed by inhibition of discharge. The hypothesis that different cardiopulmonary sympathetic afferent neurons have opposite influences on renal nerve activity was confirmed when it was demonstrated in vagotomized cats that sympathetic afferent fibers activated by stretch of the right or left ventricle or aorta caused reflex excitation of renal nerve activity, whereas activation of sympathetic afferent fibers from the pulmonary vasculature by intravascular volume expansion or pressure increase caused an inhibition of this discharge. Stretch of the right or left atrium produced no change in renal nerve activity. Thus, the complexity of cardiopulmonary sympathetic afferent influences on efferent RSNA is due to heterogeneity within the afferent rather than the efferent neural population.

Kampine and colleagues (1980) have recently summarized their studies on the role of cardiopulmonary reflexes in the regulation of efferent RSNA. Lung inflation decreased efferent RSNA via activation of pulmonary stretch receptors with vagal afferents; lesser components derived from sympathetic afferents within the lung and chest wall receptors. Rapid increases in pulmonary arterial pressure decreased efferent RSNA via vagal afferent pathways. Rapid increases in chamber volume or pressure in all four cardiac chambers decreased efferent RSNA via vagal afferent pathways. They concluded that activation of cardiopulmonary afferents may decrease effferent RSNA; receptors with vagal afferent pathways predominate over receptors with sympathetic afferent pathways.

There is evidence that both cardiac receptors with vagal afferents and sympathetic afferents are activated by coronary occlusion and chemical stimuli (*Thoren* 1979; *Uchida* 1979; *Coleridge* and *Coleridge* 1980). *Thames* and *Abboud* (1979a) examined the response to coronary occlusion (left anterior descending, LAD = anterior-lateral left ventricle; circumflex, Cx = inferoposterior left ventricle) in dogs with only carotid or with sinoaortic baroreceptors operative. LAD occlusion produced a small decrease in mean arterial pressure and a 24% increase in efferent RSNA, while Cx occlusion produced a greater decrease in mean arterial pressure and no change in efferent RSNA. The changes in left atrial pressure after LAD and Cx occlusion were similar. In carotid sinus or sinoaortic denervated dogs, coronary occlusions resulted in decreases in mean arterial pressure and efferent RSNA which were consistently greater during Cx occlusion than during LAD occlusion. These responses were abolished by vagotomy and enhanced by circumflex coronary artery injection of acetylstrophanthidin (*Thames* et al. 1980b). *Waickman* and *Abboud* (1980) have shown

that activation of cardiac afferent nerves during coronary occlusion may prevent the compensatory reflex increase in sympathetic nerve activity seen during arterial hypotension. In anesthetized dogs with sectioned aortic nerves and isolated perfused carotid sinuses, reduction in carotid sinus pressure produced an increase in efferent RSNA which was the same in the absence and presence of LAD occlusion, whereas the response was markedly suppressed in the presence of Cx occlusion. These studies demonstrate that Cx occlusion and, to a lesser degree, LAD occlusion result in reflex inhibition of efferent RSNA mediated by left ventricular receptors with vagal afferents preferentially distributed in the inferoposterior left ventricular wall. *Thames* (1979) has also shown that left ventricular epicardial application or circumflex coronary artery injection of acetylstrophanthidin produced decreases in mean arterial pressure (25 mmHg), heart rate (10 beats/min), and efferent RSNA (5.6 Hz or 40%) which were blocked by vagotomy.

Weaver and *Reimann* (1979) showed in sinoaortic denervated cats that Cx occlusion inhibited efferent RSNA and that this effect was abolished by vagotomy. Conversely, LAD or right coronary artery occlusion produced excitation of efferent RSNA. In a further study, *Weaver* et al. (1981) showed that cardiac sympathetic afferent nerves can have excitatory influences on efferent RSNA during myocardial ischemia (coronary occlusion) that oppose inhibitory influences originating from vagally innervated cardiac receptors. These cardiac sympathetic afferent neurons can also contribute to the support of arterial pressure or the genesis of hypertension in this condition. Epicardial or intracoronary administration of bradykinin or potassium chloride increased mean arterial pressure and efferent RSNA in vagotomized, sinoaortic, denervated cats (mediated by cardiopulmonary sympathetic afferents), decreased mean arterial pressure and efferent RSNA in sinoaortic, cardiopulmonary sympathetic afferent denervated cats (mediated by vagal afferents), and produced increases, decreases, or no change in efferent RSNA in cats with only sinoaortic denervation or total innervation intact (*Reimann* and *Weaver* 1980). *Felder* and *Thames* (1980) have shown that bradykinin application to left ventricular myocardium can lead to both increases and decreases in efferent RSNA in sinoaortic, denervated, vagotomized dogs. These observations suggest that coronary occlusion with myocardial ischemia and possible attendant changes in the chemical milieu of cardiac receptors (*Reimann* and *Weaver* 1980; *Coleridge* and *Coleridge* 1980) can chemically activate cardiopulmonary sympathetic afferent neurons which are able to significantly alter mean arterial pressure and efferent RSNA despite the opposition of other vascular and cardiac afferent neurons.

Volume expansion is known to decrease efferent RSNA. In anesthetized dogs with a 50% increase in blood volume produced by an acute

isotonic saline load, *Judy* et al. (1971) demonstrated a reduction in efferent RSNA to 23% of the control value which persisted after mean arterial pressure returned to control level and was inversely correlated with the natriuresis and diuresis. In anesthetized, sinoarotic, denervated rabbits with a 10% increase or decrease in blood volume (dextran infusion or hemorrhage), *Clement* et al. (1972) observed that changes in efferent RSNA were inversely correlated with alterations in blood volume: expansions decreased efferent RSNA by 41% while depletion increased efferent RSNA by 33%. The effect on efferent RSNA was reversible and abolished by bilateral vagotomy in the neck but not at the diaphragm. Interruption of vagal afferents caused a 21% increase in basal efferent RSNA, indicating that the vagal afferents exert a tonic inhibition of efferent RSNA. In unanesthetized, conscious cats with intact or denervated sinoaortic baroreceptors, *Schad* and *Seller* (1976) showed that 11% blood volume expansion decreased efferent RSNA by 48%; no differences were noted between animals with intact and denervated sinoaortic baroreceptors. *Recordati* and *Spielman* (1977) demonstrated that isotonic saline volume expansion decreased efferent RSNA by 30%–50% in normal rats, in sinoaortic, denervated plus vagotomized rats, and in vagotomized plus spinal rats. All three groups showed bradycardia with increases in right atrial and mean arterial pressure. Visceral afferent stimulation (bladder distention) increased efferent RSNA. These results suggest that efferent RSNA may be modified by activation of visceral afferent input to the spinal cord and indicate a possible role for spinal sympathetic reflexes in the control of renal function. In anesthetized rats given a 5% body weight acute isotonic saline load, *Kottra* et al. (1978) reported that efferent RSNA decreased by 50% within 10–15 min after the start of the infusion and remained decreased by 30%–40% for the ensuing 45 min; mean arterial pressure was unchanged and the degree of natriuresis and diuresis appeared to correlate with the depression of efferent RSNA. *Ricksten* et al. (1981) have shown that intravenous isotonic saline volume expansion decreases efferent RSNA in conscious unanesthetized rats (Fig. 2). Thus, volume expansion decreases efferent RSNA in several mammalian species, both anesthetized and unanesthetized. These observations are consistent with the view that low pressure cardiopulmonary baroreceptors with vagal afferents participate in the control of efferent RSNA in response to acute changes in blood volume.

Ferrario and colleagues have shown that dietary sodium deprivation decreases the reflex pressor response to carotid sinus hypotension (*Brosnihan* et al. 1978) and decreases the reflex responses of efferent RSNA to changes in mean arterial pressure (*Takeshita* and *Ferrario* 1980). This blunting was abolished following bilateral cervical vagotomy, implicating the buffering effects of either aortic or vagal afferent receptors on efferent RSNA in sodium-deprived dogs.

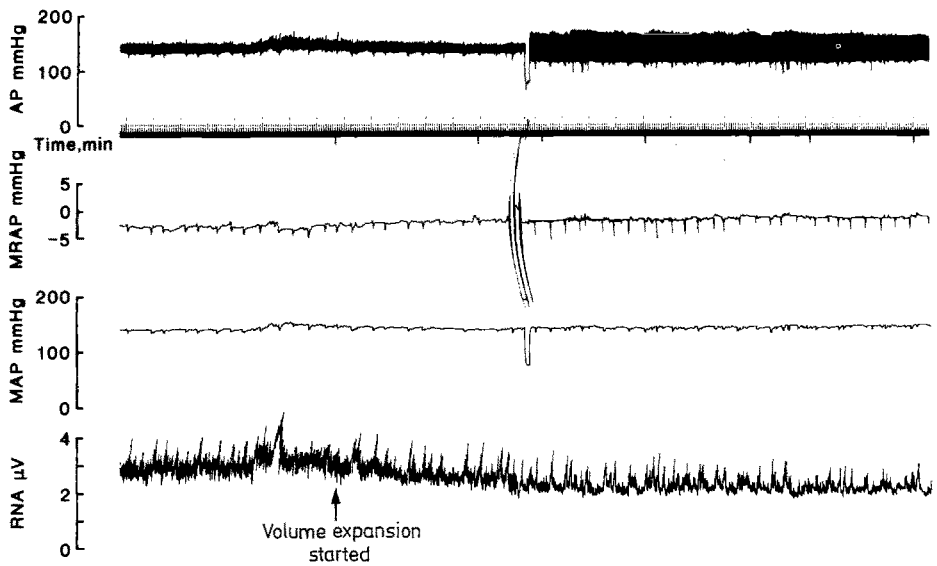

Fig. 2. Effect of intravenous isotonic saline volume expansion (*VE*) in the conscious rat. *AP*, arterial pressure, *MRAP*, mean right atrial pressure; *MAP*, mean arterial pressure; *RNA*, renal nerve activity. (*Ricksten* et al. 1981)

Somatic, visceral, chemosensitive, and other afferents are known to exert an effect on efferent RSNA. *Fedina* and colleagues (1966) showed in anesthetized cats that single shock stimulation of the afferent limb of tibial or mesenteric nerve produced a reflex discharge and subsequently an inhibition of efferent RSNA. The inhibition was related to impulses of fast-conducting A fibers while, if sufficient stimulation intensity is used for exciting the afferent C fibers, a second reflex discharge follows the initial one. *Pelletier* and *Shepherd* (1975a), in vagotomized dogs, showed that stimulation of skeletal muscle receptors with capsaicin increased efferent RSNA by 111% over the maximum level recorded when carotid sinus pressure was 40 mmHg. The same workers (*Pelletier* and *Shepherd* 1975b) showed that the effect of hypoxia on efferent RSNA was small during the control state but was larger by 56% during bilateral carotid occlusion. In the anesthetized carotid sinus denervated dog, *Whitwam* et al. (1979) showed that stimulation of the afferent limb of cutaneous nerves elicited two reflex discharges in efferent RSNA, whereas stimulation of the afferent limb of muscular nerves elicited the earlier but not the later of the reflex discharges in efferent RSNA. In anesthetized cats, *Ninomiya* and *Fujita* (1976) observed that efferent RSNA was little affected by changing skin temperature whereas changes in hypothalamic temperature elicited larger changes in efferent RSNA. In anesthetized cats, *Ninomiya* et al. (1974) showed that sinusoidal increases in intestinal pressure with a

maximal amplitude of 20 cm H_2O increased efferent RSNA by only 7%, whereas the increase in intestinal nerve activity was 107%. They concluded that reflex excitation by intestinal mechanoreceptor inputs through the sympathetic system is greater in intestinal nerves than in renal nerves. *Niijima* (1976), in anesthetized rabbits, showed that portal vein occlusion or elevation of mesenteric venous pressure produced a decrease in efferent RSNA that was similar to that produced by stimulation of the central part of a cut mesenteric branch of the splanchnic nerve; none of these responses was affected by a bilateral cervical vagotomy. It was suggested that mechanoreceptors in the mesenteric vein have reflex inhibitory input on efferent RSNA. *Kostreva* et al. (1980) showed, in dogs, that hepatic baroreceptor activation produced reflex increases in efferent RSNA that were eliminated by section of the anterior hepatic nerves. It was suggested that this hepatorenal reflex might be an important reflex mechanism that becomes activated during congestive heart failure and cirrhosis of the liver. Stimulation of the decentralized stellate ganglion decreases efferent RSNA (*Takeuchi* et al. 1968; *Prosnitz* and *DiBona* 1978) and this is abolished by carotid sinus denervation (*Prosnitz* and *DiBona* 1978). Thus, multiple afferent inputs from a wide variety of receptors with responses to different stimuli can influence efferent RSNA.

Multiple pharmacological agents are known to produce alterations in efferent RSNA. As exemplified by the study of *Aars* (1972) in the anesthetized rabbit, α-adrenoceptor antagonists (phenoxybenzamine) produce a reflex inhibition of efferent RSNA despite a fall in mean arterial pressure. Similar observations have been reported with clonidine in anesthetized, vagotomized, sinoaortic, denervated cats by *McCall* and *Gebber* (1976); these studies indicated a possible activation by clonidine of central components of the baroreceptor reflex known to decrease efferent RSNA. Similarly, β-adrenoceptor antagonists, both nonselective propranolol (*Friggi* et al. 1977a) and β-1 selective atenolol (*Friggi* et al. 1977b), decrease efferent RSNA in the anesthetized rabbit despite decreases in mean arterial pressure. In the anesthetized cat, 1-(4-oxyphenyl)-2*n*-butylaminoethanone hydrochloride (BON) markedly inhibits efferent RSNA (*Fedina* et al. 1970) in the resting state and the reflex response to bilateral carotid occlusion, acetylcholine-induced hypotension, asphyxia, or stimulation of somatic afferents. In anesthetized cats intravenous administration of L-dopa (*Watanabe* et al. 1974) or 5-hydroxytryptophan (*Baum* and *Shropshire* 1975) with an extracerebral decarboxylase inhibitor to prevent peripheral conversion of L-dopa to catecholamines results in a decrease in mean arterial pressure, heart rate, and efferent RSNA. This response is probably produced by an increase in central nervous system catecholamines since the hypotensive effect of L-dopa is accompanied by a concomitant accumulation of catecholamines in the brain. In support of a

spinal action of L-dopa to decrease efferent RSNA, similar observations were made in unanesthetized decerebrate cats (C_1 cord section) by *Coote* and *McCleod* (1974). Administration of dopamine, norepinephrine (*Baum* and *Shropshire* 1973), 5-hydroxytryptophan, and 5-hydroxytryptamine (*Baum* and *Shropshire* 1975) into the cerebral ventricle decreases efferent RSNA in anesthetized cats.

Another pharmacological agent which modulates efferent RSNA, possibly by a central nervous system effect, is angiotensin II. *Aars* and *Akre* (1968), in the anesthetized rabbit, showed that angiotensin II infusion initially produced a decrease in the normal rhythmic pulse-synchronous efferent RSNA but then produced a nonrhythmic increase in efferent RSNA associated with a further increase in mean arterial pressure. This latter response was not related to changes in baroreceptor (aortic nerve) activity and could not be attributed to stimulation of chemoreceptors or sympathetic ganglia; an effect on central sympathetic neurons was postulated. *Ferrario* et al. (1976) showed, in anesthetized dogs, that vertebral artery infusion of angiotensin II produced a pressor response in association with an increase in splanchnic preganglionic nerve activity and a decrease in efferent RSNA. Whether the renal response was the result of selectively altered central control or was a reflex response secondary to baroreceptor activation was clarified by the experiments of *Fukiyama* (1972). Vertebral artery infusion of angiotensin II in anesthetized dogs produced a rise in mean arterial pressure and an initial increase in splanchnic preganglionic nerve activity and in efferent RSNA. During the sustained rise in mean arterial pressure, the rhythmic pulse-synchronous discharge in the efferent renal nerve disappeared completely and was replaced by nonrhythmic activity while the increase in splanchnic nerve activity was sustained. Thus, multiple pharmacological agents with a wide spectrum of cardiovascular and renal actions can influence efferent RSNA.

The subject of spinal and supraspinal regulation of sympathetic nervous discharge, central nervous system organization and control of the baroreceptor reflex, and regulation of vascular resistance has been extensively reviewed recently and will not be dealt with further (*Gebber* 1980; *Spyer* 1981; *Hilton* and *Spyer* 1980).

3.2 Afferent Renal Nerves

Action potentials initiated by the activation of sensory nerve endings in the kidney have been recorded from the afferent renal nerves (*Ueda* and *Uchida* 1968) of rats (*Astrom* and *Crafoord* 1967; *Recordati* et al. 1978), cats (*Pines* 1960, 1966; *Astrom* and *Crafoord* 1968; *Beacham* and *Kunze* 1969; *Kady* 1974; *Calaresu* et al. 1978), dogs (*Ueda* et al. 1967, 1971;

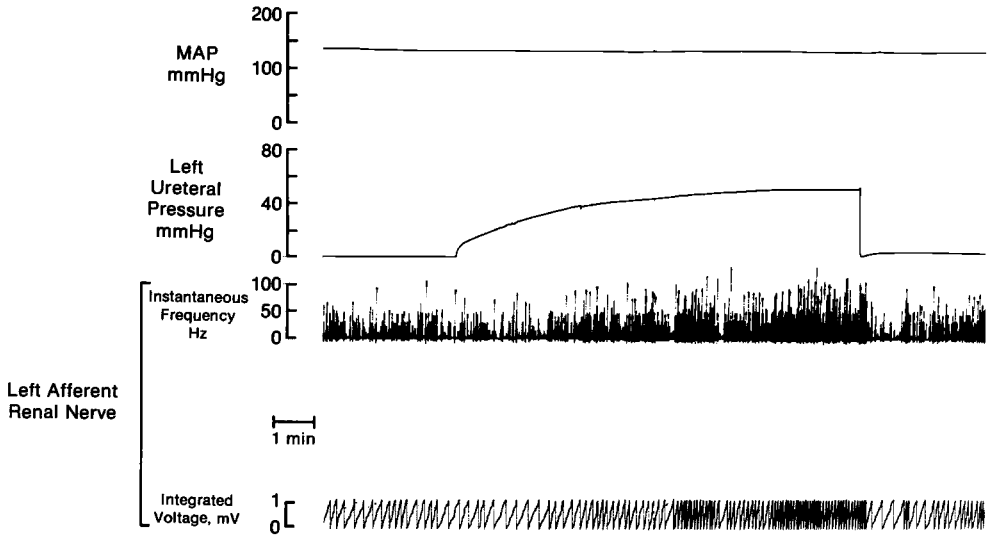

Fig. 3. Effect of ureteral occlusion on afferent renal nerve activity in the anesthetized dog. *MAP*, mean arterial pressure. (*Francisco* et al. 1980a)

Uchida et al. 1971; *Kady* 1974; *Francisco* et al. 1980), and rabbits (*Niijima* 1971, 1972a, b, 1975). These renal receptors respond to changes in intrarenal pressure as produced by alterations in renal artery pressure, renal vein occlusion, ureteral occlusion, or compression of the kidney and have been termed renal mechanoreceptors (Fig. 3). Other receptors, termed renal chemoceptive receptors, have been described by *Recordati* et al. (1978, 1980b) who have classified them into two groups in the rat. The R1 renal chemoceptive receptors are activated by renal ischemia as produced by renal artery occlusion, systemic hypotension, renal vein occlusion, or systemic asphyxia (*Recordati* et al. 1978). The R2 renal chemoceptive receptors are activated by alterations in the chemical environment of the renal interstitium as produced by changes in the excretory function of the kidney, the passage of ions from the renal pelivs across the pelvic epithelium (backflow of nondiuretic urine into the renal pelvis) (*Recordati* et al. 1980b), and injection of substances normally present in the urine into the renal artery of the cat (*Pines* 1969). The responses of these renal chemoceptive receptors are independent of changes in pelvic or intrarenal pressure. Thus, the renal nerves contain multiple afferent fibers which carry impulses centrally from renal receptors of different varieties and specificities.

Ciriello and *Calaresu* (1980) have studied the central projections of afferent renal nerve fibers in the cat. Stimulation of afferent renal nerves evoked responses bilaterally in the paramedian reticular nucleus and lateral tegmental field of the medulla and in the lateral preoptic nucleus,

the lateral hypothalamus, and the paraventricular nucleus of the hypothalamus. Fifty-seven percent of the medullary units and 74% of the hypothalamic units also responded to afferent carotid sinus nerve stimulation. Similar central projections have been described for rat renal afferent nerve fibers (*Knuepfer* et al. 1980). Thus, renal afferent information is relayed to well-defined regions of the medulla and hypothalamus presumably involved in cardiovascular regulation and body sodium and water balance. A large proportion of these units show convergence of inputs from afferent renal nerve and afferent carotid sinus nerve fibers.

3.3 Summary

As can be seen from even a cursory review of the many published reports in this area, there are multiple pathways whereby efferent RSNA may be altered. It is not yet precisely understood whether summation or interaction exists between the effects of simultaneous activation of multiple different receptors on efferent RSNA. Additionally, the influence of concomitant changes in variables that can elicit known or unknown compensatory responses has not been rigorously defined. These several qualifications make it difficult to attribute changes in efferent RSNA to a well-defined isolated reflex involving one type of receptor. Nevertheless, the available information allows some general conclusions concerning interventions which are known to produce substantial and consistent alterations in net efferent RSNA. Left atrial receptor stimulation produces a reflex decrease in efferent RSNA which is mediated by atrial receptors subserved by afferent vagal myelinated fibers. Receptors with vagal afferent fibers exert a tonic inhibitory restraint on efferent RSNA which is more pronounced when afferent input from the carotid and aortic baroreceptors is minimized. Studies involving acute increases in blood volume, with increases in left atrial and mean arterial pressure, produce reflex decreases in efferent RSNA which are largely dependent on vagal afferent fibers; the remainder of the afferent input derives from receptors subserved by the sinoaortic nerves. A role for receptors subserved by cardiopulmonary sympathetic afferent fibers in the response of efferent RSNA to volume expansion, coronary artery occlusion (myocardial ischemia), or intracoronary/epicardial administration of pharmacological agents has been proposed, but further investigation is required to define more clearly a physiological role for these pathways. Multiple other afferents (somatic, visceral, chemosensitive) as well as diverse pharmacological agents exert effects on efferent RSNA; their role in modulating physiologically important responses is less well understood. Although experiments involving the isolation and stimulation of a single receptor type, in the absence of con-

comitant or compensatory responses involving other receptor mechanisms, are important for the definition of a reflex pathway, it is apparent that under most physiological conditions the alteration in efferent RSNA is a net response to a stimulus which involves multiple receptor mechanisms.

Renal receptors, both mechanoreceptors and chemoceptive receptors, which when stimulated produce increases in afferent renal nerve activity and have central projections, have been more firmly identified in multiple mammalian species. Such observations provide the basis for considering the existence of reflexes arising in the kidney and affecting cardiovascular and renal mechanisms important in the regulation of arterial pressure, regional vascular resistance, and body sodium and water balance.

4 Physiological Functions of the Renal Nerves

4.1 Control of the Renal Circulation

The regulation of renal blood flow (*Aukland* 1976, 1980a, b) and the reflex influences of the arterial baroreceptors, cardiopulmonary mechanoreceptors, and chemoreceptors on the renal circulation (*Kirchheim* 1976; *Linden* 1975; *Donald* and *Shepherd* 1978, 1980; *Thames* 1978; *Thoren* 1979; *Coleridge* and *Coleridge* 1980) have been dealt with in several recent comprehensive reviews.

The question of whether the kidney possesses sympathetic cholinergic vasodilator fibers (*Stinson* et al. 1969) has been reexamined (*Zambraski* et al. 1978). Using isolated carotid sinus perfusion techniques to increase carotid sinus pressure and inhibit efferent RSNA, renal blood flow increased by only 5% and renal vascular resistance decreased by only 4%; these small changes in renal blood flow and renal vascular resistance were unaffected by renal arterial administration of atropine (Fig. 4). The maximum renal vasodilator response to reduction of renal perfusion pressure below the autoregulatory range was not affected by renal arterial administration of atropine. The renal vasoconstrictor response to graded direct electrical renal nerve stimulation was abolished by renal adrenergic blockade with guanethidine and never replaced by a renal vasodilator response. These experiments indicate that there are no functional renal sympathetic cholinergic vasodilator fibers. These observations are in agreement with previous studies by *Takeuchi* et al. (1961, 1965, 1971), *Brody* (1962), *Concha* and *Norris* (1968), *Ueda* et al. (1968), *DiSalvo* and *Fell* (1971), and *Gomer* and *Zimmerman* (1972). In addition, these studies provide physiological support and confirmation of *Barajas* and colleagues' sophisticated anatomical studies which demonstrate that the acetylcholinesterase-containing nerve terminals are adrenergic (*Barajas* et al. 1974, 1975, 1976).

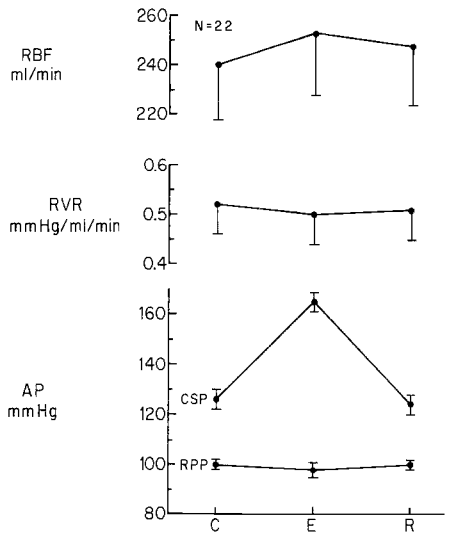

Fig. 4. Effect of increasing carotid sinus pressure (*CSP*) on renal perfusion pressure (*RPP*, held constant), renal blood flow (*RBF*) and renal vascular resistance (*RVR*) in the anesthetized dog. *C*, control; *E*, experimental; *R*, recovery; *AP*, arterial pressure. (*Zambraski* et al. 1978)

However, activation of other reflex pathways has been demonstrated to result in a reduction in efferent RSNA or a renal vasodilatation or both. Increases in hepatic portal venous pressure (portal vein occlusion) produce decreases (*Niijima* 1976) or no change (*Kostreva* et al. 1980) in efferent RSNA and renal vasodilatation (*Niijima* 1976). Stimulation of left atrial cardiopulmonary receptors decreases efferent RSNA (*Karim* et al. 1972; *Prosnitz* and *DiBona* 1978) and results in modest renal vasodilatation (*Mason* and *Ledsome* 1974; *Lloyd* and *Friedman* 1977). *Kahl, Flint,* and *Szidon* (1974) noted that the magnitude of the renal vasodilatation was minimal when initial renal vasomotor tone was low, but was substantial when initial renal vasomotor tone was high due to spontaneous renal vasoconstriction. Using conditions of controlled carotid sinus pressure and measuring renal blood flow at a constant systemic pressure, *Karim* and *Kappagoda* (1980), in a preliminary report, showed that the renal vasodilator response to left atrial receptor stimulation was greatest (11%) when carotid sinus pressure was lowest, i.e., when the inhibitory effect of carotid sinus baroreceptors on efferent RSNA was minimal. However, there was no difference between the responses at medium and high carotid sinus pressure. This effect was abolished by either cutting or cooling the cervical vagi. As reviewed by *Thames* and *Abboud* (1979a, b), coronary artery occlusion is known to produce reflex decreases in efferent RSNA and renal vasodilatation mediated by left ventricular receptors with vagal afferents located mainly in the distribution of the circumflex coronary artery (*Thames* et al. 1978; *Walter* et al. 1978). Although *Stinson* et al. (1976) suggested that the renal vasodilatation was cholinergically mediated, atropine administration decreased basal renal blood flow, thus making

these results difficult to interpret. Thoracic afferent nerve stimulation at low frequencies (3 Hz) produced an inhibition of efferent RSNA and a renal vasodilatation which was enhanced following vagotomy (*Purtock* et al. 1977). However, while it is likely that these reflex vasodilator responses are related to the simultaneous reflex decrease in efferent RSNA, studies to assess the possible role of renal sympathetic cholinergic vasodilator fibers have not generally been reported.

Aukland has extensively reviewed the available methologies for measuring the regional distribution of blood flow within the kidney (*Aukland* 1980a, b). None of the currently available techniques is sufficiently free of methodological limitations to allow meaningful interpretation of results. In particular, because of unacceptable rheological problems, it does not appear possible to estimate changes in renal cortical blood flow distribution from the deposition of microspheres.

Several recent studies deal with the relative influence of neuroadrenergic stimuli on the glomerular afferent and efferent arterioles (*Blantz* 1980). Utilizing newer micropuncture techniques in rats with accessible surface glomeruli, it has been shown that norepinephrine administration (*Myers* et al. 1975) increases efferent but not afferent arteriolar resistance when renal perfusion pressure is constant. However, *Andreucci* et al. (1976a, b) concluded, using similar parenteral infusions of norepinephrine, that the afferent glomerular arteriole was the major site of action for catecholamines. Although a preferential effect of norepinephrine on the efferent arteriole agrees with the older observations on epinephrine by *Richards* and *Plant* (1922), subsequently supported by *Smith* et al. (1940), the work of *Gomez* (1951) demonstrated that constancy of glomerular filtration rate in the face of a reduction in renal blood flow required equal changes in afferent and efferent arteriolar resistance. Subsequently, *Smith* (1951) also acknowledged this. However, *Click* et al. (1979) have studied the vascular reactivity of afferent and efferent arterioles of glomeruli transplanted into the hamster cheek pouch. Application of norepinephrine produced greater reductions in the luminal diameter of afferent than efferent arterioles, whereas application of angiotensin II produced slightly greater reductions in the luminal diameter of efferent than afferent arterioles. Afferent arterioles were more responsive to norepinephrine than angiotensin II, while the reverse was true for efferent arterioles. Thus, these direct studies indicate that both afferent and efferent glomerular arterioles respond to norepinephrine with vasoconstriction and that the afferent arteriole is more reactive to norepinephrine than the efferent arteriole. In companion studies, *Gilmore* et al. (1980) have shown that the preafferent and afferent glomerular arterioles are capable of myogenic responses when subjected to increases or decreases in extravascular pressure; a decrease in extravascular pressure decreased and an increase in

extravascular pressure increased the arteriolar luminal diameter. Angiotensin II antagonist (saralasin) and prostaglandin synthesis inhibitor (indomethacin) did not affect these responses, whereas they were abolished by papaverine. Conversely, the efferent glomerular arterioles responded passively to changes in extravascular pressure with changes in luminal diameter being inversely related to changes in extravascular pressure.

In rat micropuncture studies, parenteral angiotensin II infusion increased both afferent and efferent arteriolar resistance when renal perfusion pressure was kept constant (*Myers* et al. 1975; *Blantz* et al. 1976). Concurrent administration of the angiotensin II receptor antagonist, saralasin, restored efferent but not afferent arteriolar resistance to normal (*Steiner* and *Blantz* 1979). During conditions where endogenous intrarenal angiotensin II is increased, increases in afferent and efferent arteriolar resistance are observed. In chronic sodium deprivation, saralasin administration decreases afferent but not efferent arteriolar resistance (*Steiner* et al. 1979). Activation of the tubuloglomerular feedback system increases both afferent and efferent arteriolar resistance (*Tucker* et al. 1978); both are decreased by saralasin administration (*Tucker* and *Blantz* 1978). These observations help explain the responses of renal blood flow and glomerular filtration rate to direct electrical renal nerve stimulation. During intensities which caused less than 15% reduction in renal blood flow, it was noted that glomerular filtration rate remained normal. However, renal nerve stimulation after propranolol (*Johns* et al. 1976), angiotensin I converting enzyme inhibitor (*Johns* 1979), or angiotensin II antagonist (*Johns* 1980) administration was associated with a decrease in glomerular filtration rate despite an identical reduction in renal blood flow. It was suggested that angiotensin II liberated during renal nerve stimulation prevents glomerular filtration rate from decreasing by constricting the efferent arteriole to maintain glomerular hydrostatic pressure constant. The liberate norepinephrine would act preferentially on the afferent arteriole, while the resultant angiotensin II would act preferentially on the efferent arteriole; removal of the angiotensin II efferent arteriolar vasoconstrictor effect would not greatly affect renal blood flow, but, by decreasing glomerular hydrostatic pressure, would decrease glomerular filtration rate. Similar observations have been made in response to reductions in renal perfusion pressure in the dog (*Hall* et al. 1977a, b) and in the cat (*Johns* 1979).

Dopamine-induced renal vasodilatation has been extensively studied and has been reviewed recently by *Goldberg* and colleagues (*Goldberg* et al. 1978; *Goldberg* 1979; *Goldberg* and *Kohli* 1979). *Bell* and *Lang* (1973) have produced physiological evidence for the existence of renal dopaminergic innervation which is capable of mediating renal vasodilatation. Electrical stimulation of the hypothalamus or midbrain resulted in

renal vasodilator responses which were unaffected by guanethidine, atropine, or mepyramine but were abolished by haloperidol. The doses of haloperidol employed were shown to abolish the renal vasodilator responses to dopamine, but did not affect the femoral vasodilator responses to isoproterenol. These results indicate that the renal vasodilator responses to central stimulation were mediated by renal vascular innervation which released dopamine as a neurotransmitter. *Dinerstein* et al. (1979) have provided evidence for the existence of dopamine-containing neuronal elements in the canine kidney. Changes induced by hydrochloric acid in the excitation spectrum of catecholamine fluorophores associated with the innervation of the canine renal vasculature demonstrated that there are neuronal elements at the glomerular vascular poles which contain predominantly dopamine. In contrast, the catecholamine fluorescence in the periadventitial layer of the arcuate arteries is derived from norepinephrine. These observations agree with the studies of *Bell* et al. (1978) which, using indirect pharmacological evidence, indicated that dopamine-containing vasomotor nerves are present in the dog kidney.

Although the presence of pulse-synchronous efferent RSNA has been demonstrated in conscious unanesthetized cats, rats, and dogs (vide supra), discussion continues as to its renal hemodynamic and physiological significance. Surgical or pharmacological renal denervation in conscious unanesthetized dogs (*Berne* 1952; *Pomeranz* et al. 1968; *Sadowski* et al. 1979a, b) or normotensive man (*Hollenberg* et al. 1971) does not increase renal blood flow or decrease renal vascular resistance. In addition, although high pressure arterial baroreceptors (*Kezdi* and *Geller* 1968) and low pressure left atrial cardiopulmonary mechanoreceptors (*Karim* et al. 1972; *Prosnitz* and *DiBona* 1978) are known to influence efferent RSNA, their influence on renal blood flow and renal vascular resistance in conscious unanesthetized animals is quite small (*Vatner* 1974; *Kaczmarczyk* et al. 1978; *Gross* et al. 1979). This discrepancy may reflect the fact that the neurophysiological recording and renal hemodynamic studies have not been performed under comparable conditions. *Gross* and *Kirchheim* (1980), using conscious dogs, showed that bilateral common carotid artery occlusion increased efferent RSNA by 62%, whereas renal blood flow was unaffected whether renal perfusion pressure was held constant or allowed to rise. Using auditory stimuli, they demonstrated that a gun shot decreased renal blood flow by 40%, whereas a lesser stimulus, hand clap or whistling, increased efferent RSNA by 502%. These results suggest that the difference in the renal vasoconstrictor responses elicited by carotid occlusion and auditory stimuli was caused by a quantitatively different neural output to the kidney, with the increase in efferent RSNA to the kidney during carotid occlusion being insufficient to produce renal vasoconstriction.

However, it is abundantly clear that such increases in efferent RSNA can alter renin release and renal tubular sodium reabsorption.

In agreement with these observations are further studies by *Gross* et al. (1979) on the effect of carotid occlusion on renal blood flow in the conscious dog subjected to nonhypotensive hemorrhage. Whether renal perfusion pressure was held constant or not, renal blood flow was within 5% of control during carotid occlusion during normovolemia and hypovolemia (16% blood loss). Since the response was identical following aortic nerve section, these results indicate that the renal blood flow response was due to autoregulation without inhibitory influences through the aortic baroreceptors, since there was no renal blood flow reduction of neurogenic or humoral origin when renal perfusion pressure was held constant. These conscious unanesthetized dog studies differ from the results of *Oberg* and *White* (1970) in the anesthetized cat, and from those of *Mancia* and colleagues (1973, 1976) in the anesthetized dog. They found that withdrawal of inhibition exerted by cardiopulmonary receptors with vagal afferents produced modest effects in the presence of normally functioning arterial baroreceptors, but pronounced effects after elimination of the inhibitory influences from the arterial baroreceptors. As discussed by *Thoren* (1979), in the anesthetized animal interruption of cardiopulmonary vagal afferents will tend to increase the gain of the carotid baroreceptor reflex, whereas increased activity of the cardiopulmonary receptors following volume expansion will tend to decrease it.

These observations, taken together with the inability of the cardiopulmonary receptors to affect cardiovascular hemodynamics when the arterial baroreceptors are maximally activated, suggested that these two groups of receptor afferents may converge on the same neuron pools within the vasomotor center. However, there seems to be clear evidence for the existence of a differentiated control of sympathetic outflow to various vascular beds in response to a reduction in baroreceptor afferent activity. For example, reduction in carotid sinus pressure in anesthetized dogs with aortic nerves sectioned decreased renal blood flow by approximately 20%, whereas muscle blood flow decreased by approximately 80% (*Pelletier* and *Shepherd* 1975a). However, when excitatory influences from chemoreceptor or somatic afferents are simultaneously activated, this differentiated response is abolished and withdrawal of baroreceptor inhibition also induces a maximal renal vasoconstriction (*Pelletier* and *Shepherd* 1975b). *Folkow* et al. (1961) suggested that the central neuron pools which control the sympathetic outflow to the renal resistance vessels have a low excitability and hence a weak spontaneous or tonic activity. Therefore, in the conscious animal, a reduction in baroreceptor afferent activity probably produces only small changes in the low tonic activity of the renal vasomotor neurons. In contrast, in the anesthetized operated animal it is

likely that there is an enhanced level of tonic activity which becomes manifest when the renal vasomotor neurons are released from baroreceptor restraint. This hypothesis is supported by the fact that in those studies which reported a neurogenic renal vasoconstriction after carotid sinus hypotension an elevated resting renal vasoconstrictor tone was detected (*Kendrick* et al. 1972; *Mancia* et al. 1976; *Pelletier* and *Shepherd* 1975a).

The cardiopulmonary receptors can also influence the renal vascular response to somatic afferent input. *Thames* and *Abboud* (1979b) examined the renal vasoconstrictor responses to afferent sciatic nerve stimulation in anesthetized dogs with sinoaortic denervation. During isovolemia, sciatic stimulation produced renal vasoconstriction; this response was attenuated by volume expansion and augmented by vagotomy. Similar responses were seen when the carotid sinuses were isolated and perfused at constant pressure. Thus, in the absence of the arterial baroreceptors or with intermediate levels of carotid baroreceptor activation, volume expansion with augmentation of discharge of cardiopulmonary receptors with vagal afferents markedly attenuated the renal vasoconstrictor responses to somatic afferent stimulation.

The effects of various humoral substances on vascular neuroeffector mechanisms have been recently summarized (*Bevan* 1978; *Westfall* 1980). Evidence has accumulated which supports the existence of a presynaptic α-adrenoceptor-mediated inhibitory mechanism regulating the release of neuronal norepinephrine from adrenergic nerves (*Starke* 1977, 1981a, b; *Westfall* 1977; *Rand* et al. 1980). The postsynaptic α-adrenoceptor has been designated α-1 and the presynaptic α-adrenoceptor, α-2 (*Berthelsen* and *Pettinger* 1977). In this regard, *Robie* (1980) has evaluated the functional significance of presynaptic α-2 adrenoceptor modulation of renal sympathetic nerve function in the dog. Using α-adrenoceptor agonists and antagonists and inhibitors of neuronal uptake, there was no evidence of a physiologically significant α-adrenoceptor-mediated negative feedback mechanism on renal sympathetic nerve stimulation-induced renal vasoconstriction. On the other hand, acetylcholine produced inhibition of renal vasoconstrictor responses to renal sympathetic nerve stimulation that were dose and frequency dependent; the inhibition was blocked by atropine but unaffected by physostigmine. The effect of acetylcholine was not due to renal vasodilation per se since another renal vasodilator compound, sodium acetate, was ineffective (*Robie* 1979). Similar findings were observed with histamine (*Robie* 1981). The renal vasoconstrictor responses to renal sympathetic nerve stimulation are reduced by ureteral occlusion (*Schramm* and *Carlson* 1975) and by decreases in renal perfusion pressure (*Carlson* and *Schramm* 1978). The inhibition was only partially reversed by blockade of prostaglandin synthesis in agreement

with observations demonstrating increased renal prostaglandin production during ureteral occlusion (*Olson* et al. 1976) and reduction in renal perfusion pressure (*McGiff* et al. 1970). The remainder of the inhibition was ascribed to mechanical factors related to the presence of autoregulatory vasodilation.

During dietary sodium deprivation in dogs, the renal release of norepinephrine, renin, and prostaglandin is increased as compared to values in dogs on a normal dietary sodium intake (*Davila* et al. 1978; *Oliver* et al. 1980b; *Blasingham* et al. 1980). Although dietary sodium deprivation decreased cardiac output and increased total peripheral vascular resistance, mean arterial pressure, renal blood flow, and renal vascular resistance were unchanged. Administration of the prostaglandin synthesis inhibitors indomethacin or meclofenamate to sodium-replete dogs decreased urinary prostaglandin excretion but did not affect mean arterial pressure, cardiac output, renal blood flow, renal vascular resistance, urinary water, sodium or potassium excretion, or plasma renin activity. When administered to sodium-deprived dogs, however, indomethacin or meclofenamate decreased urinary excretion and renal release of prostaglandin, renal blood flow, and urinary flow rate, and increased renal vascular resistance; mean arterial pressure, cardiac output, urinary sodium and potassium excretion, and plasma renin activity were unaffected. Thus, chronic sodium depletion enhances the activity of three major neurohumoral systems capable of directly influencing renal vascular resistance. The renal vasoconstrictor response to indomethacin or meclofenamate seen during chronic sodium depletion but not repletion indicates that renal blood flow is maintained during chronic sodium depletion by an effect of the prostaglandins which cause renal vasodilatation. Similar conclusions were reached by *Zambraski* and *DiBona* (1979), who showed that combined renal α-adrenoceptor and angiotensin II receptor blockade did not affect the renal vasoconstrictor response to indomethacin or meclofenamate in anesthetized surgically stressed dogs. Similar findings with both pharmacological (phenoxybenzamine) and surgical renal denervation have also been reported by *Ehrhart* et al. (1979).

Taken together these results indicate that the renal vasoconstriction associated with systemic administration of prostaglandin synthesis inhibitor is not due to unopposed angiotensin II or α-adrenoceptor agonist vasoconstrictor action, but rather to the withdrawal of endogenous prostaglandin renal vasodilator activity. As recently summarized by *Epstein* and *Litschitz* (1980), there are several clinical disease states partly characterized by decreased effective blood volume with avid renal sodium retention (cirrhosis with ascites, nephrotic syndrome, chronic diuretic abuse, and congestive heart failure) wherein administration of prostaglandin synthesis inhibitors produces marked reductions in glomerular filtration rate

(acute renal insufficiency) with enhanced renal sodium retention. In dogs with experimental cirrhossis and ascites produced by common bile duct ligation, *Zambraski* and *Dunn* (1980) reported that indomethacin administration produced marked renal vasoconstriction with decreased glomerular filtration rate. Taken together, these several observations suggest that heightened renal prostaglandin synthesis may be an important part of the renal adaptive mechanism in states of reduced effective blood volume. Inhibition of these prostaglandin functions may result in marked renal functional impairment with excessive renal sodium and water retention.

In summary, a variety of reflex mechanisms operating singly or in concert are capable of producing significant renal circulatory changes which are mediated by efferent RSNA. Work in conscious unanesthetized animals has further defined the relationship between basal levels of efferent RSNA and the response of both efferent RSNA and renal blood flow to activation of some of these reflex mechanisms. In agreement with anatomical studies, there is no functional evidence to support the existence of sympathetic cholinergic vasodilator fibers in the mammalian kidney.

4.2 Control of Renal Tubular Solute and Water Transport

Investigation of renal solute and water excretion may be said to have begun with *Claude Bernard* (1859), who demonstrated an ipsilateral diuresis in the anesthetized dog following acute section of the greater splanchnic nerve. The diuresis was reversed by direct electrical stimulation of the peripheral cut end of the nerve. Research on the subject of the neural control of renal tubular transport processes has continued over the intervening years and investigators have generally employed one of two experimental approaches. If the renal nerves participate in the control of renal tubular electrolyte and water transport, then it was reasoned that increases or decreases in efferent renal nerve activity should produce reciprocal changes in renal electrolyte and water excretion. To decrease efferent renal nerve activity, the technique of renal denervation has been used; to increase efferent renal nerve activity, the technique of direct electrical stimulation of the renal nerves has been used. Less commonly, reflex interventions have been employed to decrease or increase renal nerve activity.

4.2.1 Renal Denervation

Since the initial observation of *Bernard* (1859), a large number of studies of denervation diuresis and natriuresis have been published. Two mechanisms have received support from the results of such studies. First, the increase in urinary sodium excretion has been ascribed to an increase in

glomerular filtration rate and filtered sodium load (e.g., *Berne* 1952). Second, the increase in urinary sodium excretion has been ascribed to a decrease in renal tubular sodium reabsorption (e.g., *Bonjour* et al. 1969; reviewed by *Takacs* et al. 1978). While the supportive evidence for each mechanism appeared equally distributed, newer investigations since the unequivocal demonstration that mammalian renal tubules receive adrenergic innervation (*Barajas* 1978) have provided growing support for a role of the renal nerves to directly influence renal tubular sodium and water reabsorption.

Initially, *Bencsath* et al. (1972) in the rat, demonstrated by micropuncture that acute section of the left major splanchnic nerve resulted in decreased proximal tubular reabsorption of sodium and water without a change in single nephron glomerular filtration rate. The ipsilateral diuresis and natriuresis were not associated with changes in total kidney or single nephron glomerular filtration rate or the ratio of superficial to juxtamedullary single nephron glomerular filtration rate. *Bello-Reuss* et al. (1975, 1977) acutely denervated the kidney in both hydropenic and volume-expanded rats. They observed an ipsilateral diuresis and natriuresis in the absence of a change in total kidney or single nephron glomerular filtration rate or renal plasma flow. Absolute and fractional sodium and water reabsorption in the proximal tubule were decreased. There was no change in pressure as measured in several cortical microvascular structures, indicating that changes in peritubular Starling forces were not responsible for the observed changes in renal proximal tubular reabsorption. Absolute sodium and water reabsorption increased after denervation in the loop of Henle, distal convoluted tubule, and collecting duct. During hydropenia, the contralateral innervated kidney responded to acute denervation of the other kidney with no change in urinary flow rate or sodium excretin. However, during volume expansion, the contralateral innervated kidney responded to acute denervation of the other kidney with a decrease in urinary flow rate and sodium excretion. The localization of the effect to the proximal tubule by micropuncture confirmed earlier suggestions based on indirect measurements by *Kaplan* and *Rapaport* (1951), *Blake* (1962) and *Bencsath* et al. (1971).

Wilson et al. (1979b) have confirmed that both acute and chronic renal denervation in anesthetized non-volume-expanded rats produces an ipsilateral diuresis, natriuresis, and kaliuresis without a change in glomerular filtration rate or renal plasma flow; no changes in function of the contralateral kidney were observed. Using renal clearance studies in anesthetized, hypophysectomized dogs undergoing a water diuresis, *Nomura* et al. (1972, 1976, 1977) showed that renal denervation increased ipsilateral urinary flow rate and sodium excretion without changing glomerular filtration rate or renal plasma flow. Fractional sodium delivery to the distal

nephron and fractional free water clearance were significantly increased in the denervated kidney, suggesting the proximal tubule as a site of the decreased tubular sodium and water reabsorption. The renal denervation effect of diuresis and natriuresis is not a transient one that is observed only immediately after denervation, since similar results have been observed in chronically denervated kidneys of rats (*Bencsath* et al. 1979), and dogs (*Takacs* et al. 1978). *Kurkus* et al. (1980) have shown that, in dehydrated conscious dogs, urinary osmolality, medullary total solute, and sodium content (per kg wet tissue) were significantly lower in the denervated kidney as compared to the innervated kidney. This may be explained by the fact that the weight of the denervated kidneys was significantly higher than the weight of the innervated kidneys. It was postulated that renal denervation resulted in an increase in renal tissue water content.

Pharmacological renal denervation has also been employed. In anesthetized dogs, administration of guanethidine into the renal artery with the simultaneous intravenous administration of phenoxybenzamine to antagonize the systemic vasoconstrictor effects of liberated norephinephrine produced an ipsilateral increase in the urinary excretion of water, sodium, potassium, chloride, and calcium, while renal perfusion pressure, glomerular filtration rate, and renal blood flow remained unchanged (*Williams* et al. 1971). Renal α-adrenoceptor blockade with phenoxybenzamine increased urinary flow rate and free water excretion without changing urinary sodium excretion or glomerular filtration rate in anesthetized, hypophysectomized, steroid-replaced dogs undergoing a water diuresis. It was suggested that α-adrenoceptor blockade decreased proximal tubular sodium reabsorption (*Gill* and *Casper* 1971). However, in anesthetized hydropenic dogs, renal arterial administration of phenoxybenzamine increased urinary sodium excretion without changing renal blood flow or glomerular filtration rate; by micropuncture, proximal tubular sodium and water reabsorption were unaltered, suggesting that the natriuresis derived from more distal nephron segments (*Strandhoy* et al. 1974). Renal arterial administration of phenoxybenzamine does not produce a natriuresis in conscious unanesthetized dogs (*Barger* et al. 1959a, b). Renal β-adrenoceptor blockade generally produces an antinatriuretic response which has been attributed to renal hemodynamic alterations (*Epstein* and *Braunwald* 1966; *Nies* et al. 1971; *Nomura* et al. 1978; *Prosnitz* and *DiBona* 1980), a direct renal tubular effect (*Cacciaguida* et al. 1969), or an involvement of the renal sympathetic nervous system (*Waugh* 1970; *Mroczek* et al. 1970). However, a natriuretic response has also been described (*Lees* 1968; *Klein* et al. 1971; *Carrara* and *Baines* 1976).

Recently, evidence has been presented that there is a similar effect of renal α-adrenoceptor blockade on renal tubular sodium and water reabsorption in an amphibian, the bullfrog (*Gallardo* et al. 1980). Using a

doubly perfused in situ kidney preparation, phenoxybenzamine, when added to the portal venous perfusate which is solely distributed to the tubules, produced a natriuresis and diuresis which was independent of any changes in glomerular filtration rate or renal perfusion outflow. Neural elements in close proximity to renal tubules were observed with both light and electron microscopic techniques (*Pang* et al. 1982).

It has long been argued that denervation diuresis and natriuresis is an artifact produced by the stress of anesthesia and surgery in experimental animals, which artificially increases sympathetic tone to the kidneys resulting in an effect in excess of what can be seen in the unanesthetized conscious state (*Smith* 1951). *Lifschitz* (1978) subjected conscious dogs with one kidney denervated and the other kidney intact to sequential random-ordered hemorrhage (2% body weight) and volume expansion (isotonic Ringer solution, 5% body weight). In terms of sodium handling, the denervated kidney responded as well as the innervated kidney during both hemorrhage and volume expansion. *Sadowski* et al. (1979a, b, 1980) studied conscious dogs with one kidney denervated and the other kidney intact. During hydropenia, the denervated to innervated kidney ratio for urinary sodium excretion factored for glomerular filtration rate significantly exceeded 1.0, thus indicating a defect in renal tubular sodium reabsorption in the denervated kidneys. These studies confirm the older observations in conscious unanesthetized dogs by *Benchetrit* et al. (1966). *Schneider* et al. (1978) studied the effect of chronic bilateral renal denervation on the ability of the conscious dog to adjust urinary sodium excretion to changes in dietary sodium intake. In the sham renal denervated dogs, urinary sodium excretion was the same during experimental and control phases whether on a dietary sodium intake of 100 or 3 mEq per day. In the renal denervated dogs there was no difference on the 100 mEq per day sodium diet, but on the 3 mEq per day sodium diet urinary sodium excretion was twofold higher after than before renal denervation.

Gordon et al. (1979) studied the ability of conscious rabbits with chronic bilateral renal denervation or systemic sympathetic blockade produced by reserpine or guanethidine treatment to adapt to dietary sodium restriction. In response to reduction in dietary sodium intake, neither group was able to reduce urinary sodium excretion sufficiently to avoid negative external sodium balance. This defect was reversible in the guanethidine- or reserpine-treated group. *Rogenes* and *Gottschalk* (1980) have presented data from studies in conscious euvolemic and volume-expanded rats showing that the chronically denervated kidney has a higher urinary flow rate and sodium excretion than the intact kidney. These conscious animal studies are in good agreement with several observations in man. *Gill* and *Bartter* (1966) demonstrated that normal subjects in whom autonomic insufficiency had been produced by guanethidine administra-

tion were unable to lower urinary sodium excretion sufficiently to avoid negative external sodium balance in response to a reduction in dietary sodium intake, despite decreases in glomerular filtration rate. *Wilcox* and colleagues (1977) demonstrated similar findings in patients with idiopathic autonomic insufficiency. Obese human subjects placed on a hypocaloric protein diet show a decrease in sympathetic nervous system activity, with a reduction in basal plasma norepinephrine concentration and a failure of plasma norepinephrine concentration to increase in response to upright posture. The subjects showed a significant net sodium loss (−382 mEq per 21days or −18 mEq/day on a sodium intake of 54 mEq/day) and a pronounced orthostatic decrease in systolic blood pressure (−28 mmHg) with symptoms of orthostatic hypotension (*DeHaven* et al. 1980). Thus, this dietary regime produces signs and symptoms of idiopathic autonomic insufficiency with inability of the kidney to conserve sodium in response to a modest reduction in dietary sodium intake. Although *Blaufox* et al. (1969a) demonstrated that the transplanted human kidney could normally conserve sodium on a dietary sodium intake of 10 mEq per day, these studies were conducted 46–922 days after surgery. Since *Gazdar* (1969) and *Gazdar* and *Dammin* (1970) have demonstrated neural regeneration in

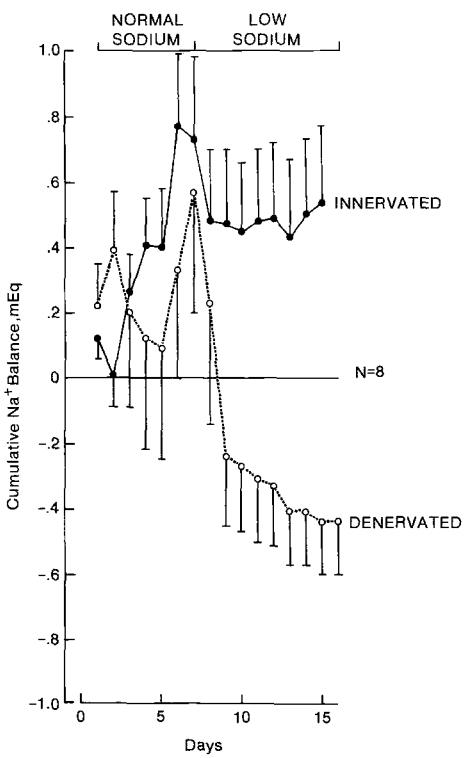

Fig. 5. Effect of renal denervation on renal adaptation to dietary sodium restriction in conscious rats. (*DiBona* and *Sawin* 1981)

human renal transplants as early as 38 days after surgery, it is clear that the results of *Blaufox* et al. (1969a) could be explained by undetected regeneration of renal nerves. Similar studies performed in the early post-transplant period will be required to accurately assess the contribution of intact renal innervation to normal renal physiological responses in man (*Blaufox* et al. 1969b; *Norvell* 1970). Recent studies in our laboratories (*DiBona* and *Sawin* 1981) demonstrate that renal denervation renders the conscious rat unable to maintain positive external sodium balance when dietary sodium intake is restricted (Fig. 5).

Thus, the evidence from studies in anesthetized and conscious unanesthetized animals and human subjects indicates that when the kidney is deprived of its innervation, renal tubular sodium and water reabsorption are directly decreased. Of even more importance is the fact that intact renal innervation appears to be essential for the kidney to express its full ability to maximally reabsorb sodium in response to a reduction in dietary sodium intake. Therefore, the renal nerves are an important component of the efferent mechanism of the body's defense against sodium and, thus, extracellular fluid volume depletion.

The direct influence of renal innervation on renal tubular sodium reabsorption has been more easily and clearly demonstrable in pathological states characterized by enhanced renal tubular sodium reabospriton. *Whelan* et al. (1952) noted that dogs with a transplanted kidney in the neck did not develop ascites as rapidly after thoracic inferior vena cava constriction (TIVC) as dogs with an abdominal kidney and suggested that this difference might be due to the transplantation of the kidney. *Brod* et al. (1954) administered the α-adrenoceptor antagonist, dibenamine, intravenously to patients with congestive heart failure. He observed an increase in fractional sodium excretion without a significant change in renal blood flow or glomerular filtration rate; cardiac output increased and mean arterial pressure decreased slightly. *Barger* et al. (1959a, b) demonstrated that renal arterial administration of phenoxybenzamine or hexamethonium produced an ipsilateral diuresis and natriuresis, without a change in renal plasma flow or glomerular filtration rate, in conscious dogs with experimental congestive heart failure due to chronic tricuspid insufficiency. *Gill* et al. (1967) showed that systemic autonomic blockade with pentolinium increased urinary sodium excretion in dogs with chronic TIVC constriction, suggesting the presence of an increased level of sympathetic activity. *Schrier* et al. (1971) observed that the antinatriuretic effect of acute TIVC constriction was abolished by systemic autonomic blockade with hexamethonium or systemic α-adrenoceptor blockade with phenocybenzamine, but not by surgical renal denervation. However, *Azer* et al. (1972) found that surgical renal denervation partially restored the natriuretic response to intravenous isotonic saline loading in dogs with acute TIVC constriction.

Slick et al. (1974) showed that either surgical or pharmacological renal denervation restored the natriuretic response to intravenous isotonic saline loading toward normal in dogs with acute TIVC constriction. This response was accompanied by a decrease in proximal tubular fractional and absolute water and sodium reabsorption in the absence of changes in systemic or intrarenal hemodynamics or changes in the intrarenal distribution of blood flow or filtrate. Thus, in experimental models of congestive heart failure, maneuvers which interrupt efferent RSNA elicit increases in urinary flow rate and sodium excretion which are attributable to decreases in renal tubular reabsorption with localization at least to the proximal tubule.

Chronic ligation of the common bile duct leads to progressive development of ascites with a blunted natriuretic response to extracellular volume expansion (*Better* and *Massry* 1972). Both surgical and pharmacological (phenoxybenzamine) renal denervation produced slight but significant ipsilateral increases in urinary sodium excretion which were similar in the normal and chronic bile duct ligated dogs. However, neither intervention restored the normal natriuretic response to extracellular volume expansion (*Chaimovitz* et al. 1974). However, oral administration of propranolol restored the natriuretic response to extracellular volume expansion halfway to normal; this was attributed to an extrarenal effect of β-adrenoceptor blockade (*Winaver* et al. 1978).

The role of the renal nerves in determining the renal function following relief of ureteral obstruction has been studied by *Wilson* (1980). The renal nerves play a role in the decreased glomerular filtration rate, renal plasma flow, and altered sodium and water excretion which occur after relief of 24-h unilateral ureteral obstruction; chronic renal denervation was not protective against these functional changes (*Wilson* et al. 1979a). Renal denervation does not prevent the increased renal tubular sodium reabsorption that occurs with a mild increase in ureteral pressure due to partial ureteral obstruction (*Wilson* et al. 1979a). There is a significant increase in glomerular filtration rate, renal plasma flow, urinary flow rate, and sodium excretion with acute renal denervation after relief of unilateral ureteral obstruction, but no such response is seen after relief of bilateral ureteral obstruction. This may relate to the observation that renal tissue catecholamine concentrations, while normal in the unilateral ureteral obstruction kidney, are markedly decreased (but not to the postrenal denervation range) in the bilateral ureteral obstruction kidneys (*Wilson* and *Honrath* 1981).

The extensive work of *Takacs, Bencsath, Szalay,* and colleagues has characterized the effect of renal denervation (major splanchnic nerve section) on several other tubular ion transport processes. In a series of dog studies it was demonstrated that renal denervation increased the excretion

and lowered the maximum tubular transport of phosphate (*Szalay* et al. 1977a), para-aminohippurate (*Szalay* et al. 1977b), glucose (*Szalay* et al. 1977c), and uric acid (*Szalay* et al. 1977e). In all studies, glomerular filtration rate was unchanged and urinary flow rate and sodium excretion were uniformly increased. It was suggested that efferent RSNA might generally regulate renal proximal tubular transport processes (*Szalay* et al. 1977d).

The effect of renal denervation on renal tubular phosphate handling in the rat has been further studied. *Szenasi* et al. (1981) reported that both acute and chronic (21 dogs) renal denervation increased urinary phosphate excretion and decreased the maximum tubular transport of phosphate; identical observations were made in thyroparathyroidectomized animals, excluding a role for parathyroid hormone. *Szalay* et al. (1980) reported that volume-expanded rats with chronic renal denervation have increased urinary excretion of water, sodium, and phosphate as compared with volume-expanded sham-denervated control rats. In both early and late proximal tubular segments of the denervated kidneys, phosphate but not sodium and water reabsorption was inhibited. Thus, the observed diuresis and natriuresis were thought to derive from inhibition of water and sodium reabsorption beyond the proximal tubule or in deep nephrons. These observations suggest that the influence of the renal nerves on proximal tubular sodium transport is different from that on phosphate transport, and that other compensatory mechanisms restore proximal tubular sodium transport toward normal in the chronically denervated kidney.

The role of the renal innveration in the renal excretory response to intravascular volume expansion has been discussed recently by *Knox* et al. (1980). They summarized the available evidence as indicating that intravascular volume expansion stimulates volume receptors, producing a decrease in efferent RSNA. The decrease in efferent RSNA directly decreases renal tubular sodium reabsorption in addition to producing changes in intrarenal hemodynamics which favor a decrease in renal tubular sodium reabsorption. This interpretation is supported by the recent studies of *Sadowski* et al. (1979a, b, 1980) who showed that the innervated kidney responded to isotonic saline volume expansion with a greater natriuretic response than the denervated kidney in both the unanesthetized and anesthetized states. Thus, the overall response of the innervated kidney to volume expansion includes a component relative to inhibition of efferent RSNA; such a component is lacking in the response of the denervated kidney. This disparity between the response of the innervated and the denervated kidney to volume expansion would be expected to be greater during anesthesia with the attendant increase in efferent RSNA. This was the case in that during the conscious state the increase in fractional sodium excretion was 1.7–6.4 fold (innervated) and 1.5–3.9 fold (denervated), and that during the anesthetized state it was 4.1–9.6 fold (innervated)

and 2.7–3.2 fold (denervated). Similar findings were observed in the rat by *Spencer* and *Yarger* (1977).

In examining the effect of renal denervation on renal function, two interrelated questions invariably arise. The first is the reliability of the renal denervation technique used, and the second is the potential adverse effects of the renal denervation technique on overall renal function.

With regard to the first question, renal denervation requires physiological verification. In general, as discussed previously (*DiBona* 1977), a marked diminution in renal tissue norepinephrine concentration has been offered as evidence of complete renal denervation. However, this often requires 2–3 days to occur and, therefore, this method cannot be used to immediately verify the completeness of acute renal denervation at the time it is performed. In addition, the sensitivity of the methods used to measure renal tissue norepinephrine concentration is such that it is usually only possible to say that there has been approximately 90% reduction in renal tissue norepinephrine concentration. It is not fully understood what level of renal tissue norepinephrine concentration (biochemistry) is required to achieve full responses to increases in efferent renal sympathetic nerve activity (physiology). However, the recent studies of *Kline* and *Mercer* (1980a) in the rat indicate that 24–32 days following renal denervation, at a time when renal tissue norepinephrine concentration was 29% of the control level, renal vascular responses to renal nerve stimulation had returned to 40% of the control values. At 52–53 days following renal denervation, renal vascular responses to renal nerve stimulation had returned to 100% of control values, but hypersensitivity to norepinephrine was still present. In subsequent studies, *Kline* et al. (1980a) showed that, following renal denervation, renal tissue norepinephrine concentration had returned to 13%, 25%, 33%, and 35% of control values at 2, 4, 6, and 8 weeks. Thus, in studies in conscious animals with denervated kidneys even minor increases in circulating norepinephrine occurring in response to stresses such as mild to modest hemorrhage (*Lifschitz* 1978) could have significant physiological renal effects. *Moss* and *Harrington* (1981) showed that 1 week following renal denervation, renal tissue norepinephrine concentration was 10% of normal and basal urinary sodium excretion was increased by 157% above the control value. Basal urinary sodium excretion returned to normal within 2 weeks, while renal tissue norepinpehrine concentration showed a linear increase to 50% of the normal value by 6 weeks. It seems that functional responses to renal nerve activation return more rapidly toward control levels than does the renal tissue norepinephrine concentration. In physiological studies, one is interested in knowing whether the functional effects of activation of the renal nerves have been abolished by the renal denervation procedure. As recently described (*DiBona* 1977; *DiBona* and *Rios* 1980), renal denervation may be considered

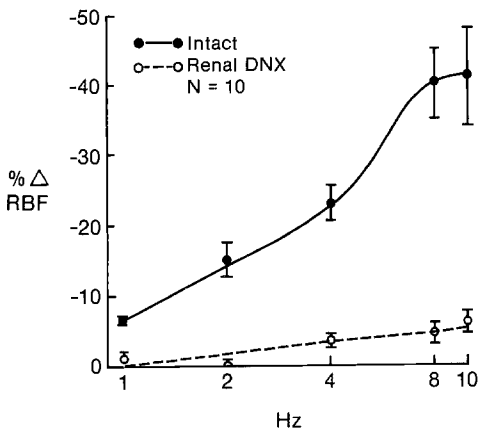

Fig. 6. Effect of acute renal denervation on the renal vasoconstrictor response to direct electrical stimulation at 10 V and 0.5 ms duration of suprarenal lumbar sympathetic chain or proximal renal nerve bundle. (*DiBona* and *Rios* 1980)

complete when the renal vasoconstrictor response to direct electrical stimulation of the suprarenal lumbar sympathetic chain or the proximal renal nerve bundle is abolished (Fig. 6). An alternative approach is to demonstrate the abolition of the reflex renal vasoconstrictor response to bilateral carotid artery occlusion after bilateral cervical vagotomy (*Kopp* et al. 1980a).

With regard to the second question, surgical renal denervation in its simplest form or in more complex forms involving autotransplantation (*Bricker* et al. 1958), or section and resuture of the renal artery, vein, and ureter (*Quinby* 1916) often adversely affects overall renal function (*Katz* and *Shear* 1975). Pharmacological renal denervation, while less traumatic, may be less complete than surgical renal denervation (*Katz* and *Shear* 1975). Thus, the interpretation of the results of studies employing renal denervation to assess the neural control of renal function has, to a certain extent, been hampered by the failure to consider these two important questions.

4.2.2 Direct Electrical Renal Nerve Stimulation

Previous studies concerning the effects of direct electrical renal nerve stimulation on renal function were predominantly focused on changes in renal hemodynamics and utilized high levels of stimulation which produced marked decreases in glomerular filtration rate and renal blood flow (*Houck* 1951; *Block* et al. 1952a, b). Subsequently, investigators interested in the effects of direct electrical renal nerve stimulation on renal tubular sodium reabsorption used more modest levels of stimulation which, while not affecting glomerular filtration rate, still reduced renal blood flow (*Johns* et al. 1976). As discussed elsewhere (*Schrier* 1974; *DiBona* 1977), "the results do not differentiate between a direct effect on active sodium trans-

port and an indirect effect mediated by some alteration in intrarenal hemodynamics."

Our own observations in this field proceeded from the work of *Barger* et al. (*Barger* et al. 1959a, b), who demonstrated a role for efferent RSNA in the renal sodium retention observed in the conscious dog with experimental congestive heart failure. Unilateral renal arterial infusion of phenoxybenzamine produced an ipsilateral natriuresis and diuresis in the absence of changes in glomerular filtration rate or renal plasma flow. Using another experimental model of congestive heart failure in the dog, acute thoracic inferior vena cava constriction (*Azer* et al. 1972; *Slick* et al. 1975), it was demonstrated that either surgical or pharmacological renal denervation partially restored the natriuretic response to isotonic saline volume expansion without changes in renal hemodynamics. The reversal of the antinatriuresis was accomplished by an inhibition of proximal tubular sodium reabsorption, i.e., a restoration of the expected renal response to isotonic saline volume expansion. These studies strongly indicated that there existed a level of efferent renal sympathetic nerve activity which could directly affect renal tubular sodium and water reabsorption in the absence of changes in glomerular filtration rate, renal blood flow, or intrarenal distribution of blood flow. The study of *La Grange* et al. (1973) provided some initial evidence that such a level of efferent RSNA did, in fact, exist. Using direct electrical renal nerve stimulation (10–15 V, 0.5 ms, 0.33–1.0 Hz) in anesthetized dogs, they demonstrated a 13%–26% decrease in urinary sodium excretion, while glomerular filtration rate and renal blood flow were unchanged. Although these observations were consistent with a direct effect of the renal nerves on renal tubular sodium reabsorption, the authors considered this possibility unlikely since, at that time, definitive evidence of renal tubular innervation was lacking. Additionally, as a methodological limitation, glomerular filtrationrate was determined by a urineless technique based on the Fick principle.

To further pursue this hypothesis, studies (*Slick* et al. 1975) were conducted in anesthetized dogs prepared for bilateral renal clearance and hemodynamic measurements. The distal portion of the transected renal nerve bundle was electrically stimulated using an intensity that was just below the threshold for a reduction in renal blood flow. This level of renal nerve stimulation produced an ipsilateral reversible decrease in urinary sodium excretion unaccompanied by changes in mean arterial or renal perfusion pressure, glomerular filtration rate, renal blood flow, or intrarenal distribution of blood flow (Fig. 7). This antinatriuretic response was abolished by renal α-adrenoceptor blockade with phenoxybenzamine (*Zambraski* et al. 1976a) (Fig. 8) or renal adrenergic blockade with guanethidine (*Slick* et al. 1975); it was unaffected by renal blockade to

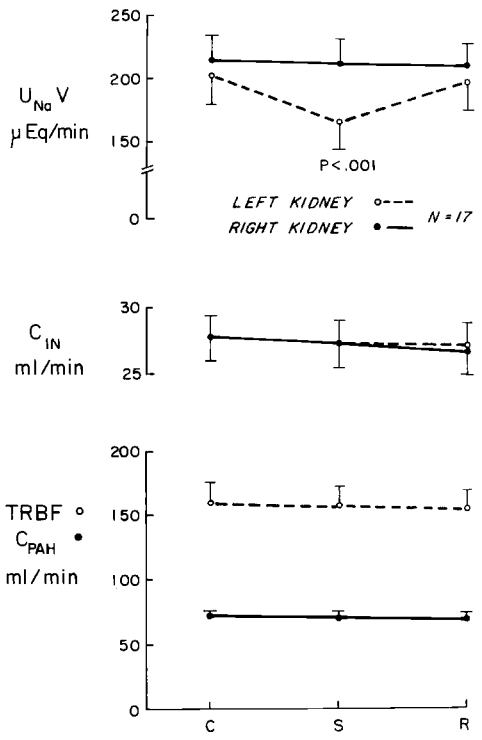

Fig. 7. Effect of low level renal nerve stimulation (0.5–2.0 Hz) on urinary sodium excretion ($U_{Na}V$) in anesthetized dogs. C_{in}, inulin clearance; *TRBF*, total renal blood flow; C_{PAH}, para-aminohippurate clearance; *C*, control, *S*, stimulation; *R*, recovery. (*Slick* et al. 1975)

angiotensin II (*Zambraski* and *DiBona* 1976) or by prostaglandin synthesis inhibition (*DiBona* et al. 1977). Thus, these studies demonstrated that low level direct electrical renal nerve stimulation directly increases renal tubular sodium reabsorption via activation of renal tubular α-adrenoceptors. The response is not mediated by either angiotensin II or prostaglandins which are known to be released in response to renal nerve stimulation (*Taher* et al. 1976; *Zambraski* and *DiBona* 1976; *Dunham* and *Zimmerman* 1970; *Davis* and *Horton* 1972; *Johns* et al. 1977).

Bello-Reuss et al. (1976), using a similar direct electrical splanchnic nerve stimulation protocol in anesthetized saline-loaded rats, found a 25% decrease in ipsilateral urinary flow rate and sodium excretion without a change in single nephron or whole kidney glomerular filtration rate or renal plasma flow. Micropuncture demonstrated an increased proximal tubular fractional and absolute sodium and water reabsorption (Fig. 9). Analysis of renal nerve fiber conduction velocities suggested that the responses were mediated by the stimulation of slowly conducting unmyelinated fibers. Direct electrical renal nerve stimulation at higher intensities (5 V, 1 ms, 2 and 5 Hz) reduced single nephron glomerular filtration rate and glomerular plasma flow; although fractional water reabsorption to the distal tubule increased, absolute water reabsorption decreased in

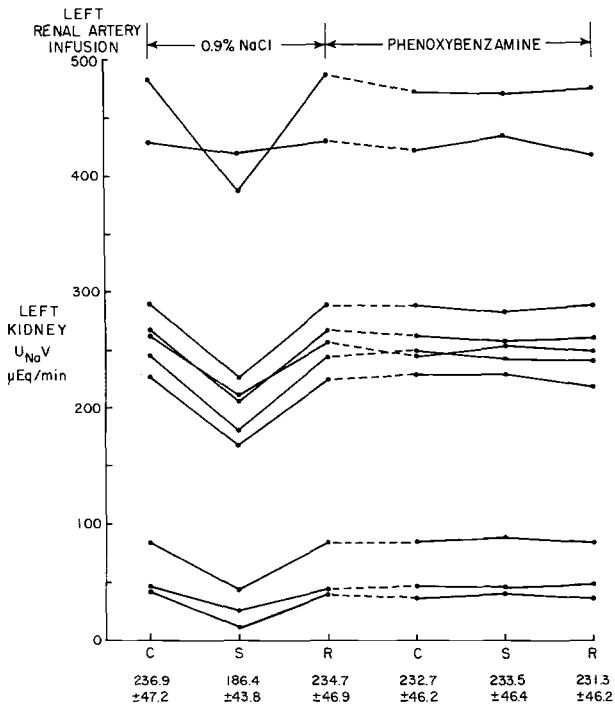

Fig. 8. Effect of renal α-adrenoceptor blockade with phenoxybenzamine on antinatriuretic response to low level renal nerve stimulation (0.5–2.0 Hz) in anesthetized dogs. $U_{Na}V$, urinary sodium excretion; *C*, control; *S*, stimulation; *R*, recovery. Numerical data are mean ± SE. (*Zambraski* et al. 1976)

parallel with single nephron glomerular filtration rate (*Hermansson* et al. 1981).

The effect of renal adrenergic stimulation with pharmacological agents on renal sodium and water handling has also been examined. *Barger* et al. (1959a, b) infused norepinephrine into the renal artery of conscious unanesthetized dogs and observed an antinatriuresis that was independent of changes in glomerular filtration rate or renal plasma flow; superimposition of phenoxybenzamine reversed the antinatriuresis. *Pearson* and *Williams* (1968) suggested that renal arterial administration of norepinephrine increased and isoproterenol decreased renal tubular sodium reabsorption, unrelated to the variable changes observed in renal blood flow and glomerular filtration rate. In anesthetized, hypophysectomized, steroid-replaced dogs, renal arterial administration of norepinephrine in the presence of renal β-adrenoceptor blockade decreased urinary flow rate and free water excretion without changing urinary sodium excretion or renal hemodynamics. From these indirect clearance studies it was suggested that α-adrenoceptor stimulation increased proximal tubular sodium re-

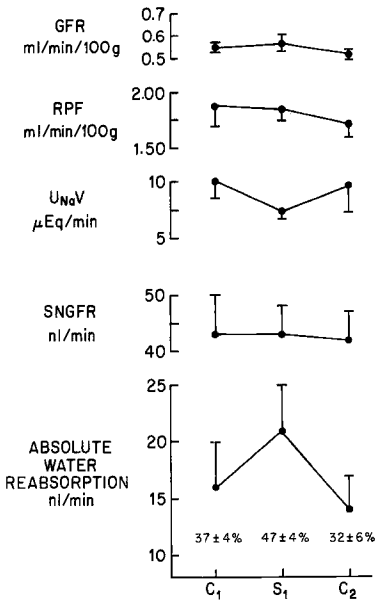

Fig. 9. Effect of low level splanchnic nerve stimulation (1.0 Hz) on renal function in anesthetized rats. *GFR*, glomerular filtration rate; *RPF*, renal plasma flow; $U_{Na}V$, urinary sodium excretion; *SNGFR*, single nephron glomerular filtration rate; percentages represent cortical proximal tubular fractional water reabsorption. C_1, control; S_1, stimulation; C_2, recovery. (*Bello-Reuss* et al. 1976)

absorption (*Gill* and *Casper* 1972). In similarly designed experiments, renal arterial administration of isoproterenol in the presence of renal α-adrenoceptor blockade increased urinary flow rate and free water excretion without changing urinary sodium excretion or renal hemodynamics. It was suggested that β-adrenoceptor stimulation decreased proximal tubular sodium reabsorption (*Gill* and *Casper* 1971). However, direct renal micropuncture studies in anesthetized hydropenic dogs using comparable experimental protocols to those of *Gill* and *Casper* (1971,1972), failed to reveal any effect of either α-adrenoceptor stimulation (*Blendis* et al. 1972) or β-adrenoceptor stimulation (*Blendis* et al. 1972; *Stein* et al. 1972) on renal proximal tubular sodium and water reabsorption.

Cant and *Vander* (1973) infused norepinephrine into the renal artery of anesthetized dogs at a dose which reduced renal blood flow by less than 10%; urinary sodium excretion fell by 36% whereas glomerular filtration rate was unchanged. *Johnson* and *Barger* (1981) used graded infusions of physiological doses of norepinephrine or epinephrine intravenously or directly into the renal artery of conscious dogs. Norepinephrine, intravenous or intrarenal, produced only modest decreases in urinary sodium excretion even at high renal arterial plasma norepinephrine concentrations Intrarenal epinephrine did not affect urinary sodium excretion, whereas intravenous epinephrine produced a marked decrease in urinary sodium excretion even at renal arterial plasma epinephrine concentrations in the lower physiological range. It was concluded that this effect is not mediated by a direct intrarenal action of epinephrine, but may be secondary to in-

creases in efferent RSNA or circulating angiotensin II concentration. It is known that intravenous epinephrine infusions increase plasma renin activity, wheras infusions directly into the renal artery do not (*Johnson* et al. 1979b). Furthermore, angiotensin II can decrease urinary sodium excretion without alteraing glomerular filtration rate or renal blood flow (*Johnson* and *Malvin* 1977). However, the direct renal tubular antinatriuretic response to increases in efferent RSNA is independent of angiotensin II (*Zambraski* and *DiBona* 1976).

4.2.3 Reflex Alterations in Efferent Renal Sympathetic Nerve Activity

Gill and *Casper* (1969) observed an antinatriuresis in experiments in which the renal nerves of a hemorrhaged animal were left intact but the blood perfusing the animal's kidney was derived from another normal animal. Although there was a significant decrease in renal blood flow and an increase in filtration fraction which complicated the interpretation, this study suggested that a reflex increase in neural stimuli to the kidney that was not sufficient to decrease glomerular filtration rate could increase renal tubular sodium reabsorption. To increase efferent RSNA more

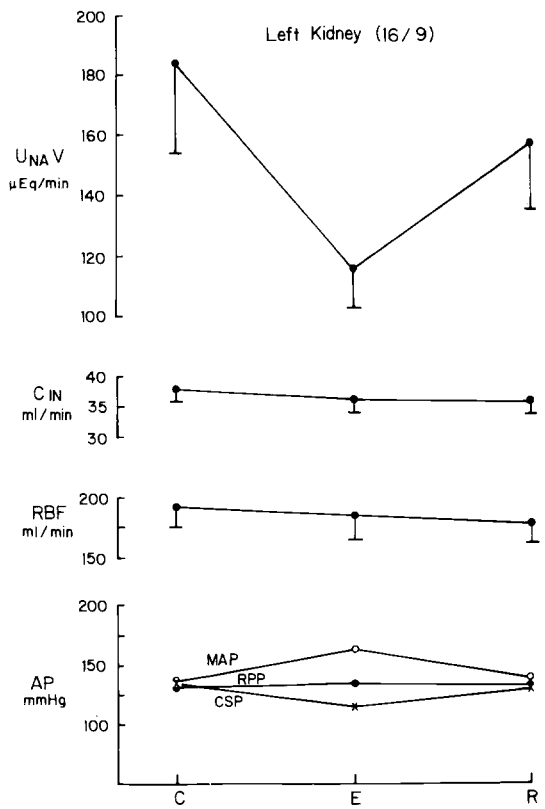

Fig. 10. Effect of decreased carotid sinus pressure (*CSP*) on renal function in anesthetized dogs. $U_{Na}V$, urinary sodium excretion; C_{in}, inulin clearance; *RBF*, renal blood flow; *MAP*, mean arterial pressure; *RPP*, renal perfusion pressure; *C*, control; *E* experimental; *R*, recovery. (*Zambraski* et al. 1976)

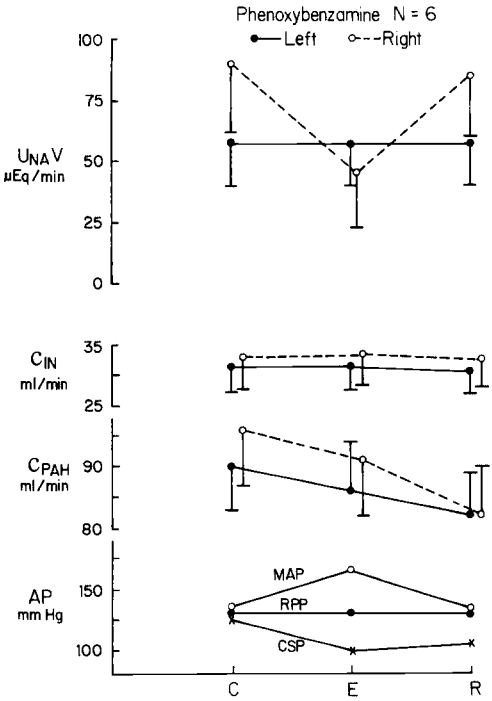

Fig. 11. Effect of left renal α-adrenoceptor blockade on the renal functional response to decreased carotid sinus pressure in anesthetized dogs. See Fig. 10 for abbreviations. (*Zambraski* et al. 1976)

physiologically, studies (*Zambraski* et al. 1967b) were performed using isolated carotid sinus perfusion to increase efferent RSNA via the carotid baroreceptor reflex. Reduction of carotid sinus pressure led to a reflex increase in efferent RSNA which produced a decrease in urinary sodium excretion without changes in renal perfusion pressure, glomerular filtration rate, or renal blood flow (Fig. 10). This antinatriuretic response was blocked by phenoxybenzamine (Fig. 11) and guanethidine. In response to bilateral common carotid artery occlusion in anesthetized dogs, the kidney with renal perfusion pressure held constant showed a decrease in urinary flow rate and sodium excretion, whereas the kidney with increased renal perfusion pressure showed a pressure diuresis and natriuresis; glomerular filtration rate and renal blood flow were constant in both kidneys (*Barger* et al. 1959b; *Prosnitz* et al. 1977). The antidiuresis and antinatriuresis were blocked by intrarenal phenoxybenzamine (*Barger* et al. 1959b).

Similarly, *de Chatel* (1978) showed that the pressure diuretic and natriuretic response to carotid occlusion was greater in the denervated than the innervated kidney. However, in conscious unanesthetized dogs, *Gross* et al. (1981) observed that glomerular filtration rate, renal blood flow, urinary flow rate, and sodium excretion were unchanged when renal perfusion pressure was held constant during bilateral carotid occlusion. Although efferent RSNA increased by 58% after bilateral carotid occlusion,

the lack of an effect on renal blood flow and tubular sodium reabsorption may relate to the low resting efferent RSNA in the conscious dog, since higher degrees of activation of efferent RSNA (auditory or emotional stimuli, +500%) caused severe renal vasoconstriction. In companion studies (*DiBona* and *Johns* 1980; *DiBona* et al. 1981), carotid baroreceptor reflex activation of efferent RSNA by 60° head-up tilting produced a decrease in urinary sodium excretion without changes in renal perfusion pressure, glomerular filtration rate, or renal blood flow. This antinatriuretic response was abolished by surgical or pharmacological (phentolamine) renal denervation and by bilateral carotid sinus nerve section (Fig. 12). Neither the antinatriuretic nor the renin-release response were affected by bilateral cervical vagotomy (*DiBona* et al. 1981). The role of the arterial chemoreceptors in the renal functional response to acute hypoxic hypoxia has recently been reviewed (*Honig* 1979). Acute hypoxic hypoxia stimulates carotid chemocreceptors, resulting in increased efferent RSNA with renal vasoconstriction but decreased renal tubular sodium and water reabsorption; renal denervation reverses the former but not the latter (*Honig* et al. 1979; *Honig* and *Schmidt* 1980). Hypercapnic acidosis has been shown to produce a decrease in urinary sodium excretion with unchanged glomerular filtration rate and renal blood flow; the antinatriuresis was significantly reversed by renal denervation (*Anderson* et al. 1980).

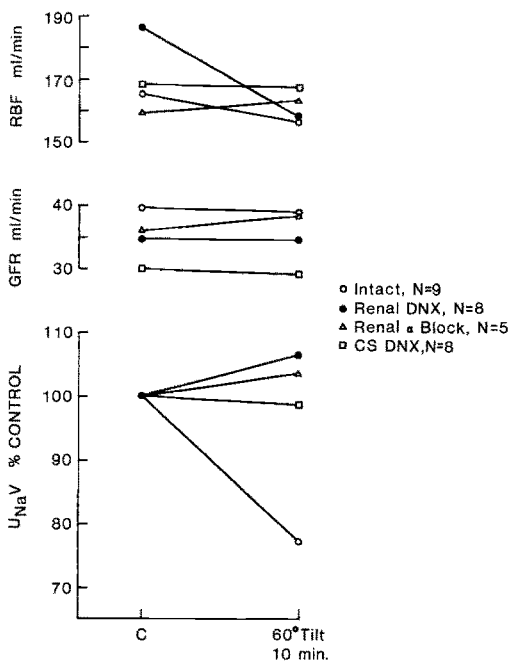

Fig. 12. Effect of 60° head-up tilt on renal function in anesthetized dogs. *RBF*, renal blood flow; *GFR*, glomerular filtration rate; $U_{Na}V$, urinary sodium excretion; *C*, control; *Renal DNX*, renal denervaton; *Renal α Block*, phentolamine; *CS DNX*, carotid sinus denervation. (*DiBona* and *Johns* 1980)

Thus, both direct and reflex increases in efferent renal sympathetic nerve activity directly increase renal tubular sodium and water reabsorption via activation of renal tubular α-adrenoceptors.

Since a physiological control system usually operates in a bidirectional manner, it was of interest to determine whether decreases in efferent RSNA would result in decreases in renal tubular sodium and water reabsorption in the absence of changes in renal hemodynamics. We chose reflex interventions as opposed to renal denervation to decrease efferent RSNA more physiologically. Activation of left atrial cardiopulmonary receptors (*Karim* et al. 1972) and stellate ganglion stimulation (*Takeuchi* et al. 1968) are both known to reflexly decrease efferent RSNA. *Prosnitz* and *DiBona* (1978) demonstrated that stellate ganglion stimulation produced reversible decreases in efferent RSNA which were associated with increases in urinary flow rate and sodium excretion in the absence of changes in renal perfusion pressure, renal blood flow, or glomerular filtration rate; thus, renal tubular sodium reabsorption decreased. These findings confirmed and extended the earlier observations of *Gilmore* (1964) and *Takeuchi* et al. (1968).

With respect to the issue of reflex control of renal sodium and water handling by atrial mechanoreceptors, two seemingly disparate opinions exist. *Goetz* et al. (1975, 1979) believe that "the left atrial volume receptor hypothesis adds little to our current understanding of the regulation of extracellular fluid balance," that "the case for the left atrial volume receptor hypothesis has been built largely on indirect evidence," and that there is insufficient evidence for the atrial receptors to "be singled out for special attention as volume receptors that influence renal function." However, equally vigorous opposing views have been expressed by *Gilmore* and *Zucker* (1975), *Gauer* and *Henry* (1976) and *Kappagoda* (1979). Some portion of the controversy relates to conceptual differences between the various investigative groups. *Goetz* et al. (1975) identify the concept of reflex volume regulation with atrial receptors, antidiuretic hormone (ADH), and renal water excretion. However, as presented by *Gauer* and *Henry* (1976), the concept of reflex volume regulation requires three things: first, a well-defined compliance of the low pressure system relating blood volume to filling pressure; second, appropriate receptor networks in the walls of the low pressure system responsive to changes in wall tension and discharging in appropriate areas of the central nervous system; and third, related efferent neurohumoral mechanisms which control thirst, renal water and sodium excretion, and redistribution of the extracellular fluid volume as the major regulators of the plasma volume. Recent studies by *Epstein* (1978) indicate that water immersion produces a central volume stimulus with engorgement of the intrathoracic circulation which leads to a natriuresis and a diuresis. Similar findings are observed after

lower body positive pressure in conscious animals (*Kass* et al. 1980). Thus, this appropriate homeostatic response is consistent with the view that central intrathoracic volume receptors are part of the afferent limb of a reflex volume-regulating system whose efferent limb involves changes in renal water and sodium excretion. Several recent studies deal with the left atrial volume receptor mechanism. *Linden* et al. (1979) demonstrated that the magnitude of the decrease in efferent RSNA during left atrial receptor stimulation was not influenced by changes in carotid sinus pressure. Using differential cooling of the cervical vagi, it has been shown that the reduction in efferent RSNA during distension of balloons in the left pulmonary vein-atrial junction, the left atrial appendage, and the left atrium and the accompanying increase in urinary flow rate are mediated solely by the Paintal-type atrial receptors which discharge into the myelinated fibers in the vagi (*Linden* et al. 1980; *Sivananthan* et al. 1981).

As noted above, controversy exists with respect to the role of ADH in the diuretic response (i.e., increased urinary flow rate) to left atrial receptor stimulation. *Goetz* et al. (1975) suggested that the use of more precise, specific, and sensitive radioimmunoassay methods for measurement of plasma ADH concentrations might provide more reliable information. *De Torrente* et al. (1975) demonstrated that left atrial balloon inflation increased left atrial pressure, decreased urinary osmolality, increased urinary flow rate, and decreased plasma ADH concentration as measured by a radioimmunoassay method; a positive free water clearance was not observed. Renal perfusion pressure was controlled and there were no significant alterations in systemic or renal hemodynamics. The observed changes were completely reversible on deflation of the left atrial balloon. In steroid-replaced, hypophysectomized dogs receiving a constant intravenous infusion of ADH, left atrial balloon inflation produced similar increases in left atrial pressure but there were no associated changes in urinary osmolality or flow rate. These authors concluded that suppression of ADH release is the primary mechanism whereby increases in left atrial pressure cause an increase in urinary flow rate. These experiments have been criticized on the basis of the failure to observe a positive free water clearance and because, based on calculations using ADH bioassay techniques, a greater fall in plasma ADH concentration than observed would be needed to account for the increase in urinary flow rate (*Kappagoda* 1979). However, since urinary flow rate increased in the presence of unchanged urinary solute excretion and osmolar clearance in the study by *de Torrente* et al. (1975), it seems clear that the increase in urinary flow rate may be accounted for by the measured decrease in plasma ADH concentration. Furthermore, as extensively discussed by *de Torrente* et al. (1975) the ADH radioimmunoassay employed in their study was characterized by greater precision, specificity, and sensitivity than those ADH

bioassay methods previously employed to assess the role of ADH in the diuretic respone to left atrial receptor stimulation in intact dogs (*Kappagoda* et al. 1974) and dogs with destruction of the posterior pituitary (*Kappagoda* et al. 1975).

With regard to the study by *Kappagoda* et al. (1975), in which electrical cauterization of the pituitary gland was used in an effort to abolish the diuretic response to left atrial receptor stimulation, several points should be noted. Previous studies have shown that as little as 7% of the hypothalamoneurohypophyseal tract is sufficient to prevent the development of diabetes insipidus (*Heinbecker* and *White* 1941). On histological examination at least one of the four dogs had incomplete ablation of the pituitary gland by electrical cauterization, and in this animal the area of destruction was actually outside the region of the pituitary gland (*Kappagoda* et al. 1975). Moreover, plasma concentrations of ADH (measured in two of the four dogs, one having incomplete hypophysectomy) were not detectable by their bioassay even though histological examination revealed incomplete hypophysectomy. This result again raises questions concerning the sensitivity of ADH bioassay technique used, and perhaps offers an explanation why this group has been unable to detect a decrease in plasma ADH concentration during left atrial receptor stimulation using this same ADH bioassay technique (*Kappagoda* et al. 1974). While *Ledsome* and *Linden* (1968) have shown that the diuretic response to left atrial balloon inflation with mitral obstruction was 2.7 times control urine flow, whereas that to left pulmonary vein-atrial junction balloon inflation with pulmonary vein distension was 1.5 times control urine flow, statistical analysis of this difference was not presented and there were no other detectable differences in the renal responses to these two stimuli (*Kappagoda* et al. 1974). These conflicting views on the role of ADH in the diuretic response to left atrial receptor stimulation cannot be ascribed to different techniques of left atrial receptor stimulation, since inflation of a balloon within the left atrium was used by both *de Torrente* et al. (1975) and *Kappagoda* et al. (1974, 1975).

In addition, *Thames* and *Schmid* (1979) have recently demonstrated, using ADH radioimmunoassay techniques, that cardiopulmonary receptors with vagal afferents tonically inhibit the secretion of ADH.

Kappagoda et al. (1979a) have recently described an as yet unidentified circulating humoral diuretic agent which is released during left atrial receptor stimulation. Dog plasma samples obtained during control periods and periods of left atrial receptor stimulation were applied to the Malphigian tubules of *Rhodnius prolixus.* Tubules suspended in dog plasma samples obtained during left atrial receptor stimulation secreted less fluid than when suspended in dog plasma samples obtained during control periods. Cutting or cooling the cervical vagi abolished these differences along with

the diuretic response to left atrial receptor stimulation. It was suggested that left atrial receptor stimulation resulted in a release of a circulating humoral diuretic agent which is responsible for the increase in urinary flow rate. Further studies from the same group (*Knapp* et al. 1980) examined the possibility that either angiotensin II or bradykinin were involved in the diuretic response to left atrial receptor stimulation. The diuretic response was unaffected by administration of angiotensin-converting enzyme inhibitor. Furthermore, neither angiotensin II nor bradykinin significantly influenced the rate of secretion of Malphigian tubules of *Rhodnius prolixus*. Therefore, angiotensin II and bradykinin are unlikely humoral mediators of the diuretic response to left atrial receptor stimulation. Further studies employing ADH radioimmunoassay techniques as well as identification of substances of mammalian origin which inhibit secretion of the malphigian tubules are required to assess the relative contributions of circulating humoral substances (ADH, others) to the diuretic response during left atrial receptor stimulation.

The mechanism of the associated natriuretic response to left atrial receptor stimulation has been examined in further detail. *Prosnitz* and *DiBona* (1978) showed that activation of left atrial cardiopulmonary receptors produced a reversible decrease in efferent RSNA which was associated with an increase in urinary flow rate and sodium excretion in the absence of changes in renal perfusion pressure, glomerular filtration rate, renal blood flow, or intrarenal distribution of blood flow (Figs. 13, 14). Bilateral cervical vagotomy abolished the decrease in efferent RSNA and the diuretic and natriuretic response to left atrial receptor stimulation.

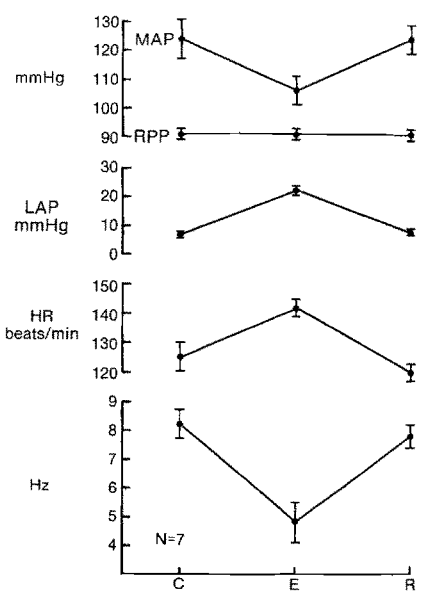

Fig. 13. Effect of left atrial balloon inflation on hemodynamic measurements and efferent renal sympathetic nerve activity in anesthetized dogs. *MAP*, mean arterial pressure; *RPP*, renal perfusion pressure; *LAP*, left atrial pressure; *HR*, heart rate; *C*, control; *E*, experimental; *R*, recovery. (*Prosnitz* and *DiBona* 1978)

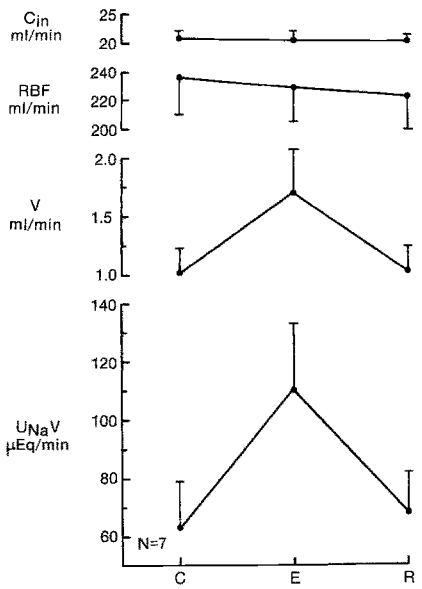

Fig. 14. Effect of left atrial balloon inflation on renal function in anesthetized dogs. C_{in}, inulin clearance; *RBF*, renal blood flow; *V*, urinary flow rate; $U_{Na}V$, urinary sodium excretion; *C*, control; *E*, experimental; *R*, recovery. (*Prosnitz* and *DiBona* 1978)

Infusion of exogenous ADH abolished the diuretic response, whereas the decrease in efferent RSNA and the natriuretic response to left atrial receptor stimulation were preserved. It was suggested that left atrial receptor stimulation produces a reflex whose afferent limb is in the vagus nerves and whose efferent limb for the diuretic response is suppression of ADH release and for the natriuretic response is a suppression of efferent RSNA. *Kappagoda* et al. (1979b) have examined the effect of renal denervation on the diuretic and natriuretic response to left atrial receptor stimulation. Whether the left atrial receptors were stimulated by large balloons in the left atrium or small balloons in the left pulmonary vein-atrial junction and the left atrial appendage, both the diuretic and natriuretic responses were significantly attenuated in the denervated kidney as compared to the innervated kidney in the same dog. *Chapman* et al. (1971), comparing the innervated and denervated kidney in the same dog, also demonstrated that the diuresis and natriuresis occurring in response to left atrial receptor stimulation were dependent on intact renal innervation.

As reviewed by *Kinney* et al. (1974), paroxysmal atrial tachyarrhthmia in man is associated with a diuresis and natriuresis which is due to a decrease in renal tubular sodium and water reabsorption, possibly at the level of the proximal tubule. Experimental studies in animals using cardiac pacing techniques have also demonstrated diuretic and natriuretic responses, but these responses have been said to be mediated by sinoaortic baroreceptors and to be independent of changes in bioassayed plasma ADH concentrations (*Goetz* and *Bond* 1973) or dependent on changes in plasma

ADH concentration mediated by left atrial receptors with vagal afferents (*Boykin* et al. 1974; *Grossman* et al. 1974). *Kinney* et al. (1974) have pointed out that the uniformly observed natriuretic response in patients cannot be completely explained by changes in plasma ADH concentrations. *La Grange* and *Mitchell* (1978) used left atrial pacing in anesthetized dogs and showed that the increased left atrial pressure was accompanied by a diuresis, natriuresis, and kaliuresis, in the absence of any changes in renal perfusion pressure or glomerular filtration rate; renal plasma flow decreased. Surgical or pharmacological (phenoxybenzamine) renal denervation blocked the excretory responses. Thus, these studies support the hypothesis that the diuresis and natriuresis of paroxysmal atrial tachyarrhythmia are due to a cardiorenal reflex involving left atrial receptors with vagal afferents and efferent RSNA.

Although *Mills* and *Osbaldiston* (1968) and *Stitzer* and *Malvin* (1975) did not observe a diuretic or natriuretic response to right atrial receptor stimulation via balloon inflation, *Kappagoda* et al. (1973) clearly demonstrated increases in urinary flow rate (18%–34%) and sodium excretion (15%) during distension of balloons in either the right atrial appendage or superior vena cava-atrial junction. The responses were reversibly attenuated by cooling the right cervical vagus. In conscious dogs, *Goetz* et al. (1981) demonstrated that right atrial epicardial receptor anesthesia produced reversible decreases in urinary flow rate and sodium excretion which were independent of changes in plasma ADH or renin concentrations.

The effects of left atrial receptor stimulation on the renal excretion of water and sodium in conscious unanesthetized dogs has been studied extensively by *Reinhardt, Kaczmarczyk*, and colleagues (*Reinhardt* et al. 1980a, b; *Kaczmarczyk* et al. 1980). These workers have demonstrated that increasing left atrial pressure by constricting the mitral valve orifice with an implanted purse string suture increases urinary flow rate and sodium excretion independent of changes in renal perfusion pressure, glomerular filtration rate, or renal blood flow. Although they found that the natriuretic response to increasing left atrial pressure was not affected by renal denervation, the natriuretic response to ingestion of a sodium-rich meal which produced a comparable rise in left atrial pressure was abolished by renal denervation (*Simgen* et al. 1979). These disparate results may be explained by the experimental design which, rather than comparing the responses of an innervated and denervated kidney within the same dog to either intervention, studied the responses of both kidneys to either intervention before and after bilateral renal denervation.

The effect of cardiac denervation on the diuretic and natriuretic responses to left atrial receptor stimulation has been studied by several groups. Using "pharmacological denervation" of both heart and kidney (bretylium, atropine, atenolol), *Linden* and *Sreeharan* (1979) showed that

the natriuretic response to left atrial receptor stimulation was abolished. *Reinhardt* et al. (1980a, b), in conscious unanesthetized dogs, demonstrated that both the diuretic and natriuretic responses to left atrial receptor stimulation were abolished by total cardiac denervation. *Fater* et al. (1980), working with *Goetz,* have also demonstrated that total cardiac denervation abolished the diuretic and natriuretic response to left atrial balloon inflation. In contrast to the earlier views expressed by *Goetz* and colleagues (1975), these authors now state that "the diuresis elicited by inflating a balloon in the left atrium is mediated by a reflex arising from cardiac receptors" (*Fater* et al. 1980), and "the diuresis elicited by increasing left atrial pressure with a balloon is reflexly elicited from left atrial receptors" (*Schultz* et al. 1980).

It should be noted that left atrial receptor stimulation does not produce a diuretic or natriuretic response in the monkey (*Gilmore* and *Zucker* 1978; *Cornish* and *Gilmore* 1981), which is probably explained by the fact that their left atrial receptors are substantially less sensitive than those in the dog (*Zucker* and *Gilmore* 1975).

These several observations indicate that left atrial receptor stimulation (increased left atrial pressure due to left atrial balloon inflation) produces an increase in urinary flow rate and sodium excretion independent of systemic or renal hemodynamic changes. This neurogenic reflex mechanism is dependent on an afferent limb involving unencapsulated end-organs in the left atrial endocardium served by myelinated vagal fibers. The efferent limb involves a decrease in efferent RSNA which totally accounts for the increase in urinary sodium excretion and partly accounts for the increase in urinary flow rate. The possibility remains that an as yet unidentified circulating humoral agent, in addition to suppression of ADH, contributes to the increase in urinary flow rate but not sodium excretion.

Activation of other cardiac receptors has been demonstrated to produce reflex changes in renal water and sodium excretion. *Lazzara* et al. (1970) showed that coronary sinus occlusion in dogs led to increases in urinary flow rate, glomerular filtration rate, and renal blood flow at constant renal perfusion pressure; these reponses were absent in the denervated kidney. *Wennegren* et al. (1976), in the cat, used direct electrical stimulation to activate cardiac unmyelinated vagal fibers which mainly originate from ventricular receptors. At constant renal perfusion pressure, there were increases in urinary flow rate, sodium excretion, and renal blood flow; data on glomerular filtration rate were not reported. Similar diuretic, natriuretic, and renal vasodilatory responses were seen with stimulation of either cardiac or aortic nerves or intra-arterial administration of papaverine. Thus, the excretory responses were most likely mediated by changes in renal hemodynamics, probably including an increase in glomerular filtration rate, as opposed to a specific decrease in renal tubular

sodium reabsorption. Clinically, patients with acute myocardial infarction and moderate left ventricular failure have higher levels of glomerular filtration rate and daily excretion rates of water and sodium than those patients without left ventricular failure or with pulmonary edema (*Bennett* and *Keddie* 1974; *Effendigil* et al. 1975; *Bennett* et al. 1977, 1979).

In view of the extensive sensory functions of the liver (*Sawchenko* and *Friedman* 1979), hepatorenal reflex responses have been described. *Liang* (1971) observed that increases in hepatic portal venous pressure produced increases in urinary flow rate and chloride excretion which were associated with increases in renal plasma flow and glomerular filtration rate; these responses were reversibly abolished by application of local anesthetics to the renal neurovascular pedicle. *Niijima* (1976) provided evidence that this was a neurogenic reflex involving efferent RSNA by demonstrating that portal vein occlusion decreased efferent RSNA in anesthetized rabbits. In our laboratory, we have observed (unpublished observations) that portal vein occlusion in anesthetized dogs (20 tests in 4 dogs) decreased efferent RSNA from 9.8 ± 0.5 to 7.4 ± 0.4 Hz in association with a decrease in mean arterial pressure from 134 ± 5 to 125 ± 5 mmHg; on release of the portal vein occlusion, efferent RSNA returned to 9.4 ± 0.4 Hz and mean arterial pressure returned to 137 ± 4 mmHg.

Shock avoidance has been employed as a generalized environment stress which probably increases sympathetic activity. In conscious dogs, shock avoidance decreases urinary flow rate and sodium excretion without changing glomerular filtration rate, indicating an increase in renal tubular sodium and water reabsorption (*Grignolo* et al. 1980). This response was abolished by the intravenous administration of propranolol (*Koepke* et al. 1981). To determine whether efferent renal nerves and/or renal β-adrenoceptors are involved in this response, studies must be performed in dogs with renal denervation and renal arterial administration of β-adrenoceptor antagonists.

4.2.4 Characterization of Catecholamine Receptors

The subject of catecholamines and sodium excretion, in terms of characterization of the renal tubular adrenoceptors involved, has been reviewed by *Baines* and *Morgunov* (1980). *Morel* (1981) and *Morel* et al. (1981) identified catecholamine-sensitive adenylate cyclase receptors in microdissected segments of the rabbit nephron. β-Adrenoceptors were identified in the distal convoluted and cortical collecting tubule but not in the proximal convoluted or straight tubule. α-Adrenoceptors were not found in the distal convoluted tubule or the cortical collecting tubule and observations were not reported for the proximal tubule. *Besarab* et al. (1977), in the isolated perfused rat kidney, showed that the simultaneous administration

of norepinephrine and phenoxybenzamine decreased fractional sodium excretion without changing glomerular filtration rate or perfusion medium flow. The combination of norepinephrine and propranolol did not affect fractional sodium excretion. However, both phenylephrine and isoproterenol, when given alone, also decreased fractional sodium excretion without affecting glomerular filtration rate or perfusion medium flow. The results were interpreted as showing that humoral β-adrenoceptor stimulation increases renal tubular sodium reabsorption; however, the phenylephrine response is at variance with this view.

Pastoriza (1979) performed simultaneous microperfusion experiments in the proximal convoluted tubule and peritubular capillaries of anesthetized rats. When added to the peritubular capillary perfusate, norepinephrine increased and phentolamine decreased net fluid reabsorption. The results were interpreted as showing that humoral stimulation of α-adrenoceptors located at the basolateral membrane enhances proximal tubular fluid reabsorption by a direct tubular action. In isolated perfused rabbit cortical collecting tubules, isoproterenol in the bath decreases the negative potential difference and increases net chloride reabsorption (*Iino* et al. 1979; *Iino* and *Brenner* 1979). In the isolated perfused mouse medullary thick ascending limb of Henle's loop, isoproterenol and norepinephrine (bath) increased the lumen positive potential difference and chloride efflux; this effect was inhibited by propranolol (*Polhemus* and *Hall* 1980). *Bello-Reuss* (1980) has studied the effect of catecholamines on fluid reabsorption by the isolated perfused superficial proximal convoluted and straight portions of the rabbit renal tubule. Norepinephrine, at concentrations of 10^{-7} M or higher, enhanced fluid reabsorption in the proximal convoluted but not the straight tubule; it was inactive when added to the luminal perfusion. A similar stimulatory effect was seen with isoproterenol in the presence of phentolamine. The effects of both norepinephrine and isoproterenol were blocked with propranolol. Norepinephrine, in the presence of propranolol, produced a slight decrease in fluid reabsorption. These results were interpreted as demonstrating that humoral β-adrenoceptor stimulation increases and α-adrenoceptor stimulation decreases fluid reabsorption in the rabbit superficial proximal convoluted tubule. However, the effect of a pure α-adrenoceptor agonist such as phenylephrine or methoxamine was not evaluated.

Using simultaneous proximal tubular and peritubular capillary microperfusion techniques in the rat, *Chan* (1980a, b) showed that norepinephrine in the peritubular capillary perfusate increased proximal tubular water and bicarbonate reabsorption through stimulation of peritubular α-adrenoceptors (phenoxybenzamine block). *Hollingsead* and *Willis* (1980) gave renal arterial infusions of β-adrenoceptor agonists or antagonists during continuous renal arterial infusion of phentolamine to anesthetized

rabbits. The β-adrenoceptor agonists or antagonists produced no change in mean arterial pressure, heart rate, urinary flow rate, glomerular filtration rate, or renal plasma flow. β-Adrenoceptor antagonists (propranolol) increased and β-adrenoceptor agonists (norepinephrine, isoproterenol) decreased fractional sodium excretion. These results were interpreted as showing that humoral β-adrenoceptor stimulation increases and blockade decreases renal tubular sodium reabsorption. Previous studies in our laboratory indicate that renal tubular α-adrenoceptors mediate the direct increase in renal tubular sodium reabsorption observed following either direct electrical renal nerve stimulation (*Zambraski* et al. 1976) (Fig. 8) or physiological reflex activation of the efferent renal sympathetic nerves (*Zambraski* et al. 1967b; *DiBona* and *Johns* 1980) (Figs. 11, 12). More recent studies in our laboratory (*DiBona* and *Osborn* 1981) demonstrate that neither renal β-1,2 (D,L-propranolol) nor β-1 (atenolol) adrenoceptor blockade affected the antinatriuretic response to low level renal nerve stimulation (Fig. 15). In contrast, renal α-adrenoceptor blockade with phentolamine, phenoxybenzamine or, prazosin (α-1) markedly inhibits this response (Fig. 15).

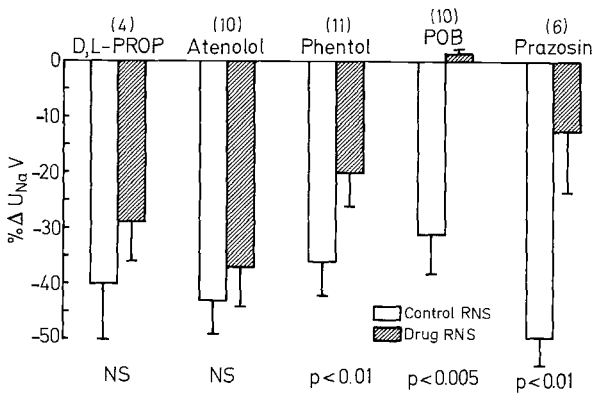

Fig. 15. Effect of various adrenoceptor antagonists (administered into the renal artery) on the antinatriuretic response to low level renal nerve stimulation (1.0 Hz) in anesthetized dogs. %Δ $U_{Na}V$, percent change in urinary sodium excretion; *RNS*, renal nerve stimulation; *D,L-PROP*, D,L-propranolol; *PHENTOL*, phentolamine; *POB*, phenoxybenzamine; *NS*, not significant; ( ), number of dogs

With respect to dopamine, clearance studies indicate that exogenous dopamine is natriuretic (*Goldberg* and *Weder* 1980). Intravenous infusion of dopamine in the cat increases urinary flow rate, sodium, potassium, and chloride excretion without affecting mean arterial pressure, glomerular filtration rate, renal blood flow, or efferent RSNA; a direct action of dopamine to decrease renal tubular reabsorption was postulated (*Wassermann*

et al. 1980). However, rat renal micropuncture studies indicate that dopamine increases proximal tubular sodium and water reabsorption (*Greven* and *Klein* 1977), whereas dopamine in the bathing medium decreased fluid reabsorption in the isolated perfused proximal straight tubule of the rabbit, a segment unresponsive to norepinephrine (*Higashi* and *Bello-Reuss* 1980). *Arruda* and *Sabatini* (1980) have reported that endogenously formed dopamine inhibits water transport in the isolated toad bladder. A recent review of the literature pertaining to dopamine and its effect on urinary sodium excretion concludes that there is insufficient evidence to support a direct action of dopamine on renal tubular sodium reabsorption (*Goldberg* and *Weder* 1980).

The precise characterization of the adrenoceptor involved in directly influencing renal tubular sodium reabsorption in response to changes in efferent RSNA has not been achieved with in vitro studies employing humoral adrenergic agonists and antagonists. It is possible that the results of such in vitro studies employing humoral adrenergic agonists and antagonists might not be relevant to the characterization of the adrenoceptor mediating the changes in renal tubular sodium reabsorption observed after physiological alteration of efferent RSNA in vivo, either directly or reflexly.

4.2.5 Summary

Bidirectional alterations in efferent RSNA, produced either directly (renal nerve stimulation, renal denervation) or by activation of physiological reflexes (carotid sinus baroreceptors, left atrial mechanoreceptors), cause parallel changes in renal tubular sodium and water reabsorption which are directly mediated by adrenergic nerve terminals in contact with renal tubular epithelial cells. Renal hemodynamic factors, peritubular physical forces, and circulating humoral substances are not involved. The proximal tubule has been identified as one site of action for this neural control mechanism for solute and water transport. The efferent renal sympathetic nerves are participants in the efferent limb(s) of the mechanism(s) involved in the avid renal sodium retention of certain edema-forming conditions as well as the normal physiological response to dietary sodium deprivation. This neural control mechanism is operative in the conscious unanesthetized animal. Current evidence favors the view that the mechanism operates via renal tubular α-adrenoceptors, although improved ability to characterize renal tubular epithelial cell membrane catecholamine receptor anatomy will provide further information on this issue.

4.3 Control of Renal Hormonal Systems

This section will deal with the effects of efferent RSNA on the renal production of renin, prostaglandin, and kallikrein.

4.3.1 Renin

Three primary mechanisms are involved in the release of renin from the juxtaglomerular granular cells of the kidney: the renal vascular baroreceptor mechanism, the macula densa receptor mechanism, and the direct sympathetic neural control mechanism. These mechanisms have been the subject of several recent review (*Davis* and *Freeman* 1976; *Reid* et al. 1978; *Fray* 1980). Specifically, the role of the central nervous system in influencing renin secretion via the efferent renal sympathetic nerves and catecholamines has been summarized in detail by *Reid* et al. (1978). In addition, the subject of pharmacological alteration of renin release has been comprehensively reviewed (*Keeton* and *Campbell* 1980). Therefore, this section will focus on more recent contributions.

4.3.1.1 Direct Stimulation of the Renal Nerves. In accord with *La Grange* et al.'s (1973) early findings, RNS, at an intensity which does not change renal hemodynamics but decreases urinary sodium excretion, increases renin release (*Taher* et al. 1976; *Zambraski* and *DiBona* 1977; *Kopp* 1980). It is possible that the associated decrease in urinary sodium excretion might have contributed to the renin release via activation of the macula densa receptor mechanism. However, *Osborn* et al. (1981a) have recently reported that there is a level of RNS (0.5 Hz) which reversibly increases renin release in the absence of changes in renal perfusion pressure, renal blood flow, glomerular filtration rate, or urinary sodium excretion. In the absence of input stimuli to either the baroreceptor or the macula densa receptor, this renin release derives from direct renal nerve stimulation of the juxtaglomerular granular cells.

4.3.1.2 Reflex Stimulation of the Renal Nerves. As recently reviewed by *Thames* (1978), *Thoren* (1979), and *Donald* and *Shepherd* (1980), the interaction between the high pressure (carotid and aortic) and low pressure (cardiopulmonry) baroreceptors can significantly influence renin release via modulation of efferent RSNA. Renin release increases when there is a decrease in the inhibitory activity of any one of the three peripheral receptor systems (carotid, aortic, cardiopulmonary) if such withdrawal does not alter the activity of the other two. Vagally innervated cardiopulmonary receptors exert a tonic inhibition of renin release and are

more sensitive to modest decreases in blood volume than are carotid baroreceptors.

With respect to the effects of carotid sinus hypotension on renin release, as indicated by *Donald* (1979), only in those studies in which the animals were vagotomized and in which renal perfusion pressure was held constant did consistent and significant increases in renin release occur. Similar findings have been observed in conscious unanesthetized dogs (*Rocchini* and *Barger* 1979; *Gross* et al. 1981b). The renin release response to bilateral carotid occlusion is associated with decreased renal blood flow in anesthetized dogs and cats (*Jarecki* et al. 1978; *Powis* and *Donald* 1979; *Ammons* et al. 1980). Both these responses to carotid occlusion are mediated via efferent RSNA. This has been demonstrated by blockade of the renin release response with renal denervation (*Jarecki* et al. 1978) or propranolol (*Powis* and *Donald* 1979; *Ammons* et al. 1980; *Gross* et al. 1981). Furthermore, *Gross* et al. (1980) have demonstrated an increase in efferent RSNA in conscious dogs after carotid occlusion. In the study by *Powis* and *Donald* (1979) phenoxybenzamine abolished the decrease in renal blood flow produced by carotid occlusion but not by suprarenal aortic constriction.

Mursch and *Bishop* (1980) studied the renin release response to vagal cold block before and after nonhypotensive hemorrhage in conscious dogs. Vagal cold block increased mean arterial pressure and heart rate but decreased renin release without changing renal blood flow before and after nonhypotensive hemorrhage. Thus, the increase in mean arterial pressure was sufficient to inhibit the renin secretory response to reflex increases in efferent RSNA, probably acting through carotid sinus or renal vascular baroreceptors.

In a recent series of studies, *Stella* and colleagues (*Stella* et al. 1978a,b; *Dampney* et al. 1979) utilized head-up tilt in anesthetized cats to study the interaction of vagal and sinoaortic reflexes in the postural control of circulation and renin release. Bilateral cervical vagotomy did not affect the hemodynamic change to posture but markedly reduced the renin release response from the innervated kidney. After sinoaortic denervation, a marked and sustained arterial hypotension occurred during tilting and the postural increase in renin release from the denervated kidney. It was concluded that maintenance of arterial pressure during tilting is mainly due to sinoaortic reflexes, whereas vagal reflexes are mostly responsible for the postural increase in renin release. However, *DiBona* et al. (1981) have recently shown that bilateral cervical vagotomy does not affect the antinatriuretic (*DiBona* and *Johns* 1980) or renin response to 60° head-up tilt in anesthetized dogs. The renin release response to head-up tilting has been examined in conscious dogs (*Grandjean* et al. 1978). Head-up tilt increased renal venous plasma renin activity (PRA) from the innervated but

not the denervated kidney. After furosemide administration, renal venous PRA increased bilaterally but the response to the innervated kidney exceeded that of the denervated kidney. In the nonhypotensive phase of progressive slow hemorrhage, renal venous PRA increased bilaterally but the response of the innervated kidney exceeded that of the denervated kidney. When hypotension supervened, renal venous PRA increased equally from both kidney.

The effect of peripheral venous pooling (thigh cuff) on PRA was studied in normal human subjects and four bilaterally nephrectomized patients with functioning renal transplants (*Kiowski* and *Julius* 1978). In normal human subjects, increases in PRA were associated with decreases in right atrial pressure, cardiopulmonary blood volume, and cardiac output while arterial pressure was unchanged. The PRA response was abolished by propranolol and was attenuated or absent in the four patients with recent renal transplants (3–7 months before study). It was concluded that this reflex-mediated increase in PRA arose from stimulation of cardiopulmonary receptors. *Fisher* and *Malvin* (1980) examined the mechanism of the decrease in renin release produced by intravascular volume expansion. In anesthetized dogs they found the decrease in renin release produced by isotonic iso-oncotic dextran administration to be unaffected by bilateral cervical vagotomy or by surgical renal denervation. They concluded that the renin release response to intravascular volume expansion was independent of the vagi or the renal nerves and that the renin-angiotensin system was not part of the efferent limb of the cardiopulmonary reflex during adjustments to changes in blood volume. However, *Holdaas* and *DiBona* (1981) demonstrated that the renin release response to nonhypotensive hemorrhage in sodium-replete dogs was abolished by preventing the associated decrease in left atrial pressure by inflating a balloon in the left atrium (Fig. 16). *Livnat* and *Zehr* (1980) have shown that left circumflex coronary artery occlusion reflexly inhibits the renin release and renal vasoconstrictor response to nonhypotensive hemorrhage in sodium-depleted dogs. The renin release and renal vasoconstrictor responses were dependent on intact renal innervation and the inhibitory effect of left circumflex coronary artery occlusion was dependent on intact vagi. Continuous positive pressure ventilation decreases intrathoracic blood volume causing reflex decreases in renal function and increases in renin release which are mediated by the renal nerves (*Fewell* and *Bond* 1979; *Bond* and *Lightfoot* 1981).

Zimmerman and *Ganong* (1980) recently showed that 5-hydroxytryptophan and L-tryptophan act on the central nervous system to produce an increase in PRA which is mediated via efferent RSNA and occurs without an associated increase in sympathetic output to the heart or blood vessels. Since the PRA response was abolished by administration of agents which

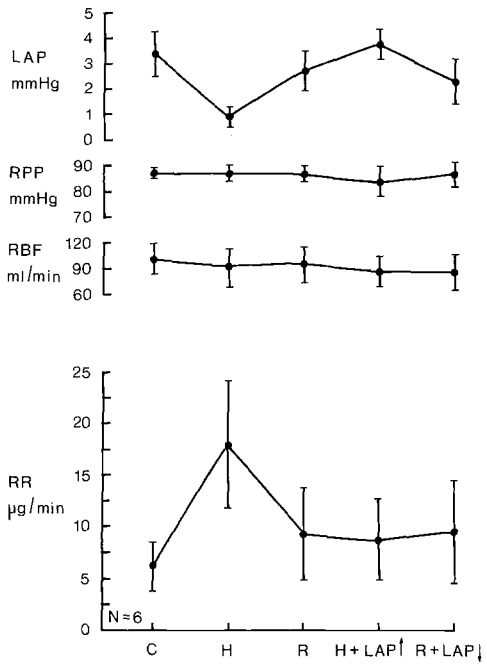

Fig. 16. Effect of nonhypotensive hemorrhage and left atrial balloon inflation on renal function and renin release (*RR*) in anesthetized dogs. *LAP*, left atrial pressure; *RPP*, renal perfusion pressure; *RBF*, renal blood flow; *C* control; *H* hemorrhage; *R*, recovery. (*Holdaas* and *DiBona* 1981)

inhibit central nervous system aromatic amino acid decarboxylase, it was suggested that the release of 5-hydroxytryptamine (serotonin) within the central nervous system was responsible for the observed response.

4.3.1.3 Role of β-Adrenoceptors in the Neural Control of Renin Release. *Taher* et al.'s (1976) demonstration that the renin release produced by low level renal nerve stimulation was blocked by propranolol suggested that renin release solely derived from neural stimulation of juxtaglomerular granular cells (i.e., no renal hemodynamic changes) was mediated by β-adrenoceptors. However, since urinary sodium excretion decreased in these studies, it remained possible that activation of the macula densa mechanism contributed to the observed renin release response. Recently *Osborn* et al. (1981a) demonstrated that renal nerve stimulation at 0.5 Hz increases renin release without affecting renal perfusion pressure, renal blood flow, glomerular filtration rate, or urinary sodium excretion. In the absence of changes in input stimuli to either the baroreceptor or macula densa receptor, the observed renin release derives from neural stimulation of juxtaglomerular granular cells. The renin-release response was completely abolished by renal β-1 adrenoceptor blockade with atenolol (Fig. 17), while it was unaffected by renal β-2 adrenoceptor blockade with butoxamine. Using a slightly higher level of RNS which produced a 5% decrease in renal blood flow and a 50% decrease in urinary sodium excretion, *Kopp* et al. (1980a) have recently shown that the renin release response was

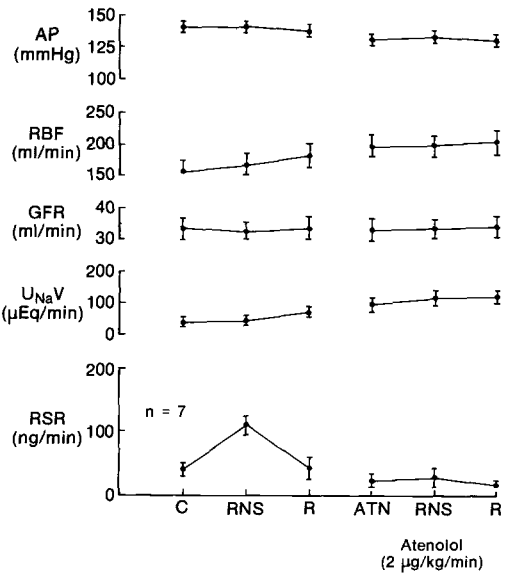

Fig. 17. Effect of renal β-1 adrenoceptor blockade with atenolol on renal function and renin secretion rate (*RSR*) responses to low level renal nerve stimulation (0.5 Hz) in anesthetized dogs. *AP*, arterial pressure; *RBF*, renal blood flow; *GFR*, glomerular filtration rate; $U_{Na}V$, urinary sodium excretion; *C*, control; *RNS*, renal nerve stimulation; *R*, recovery; *ATN*, atenolol. (*Osborn* et al. 1981a)

almost completely abolished by a different β-1 adrenoceptor antagonist, metoprolol, given intravenously. Using a higher level of RNS which produced a 30% decrease in renal blood flow in cats, *Johns* (1981) demonstrated that the renin release response was inhibited by the β-1 adrenoceptor antagonist, atenolol, but unaffected by the β-2 adrenoceptor antagonist, ICI 118,551. Taken together, these studies indicate that renin release solely due to renal nerve stimulation, i.e., no change in input stimuli to either the baroreceptor or macula densa receptor mechanisms, is mediated by β-1 adrenoceptors located on the juxtaglomerular granular cells.

Although renin release can be induced by exogenous β-adrenoceptor agonists in vivo and vitro, the final step in activation of the juxtaglomerular granular cells may not be identical to the produced by neuronally released norepinephrine. There may be differences in receptor location (vascular versus interstitial) and subtle, perhaps undetectable, differences in renal hemodynamics produced by exogenous adrenergic agonists that might differ from those produced by activation of the renal sympathetic nerves. It should be noted, however, that recent studies in conscious dogs by *Himori* et al. (1979, 1980) using isoproterenol and β-1 or β-2 adrenoceptor antagonist administration demonstrated that the isoproterenol-induced increase in PRA is due to activation of β-1 adrenoceptors. In addition, both *Kopp* et al. (1981b) and *Campbell* et al. (1979) have shown that administration of prenalterol, a β-1 adrenoceptor agonist, increases renin release in dogs (blocked by metoprolol) or increases PRA in rats, respectively. Using humoral stimulation of renal β-adrenoceptors in

anesthetized dogs pretreated with indomethacin, *Olson* et al. (1980b) examined the renin release response to the nonselective β-1/β-2 adrenoceptor agonist, isoproterenol, before and after either selective β-1 adrenoceptor blockade with atenolol or nonselective β-1/β-2 adrenoceptor blockade with sotalol. The renin release response to isoproterenol was unaffected by atenolol but was inhibited by sotalol. Although the results were interpreted as demonstrating that renal β-2 adrenoceptor stimulation increases renin release, data from experiments employing a selective β-2 adrenoceptor antagonist (e.g., butoxamine) were not presented.

The issue of extrarenal β-adrenoceptor mediation of renin release (*Reid* et al. 1972) has been restudied by *Johnson* et al. in conscious dogs (1979a, b). Intravenous infusion of epinephrine raised PRA considerably more than infusion of norepinephrine, whereas renal arterial infusion to produce similar renal arterial concentrations did not affect PRA; the PRA response was blocked by propranolol. The circulating concentrations of epinephrine achieved were less than those occurring after insulin administration of hemorrhage. It was concluded that circulating epinephrine in the physiological range plays a role in the control of PRA by activation of an extrarenal β-adrenoceptor (*Johnson* 1979b). In a subsequent study the PRA response to infused epinephrine was shown to be independent of the renal nerves, changes in renal perfusion pressure, hematocrit, plasma potassium, and prostaglandin concentration (*Johnson* 1979a).

4.3.1.4 Role of α-Adrenoceptors in the Neural Control of Renin Release. With respect to an inhibitory effect α-adrenoceptor stimulation on renin release, clonidine, an α-adrenoceptor agonist, is known to decrease PRA, but this results from a centrally mediated decrease in efferent RSNA (*Nolan* and *Reid* 1978; *Leavitt* et al. 1980). However, other observations suggest that α-adrenoceptor stimulation increases renin release. *Blair* (1979) reported that intrarenal phenoxybenzamine suppressed renin release in anesthetized dogs with systemic β-adrenoceptor blockade. Subsequently, *Blair* (1980) reported that both phenylepinephrine and methoxamine, given into the renal artery, increased renin release without affecting renal blood flow. However, both these studies were performed at a constant renal perfusion pressure of 90 mmHg, which engages the baroreceptor mechanism for renin release through autoregulatory renal vasodilatation. In addition, data on glomerular filtration rate and urinary sodium excretion were not reported, so that activation of the macula densa receptor mechanism cannot be excluded. *Powis* and *Donald* (1979) reported that renal α-adrenoceptor blockade with phenoxybenzamine abolished the renin release response and the renal vasoconstrictor response to bilateral carotid occlusion. However, in all these studies the changes in renal neuroadrenergic activity increased renal vascular resistance and prob-

ably decreased distal tubular delivery of sodium chloride. Thus, the neuroadrenergic stimuli used also altered the stimuli to the nonneuroadrenergic mechanisms for renin release. *Olson* et al. (1980a) reported that infusion of phenylephrine into the renal artery of denervated kidneys in β-adrenoceptor-blocked dogs decreased renal blood flow and urinary sodium excretion and increased renin release; only the renin release was blocked by indomethacin. In addition, no increase in renin release was seen when phenylephrine was infused into nonfiltering kidneys. They concluded that renal α-adrenoceptor activation led to a decrease in distal tubular sodium chloride delivery which stimulated the macula densa to release renin via a prostaglandin-dependent pathway. However, it is possible that the renal vasoconstriction produced by phenylephrine could lead to prostaglandin release (*McGiff* et al. 1972) and subsequent renin release independent of events occurring at the macula densa receptor. In addition, it is not known whether the nonfiltering kidney releases prostaglandins in response to infusion of α-adrenoceptor agonists.

Recent studies by *Osborn* et al. (1982) serve to further define the role of α-adrenoceptors in the renin release response to RNS. RNS at 0.5 Hz increased renin release without changing renal perfusion pressure, renal blood flow, glomerular filtration rate, or urinary sodium excretion. This renin release, in the absence of changes in input stimuli to either the baroreceptor or the macula densa receptor, is due to neural stimulation of juxtaglomerular granular cells. Renal α-adrenoceptor blockade with phentolamine did not affect the renin release response (Fig. 18), whereas phenoxybenzamine blocked the renin release. The doses of phentolamine and phenoxybenzamine were equipotent in reducing the renal vasoconstrictor responses to graded levels of RNS. Phenoxybenzamine did not affect the

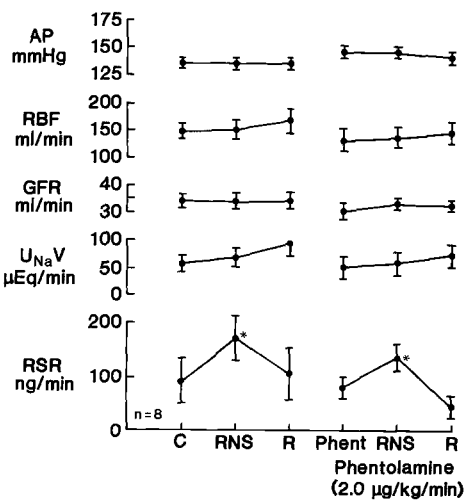

Fig. 18. Effect of renal α-adrenoceptor blockade with phentolamine on renal function and renin secretion rate (*RSR*) responses to low level renal nerve stimulation (0.5 Hz) in anesthetized dogs. See Fig. 17 for abbreviations. *PHENT*, phentolamine. (*Osborn* et al. 1982)

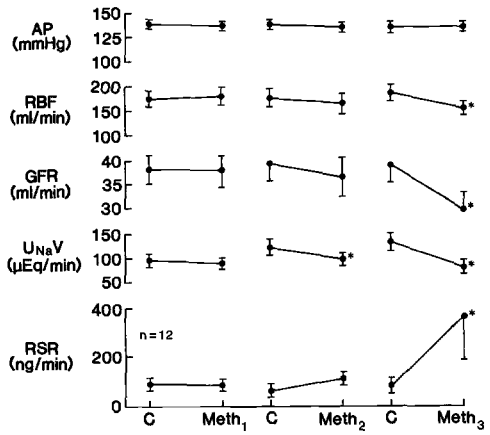

Fig. 19. Effect of renal α-adrenoceptor stimulation with methoxamine on renal function and renin secretion rate (*RSR*) in anesthetized dogs. $Meth_1$, 0.05–0.10 ng/kg/min; $Meth_2$, 0.09–0.40 ng/kg/min; $Meth_3$, 0.40–2.0 ng/kg/min. See Fig. 17 for abbreviations; *METH*, methoxamine. (*Osborn* et al. 1982)

renin release response to renal β-adrenoceptor stimulation with isoproterenol. Renal α-adrenoceptor stimulation with methoxamine (Fig. 19) at doses which did not affect renal perfusion pressure, renal blood flow, glomerular filtration rate, or urinary sodium excretion did not change renin release. Infusion of higher doses of methoxamine which decreased renal blood flow and urinary sodium excretion increased renin release. It was concluded that renin release in response to direct neuroadrenergic stimulation of the juxtaglomerular granular cells without engagement of baroreceptor or macula densa receptor mechanisms is not mediated by intrarenal α-adrenoceptors. Phenoxybenzamine appears to affect the renin-release response to RNS through mechanisms dissimilar from phentolamine, which is in keeping with recent observations of *Kalsner* and *Chan* (1979) that these two compounds have different α-adrenoceptor antagonist properties. Isolated renal α-adrenoceptor stimulation (i.e., no baroreceptor or macula densa receptor engagement) does not increase or decrease renin release.

4.3.1.5 Role of Prostaglandins in Neural Control of Renin Release. There is a close interrelationship between renal hemodynamics, neuradrenergic tone to the kidney, and the renal production of renin and prostaglandin. Close intrarenal infusion of the prostaglandin precursor, arachidonic acid, increased PRA in rabbits, while inhibition of prostaglandin synthesis by indomethacin decreased it (*Larsson* et al. 1974). Renal artery constriction to decrease renal perfusion pressure resulted in increased renal secretion of PGE_2 and $PGF_2\alpha$ (*Dunn* et al. 1978). Intrarenal infusion of PGE_2 and PGI_2 resulted in renal vasodilatation and renin release in propranolol-treated denervated nonfiltering kidneys (*Gerber* et al. 1979). Thus, renin release can be produced by prostaglandins in a baroreceptor-isolated kidney. Reduction of renal perfusion in renal venous PRA which was abol-

ished by indomethacin (*Data* et al. 1978). *Blackshear* et al. (1979), in filtering kidneys, demonstrated that this was true only for pressure reductions within the autoregulatory range for renal blood flow; below that level renin release was not affected by prostaglandin synthesis inhibitors (*Seymour* and *Zehr* 1979).

An increased release of prostaglandins following administration of ethacrynic acid was demonstrated by *Williamson* et al. (1976). Dietary sodium deprivation increases the renal release of prostaglandin, renin, and norepinephrine (*Davila* et al. 1978; *Oliver* et al. 1980b). A role for prostaglandins in macula densa-mediated renin release has been put forward by several workers. *Olson* et al. (1980c) infused papaverine into the renal artery of a denervated filtering kidney in β-adrenoceptor-blocked dogs. In this preparation, the influence of circulating catecholamines, renal sympathetic nerves, and changing input from the renal vascular baroreceptor have been eliminated, thus leaving only the macula densa receptor mechanism operative. A reduction in renal perfusion pressure decreased urinary sodium excretion and increased renin release; only the increase in renin release was blocked by indomethacin. Both *Francisco* et al. (1980b) and *Abe* et al. (1980) have studied the prostaglandin dependence of renin release in response to stimulation of the macula densa receptor by dietary deprivation. In both studies, the increase in plasma renin activity occurring during dietary sodium deprivation was abolished by indomethacin. *Yun* et al. (1977) have also reported decreased renin release by indomethacin during dietary sodium deprivation in anesthetized dogs. This inhibition occurred despite the fact that administration of indomethacin resulted in marekd changes in systemic and renal hemodynamics which would be expected to increase renin release as was observed by *Opgenorth* et al. (1980). In the study by *De Forrest* et al. (1980) indomethacin only reduced the renin release response to sodium deprivation in the presence of propranolol. Similar results were found by *Frolich* et al. (1976) in man.

It is known that renal nerve stimulation at intensities which produce renal hemodynamic changes increases renal prostaglandin release (vide infra). Reflex activation of efferent RSNA by orthostasis increased PRA which was reduced by indomethacin (*Rumpf* et al. 1975). The role of prostaglandins in the PRA response to hemorrhage has been examined by *Romero* et al. (1976) in rabbits and *Henrich* et al. (1978) in dogs. While *Romero* et al. demonstrated a decrease of PRA response to hemorrhage by prostaglandin synthesis inhibitors, *Henrich* et al. found no inhibitory effect on PRA response by the durgs. The effects of hemorrhage on systemic and renal hemodynamics were not reported by *Romero* et al., but *Henrich* et al. reported decreases in mean arterial pressure, renal blood flow, and renin release. Indomethacin potentiated the renal hemodynamic responses to hemorrhage in the innervated kidney, which may have influ-

enced the renin release per se. The complexity of the renin release response to hypotensive hemorrhage was later demonstrated by *Henrich* et al. (1979). They showed that neither controlled renal perfusion pressure, propranolol, nor indomethacin alone could block the renin release response to hypotensive hemorrhage. However, the combination of controlled renal perfusion pressure and propranolol or the combination of propranolol and indomethacin abolished the renin release response to hypotensive hemorrhage. The combination of controlled renal perfusion pressure and indomethacin had no effect on the renin release response. Thus, their findings suggest that the renin release occurring during hypotensive hemorrhage is mediated by renal β-adrenoceptors, by the renal baroreceptor mechanism, and possibly by the macula densa mechanism. The baroreceptor mechanism and probably the macula densa mechanism are prostaglandin mediated.

Whether prostaglandins are involved in β-adrenoceptor-mediated renin release has been examined by the use of β-adrenoceptor agonists. *Berl* et al. (1979) and *Johnson* et al. (1979a) found no effect in dogs. However, in both studies administration of the drugs was associated with changes in renal hemodynamics although renal perfusion pressure was held constant in the study by *Berl* et al. In rats β-adrenoceptor-mediated renin release produced by a β-1 adrenoceptor agonist or by hypoglycemia was found to be reduced by indomethacin (*Campbell* et al. 1979; *Campbell* and *Zimmer* 1980). No measurements of renal hemodynamic or excretory function were reported. Using a model of hemorrhagic hypotension in anesthetized rats, *Gerber* et al. (1980) reported that the increase in plasma renin activity was partially blocked by propranolol or indomethacin when administered alone and completely inhibited by the combination. In adrenalectomized rats indomethacin administration completely inibited the increase in plasma renin activity following hemorrhagic hypotension. These data suggest that the β-adrenoceptor- and prostaglandin-dependent pathways for renin release following hemorrhagic hypotension function independently, i.e., in parallel rather than in series. Furthermore, the β-adrenoceptor pathway requires intact adrenals, suggesting a role for circulating epinephrine in the renin release response to hemorrhagic hypotension. In addition, in adrenalectomized animals, the renin-releasing influence of the reflex increase in efferent RSNA occurring in response to hemorrhagic hypotension must be linked in series to the prostaglandin-dependent pathway for renin release. Using isolated rat glomeruli, *Beierwaltes* et al. (1980) showed that β-adrenoceptor stimulation with isoproterenol stimulated renin release which was unaffected by pretreatment with mechlofenamate.

Although renal nerve stimulation increases renal prostaglandin release, *Kopp* et al. (1980a) found that neither indomethacin nor diclofenac sodi-

um, 5 mg/kg intravenously, affected the renin release response to a low level of direct renal nerve stimulation which produced slight changes in renal hemodynamics and urinary sodium excretion. However, *Thames* et al. (1980) found that intrarenal arterial administration of indomethacin abolished the renin release response to a low level of direct renal nerve stimulation which produced no changes in renal hemodynamics or urinary sodium excretion. Further studies using different doses of various prostaglandin synthesis inhibitors adminstered systemically or locally into the the kidney in conjunction with graded levels of direct renal nerve stimulation will be required to clarify the issue of whether neurally stimulated β-adrenoceptor-mediated renin release is prostaglandin dependent.

4.3.1.6 Integrated Aspects of the Neural Control of Renin Release. There is considerable evidence that three primary mechanisms are involved in the control of renin release from the juxtaglomerular granular cells of the kidney. The first mechanism, direct sympathetic nervous control, is mediated by β-1 adrenoceptors on the juxtaglomerular granular cells. The second, the renal vascular baroreceptor mechanism, responds to changes in wall tension in the afferent arteriole. The third, the macula densa receptor mechanism, senses changes in the rate of sodium chloride delivery to the distal tubule. The latter two mechanisms are influenced indirectly by renal sympathetic nerve activity which, by causing α-adrenoceptor-mediated vasoconstriction, produces a reduction in renal blood flow and glomerular filtration rate; these alterations will produce a change in distal tubular delivery of sodium chloride. Additionally, activation of α-adrenoceptors in proximal tubular nerve terminals can increase proximal tubular sodium chloride transport with a resultant decrease in distal tubular sodium chloride delivery in the absence of changes in renal hemodynamics. Thus, the renin release response to increases in efferent RSNA can be the result of a complicated interaction of several mechanisms.

In response to high level renal nerve stimulation which produces substantial changes in renal hemodynamics (50% decrease in renal blood flow) and urinary sodium excretion, *Kopp* et al. (1981a) have shown that the renin release is totally blocked by a combination of β-1 and α-adrenoceptor blockade. Prostaglandin synthesis inhibitors, when given alone, produced a degree of inhibition of renin release which was similar to that produced by either β-1 or α-adrenoceptor blockade alone. The inhibition of renin release produced by the combination of prostaglandin synthesis inhibition and β-1 adrenoceptor blockade was additive, whereas that produced by the combination of prostaglandin synthesis inhibition and α-adrenoceptor blockade was not greater than that produced by either intervention alone. α-Adrenoceptor blockade abolished the renal vasoconstrictor whereas β-1 adrenoceptor blockade and prostaglandin synthesis inhibi-

tion did not affect it. Thus, high level renal nerve stimulation, which produces substantial changes in renal hemodynamics and urinary sodium excretion, results in renin release which is partly due to an activation of the β-1 adrenoceptor mechanism. The remaining portion of the renin release is dependent on prostaglandin synthesis and derives from the α-adrenoceptor-mediated renal vasoconstriction with activation of the baroreceptor and macula densa receptor mechanisms.

Using conscious sodium-depleted rats, *Schiffrin* et al. (1980) have reported similar results. Both indomethacin and propranolol lowered PRA, and combined administration produced an additive effect. Both intracerebroventricular clonidine and parenteral propranolol lowered PRA but their combined administration did not produce an additive effect. Thus, the central nervous system, through a central α-adrenoceptor pathway with peripheral mediation by β-adrenoceptors, is involved in producing the elevated PRA observed in the conscious sodium-depleted rat. Although a prostaglandin-dependent pathway acting in parallel to the β-adrenoceptor was postulated, studies employing α-adrenoceptor blockade were not reported. It is possible that the heightened level of circulating catecholamines, characteristic of sodium depletion, may be contributing to the prostaglandin-dependent renin release via renal vasoconstriction (i.e., a series as opposed to a parallel pathway), as is observed with direct RNS (*Kopp* et al. 1981a).

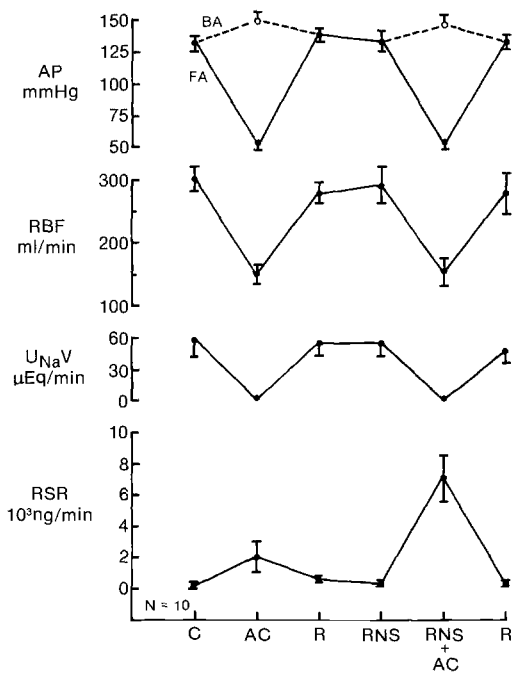

Fig. 20. Effect of suprarenal aortic constriction with and without concomitant low level renal nerve stimulation (0.25 Hz) on renal function and renin secretion rate (*RSR*) in anesthetized dogs. See Fig. 17 for abbreviations; *BA*, brachial artery; *FA*, femoral artery; *AC*, aortic constriction. (*Thames* and *DiBona* 1979)

Thames and *DiBona* (1979) have demonstrated that subthreshold levels of efferent RSNA can modulate the renin-release response to nonneural stimuli. A level of direct renal nerve stimulation (0.25 Hz) which, by itself, did not affect renin release, renal hemodynamics, or urinary sodium excretion, significantly augmented the renin release response to reduction in renal perfusion pressure to 50 mmHg (Fig. 20). Using different levels of direct renal nerve stimulation and renal perfusion pressure, a close interaction between the magnitudes of the two input stimuli can be shown to determine the degree to which the renin release is augmented. Using two different models of a nonfiltering kidney in which the macula densa receptor is rendered nonfunctional, the augmentation phenomenon appears to be dependent on an intact macula densa receptor mechanism (*Osborn* et al. 1979; *Holdaas* et al. 1981).

4.3.2 Prostaglandin

Renal nerve stimulation at intensities producing renal hemodynamic changes increases release of prostaglandins into the renal vein in dogs (*Dunham* and *Zimmerman* 1970; *Davis* and *Horton* 1972; *Mancia* et al. 1974) and in rabbits (*Johns* et al. 1977). Indomethacin blocked this increase in prostaglandin release (*Davis* and *Horton* 1972). The effect of RNS at lower intensities on renal prostaglandin production is not known.

4.3.3 Kallikrein

As recently reviewed by *Levinsky* (1979) and *Carretero* and *Scicli* (1980), there is evidence that adrenergic stimulation increases renal kallikrein production. Recently our laboratory (*Lawton* et al., personal communication) has examined the effects of graded renal nerve stimulation on urinary kallikrein excretion (esterolytic assay). At levels of renal nerve stimulation that produced no or minimal changes in renal blood flow and glomerular filtration rate (0.5 Hz), urinary kallikrein excretion increased by 50%. At higher levels of renal nerve stimulation that produced decreases in renal blood flow and glomerular filtration rate, urinary kallikrein excretion decreased in parallel to prestimulation levels (1.0 and 2.0 Hz) or below (4.0 Hz). *Diz* et al. (1980) showed that renal denervation in rats decreased PRA but not urinary PGE_2 or kallikrein excretion.

4.4 Renorenal Reflexes

Responses occurring in one kidney produced by interventions on the same (ipsilateral) or the other (contralateral) kidney which are mediated by neurohumoral mechanisms are called renorenal reflexes. Previous attempts

to demonstrate the existence of a renorenal reflex have employed direct electrical stimulation of afferent renal nerves or physiological stimulation of a renal receptor.

Direct electrical stimulation of afferent renal nerves produced a decrease in ipsilateral efferent RNSA and in arterial pressure in rabbits (*Aars* and *Akre* 1970) and dogs (*Ueda* et al. 1967). In the cat, however, direct stimulation of afferent renal nerves elicits a contralateral and ipsilateral increase in efferent RSNA that is associated with an increase in arterial pressure and heart rate, no change in contralateral renal blood flow or renin release from either kidney, and mesenteric and iliac vasoconstriction (*Calaresu* et al. 1976, 1977). In other studies (*Calaresu* et al. 1978) it was demonstrated that spinal cord destruction (C-2–L-5) and administration of doses of nicotine known to block transmission at sympathetic ganglia abolished the renorenal reflex. In addition, involvement of dorsal root reflexes was excluded by demonstrating that administration of bicuculline failed to affect the renorenal reflex. Two renorenal reflexes, corresponding to selective stimulation of renal afferent A or C fibers, were described. *Francisco* and *DiBona* (1979) have stimulated afferent renal nerves in the dog. With increasing frequency of stimulation from 1 to 16 Hz, there was a slight rise in mean arterial pressure with no change in either kidney renal blood flow but a frequency-dependent increase in femoral artery blood flow. The increases in mean arterial pressure and femoral artery blood flow were abolished by either phentolamine or guanethidine administered intravenously.

Golin et al. (1980) have stimulated afferent renal nerves in the cat. There was a transient modest increase in mean arterial pressure which slowly declined to the control level. When renal perfusion pressure was held slightly below control values, afferent renal nerve stimulation produced small and equal decreases in urinary flow rate and sodium excretion, glomerular filtrtion rate, and renal blood flow in both the innervated and denervated kidney. Therefore, direct electrical stimulation of the afferent renal nerves does not produce significant alterations in renal hemodynamics of either the ipsilateral or contralateral kidney of the cat or dog. However, the situation is clearly different in the rat, since *Mahoney* et al. (1978) have shown that afferent renal nerve stimulation produces vasodilatation in the hindquarters and vasoconstriction in the mesenteric and renal vascular beds, with little change in arterial pressure. These responses are identical to those observed during direct electrical stimulation of the anteroventral thrid ventricle (AV3V) (*Fink* et al. 1978). The responses to afferent renal nerve stimulation are abolished by acute lesioning of the AV3V as well as by hexamethonium, whereas bilateral adrenalectomy has no effect (*Brody* et al. 1979; *Brody* and Johnson 1980). Spinal cord section at T-6 abolishes the renal vasoconstriction and hindquarters vasodila-

tation while preserving the mesenteric vasoconstriction. Lesions of the nucleus tractus solitarii (NTS) alternate the hindquarters vasodilatation while preserving the mesenteric and renal vasoconstriction. Thus, afferent renal nerve stimulation elicits a vascular renomesenteric reflex at the spinal level and the NTS is a component of the selective reflex arc between the kidney and the hindquarters circulation (*Webb* et al. 1981).

Several investigators have employed physiological stimulation of renal receptors in an attempt to elicit a renorenal reflex. *MacFarlane* (9170), using nonquantitative morphological methods, demonstrated that renal intra-arterial injections of acetylcholine produced contralateral renal vasoconstriction that was abolished by denervation of either kidney. However, *Kottra* and *Takacs* (1980) repeated these experiments using electromagnetic flow meter measurements of renal blood flow and measuring efferent RSNA to the contralateral kidney. Despite a substantial ipsilateral renal vasodilatation, contralateral renal blood flow was unchanged and the small increase in efferent RSNA was related to changes in mean arterial pressure. *Vaughn* et al. (1971) showed that the renal hemodynamic response to acute unilateral ureteral occlusion is an increase in ipsilateral renal blood flow for the first 3–6 h followed by a gradual decrease to levels below control at 12–24 h; the contralateral kidney shows an early decrease in renal blood flow followed by a gradual return to control levels. *Francisco* et al. (1980a) demonstrated that this contralateral renal vasoconstrictor response to ipsilateral ureteral occlusion is a renorenal reflex. The efferent limb consists of a renal mechanoreceptor which, in response to increased intrarenal pressure produced by ureteral occlusion, sends afferent signals along the ipsilateral afferent renal nerves through the spinal cord to supraspinal centers. The efferent limb consists of contralateral afferent renal sympathetic nerve fibers. In support of the involvement of supraspinal centers, spinal cord section at T-6 abolished the contralateral renal vasoconstrictor response to ipsilateral ureteral occlusion. In the spinal cat, *Beacham* and *Kunze* (1969) showed that increases in ureteral pressure still produced increases in both ipsilateral afferent and efferent renal nerve activity, suggesting that participation of supraspinal centers was not required for this reflex. They also observed a decrease in mean arterial pressure without a change in ipsilateral renal blood flow, when ureteral pressure was increased to 25–30 mmHg, whereas *Francisco* et al. (1980) observed an increase in mean arterial pressure and an increase in ipsilateral renal blood flow when ureteral pressure was increased to 60–80 mmHg. These differences in hemodynamic responses suggest the possibility that different renal mechanoreceptors were activated in the two studies.

Kady (1974), in both cats and dogs, showed that increases in renal vein or ureteral pressure increased afferent and decreased efferent renal

nerve activity and decreased renal vascular resistance in the ipsilateral kidney; renal denervation reversed the ipsilateral renal vascular response from a vasodilatation to a vasoconstriction. *Kostreva* et al. (1981) have provided preliminary evidence in confirmation of Kady's results. In anesthetized vagotomized dogs, renal vein occlusion increased ipsilateral afferent renal activity and decreased contralateral efferent renal nerve activity. This decrease in contralateral efferent renal nerve activity was accompanied by a decrease in contralateral renal vascular resistance; denervation of the kidney with the renal vein occlusion eliminated both the decrease in contralateral efferent renal nerve activity and renal vascular resistance. Renal vein occlusion also inhibited cardiopulmonary sympathetic efferent nerve activity. This was associated with a decrease in right but not left ventricular contractile force; heart rate was unaffected. Denervation of the kidney with the renal vein occlusion eliminated both the decrease in cardiopulmonary sympathetic efferent nerve activity and right ventricle contractile forces. Thus, there is good electrophysiological and functional evidence for the existence of renorenal as well as renocardiac reflexes derived from interventions which activate renal mechanoreceptors.

DiBona and *Rios* (1980) demonstrated that, following acute renal denervation in saline-loaded rats, the ipsilateral diuresis and natriuresis are accompanied by a compensatory antidiuresis and antinatriuresis from the contralateral kidney. As reflected by direct measurements of contralateral efferent RSNA and its reversal by contralateral acute renal denervation, the compensatory contralateral renal response is mediated by the efferent renal sympathetic nerves (Fig. 21). Similar findings were subsequently reported by *Colindres* et al. (1980) who also showed that the anticipated

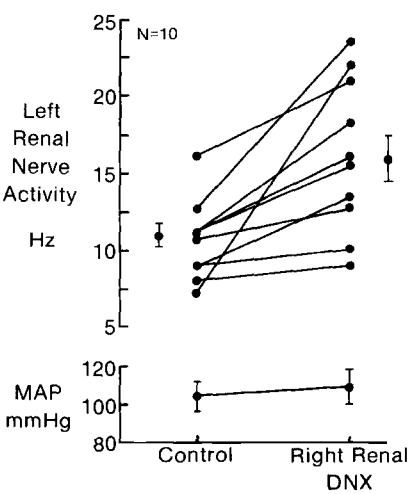

Fig. 21. Effect of acute right renal denervation on efferent renal sympathetic nerve activity to the left kidney in anesthetized rats. *MAP*, mean arterial pressure; *DNX*, denervation. (*DiBona* and *Rios* 1980)

compensatory contralateral renal response was prevented by prior chronic renal denervation. *Moss* and *Harrington* (1980) demonstrated, in nondiuretic rats, that the ipsilateral diuresis and natriuresis which followed acute renal denervation was accompanied by a contralateral natriuresis without diuresis which was blocked by prior denervation of the kidney. These compensatory renal responses may be initiated via stimulation of the R2 renal chemoceptive receptors. Neurophysiological recording studies (*Recordati* et al. 1980a) have shown that ipsilateral or contralateral stimulation of both R1 and R2 renal chemoceptive receptors elicits increases in efferent RSNA which, while not altered by baroreceptor denervation, were enhanced by C-1 spinal cord section. These observations suggest that renal chemoceptive receptors and afferent renal nerve activity might influence ipsilateral and contralateral efferent RSNA through neural reflexes which are likely to be integrated at the spinal and supraspinal levels.

The mechanism of the hemodynamic and renal excretory responses to acute unilateral nephrectomy have been studied. Acute unilateral nephrectomy produces an increase in mean arterial pressure, a decrease in cardiac output, and a rise in urinary cation (sodium and potassium) excretion in the absence of changes in glomerular filtration rate or renal blood flow (*Humphreys* and *Ayus* 1978; *Humphreys* et al. 1980). Bilateral cervical vagotomy or atropine administration abolished the cardiovascular hemodynamic changes, but the increase in urinary cation excretion was still observed (*Humphreys* et al. 1980). However, bilateral carotid sinus denervation abolished both the cardiovascular hemodynamic and renal excretory alterations (*Ayus* et al. 1978). These observations suggest that this renorenal reflex response involves the caroid sinus baroreceptors as the major afferent pathway, with efferent vagal pathways mediating the cardiovascular hemodynamic responses. The renal excretory response of the remaining kidney is not a pressure diuresis, since it occurred following bilateral cervical vagotomy and atropine administration when mean arterial pressure was unchanged; it may be related to carotid baroreceptor-mediated reflex withdrawal of efferent RSNA.

Renal mechanoreceptors have been implicated in a renoadrenal reflex arc that is of importance in the maintenance of potassium homeostasis (*Hiatt* et al. 1981). In ureter-ligated or nephrectomized dogs infused with potassium, a nonrenal potassium homeostatic mechanism retards the development of hyperkalemia by promoting the transfer of potassium from extracellular to intracellular fluid. The potassium transfer ability in ureter-ligated dogs is less than that of equally anuric nephrectomized dogs. However, the potassium transfer ability in ureter-ligated dogs can be raised to the nephrectomy level if the kidneys are denervated or by bilateral cervical vagotomy; vagotomy is without effect in ureter-ligated dogs with bilateral

adrenalectomy or in nephrectomized dogs. Epinephrine infusion increases potassium transfer ability in anuric dogs. These studies indicate that ureteral ligation, possibly by activation of renal mechanoreceptors due to increased intrarenal pressure, initiates afferent neural impulses which course through the renal and vagus nerves and impair the potassium transfer ability by inhibiting epinephrine section from the adrenal. With renal denervation or bilateral cervical vagotomy, there is release of inhibition with resultant epinephrine secretion and restoration of potassium transfer ability to the nephrectomy level; unless the adrenals – the source of epinephrine – are removed. In the absence of neural impulses from the kidney, i.e., nephrectomized dogs, bilateral cervical vagotomy has no effect on potassium transfer ability.

4.5 Hypertension

Several studies described a role for the renal nerves in contributing to the initiation and/or maintenance of the hypertensive state (*Fink* and *Brody* 1978; *Fink* and *Bryan* 1980). Renal denervation has been shown to delay the onset of hypertension in the spontaneously hypertensive rat (SHR) (*Liard* 1976; *Kline* et al. 1978; *Winternitz* et al. 1980) and the New Zealand genetically hypertensive rat (*Diz* et al. 1981), to delay the onset of DOCA-salt-induced hypertension (*Katholi* et al. 1980a), and to lower arterial pressure in established one-kidney one-clip hypertension (*Katholi* et al. 1981b). In both DOCA-salt hypertensive rats, New Zealand genetically hypertensive rats and SHRs, the delay in onset of hypertension produced by renal denervation was associated with an increase in urinary sodium excretion and reduced sodium retention; the eventual development of hypertension coincided with renal reinnervation, a decrease in urinary sodium excretion, and an increased sodium retention. However, *Kline* et al. (1980c) noted that SHRs subjected to a second renal denervation 3 weeks after the initial operation continued to develop hypertension similar to those having only one operation and suggested that the delayed rise in arterial pressure in renal-denervated SHRs is not due to renal reinnervation. In one-kidney one-clip rats, the necessity of the renal nerves for maintenance of hypertension was independent of alterations in renin, sodium intake or excretion, water intake, or renal function. The depressor effect of renal denervation was associated with a decrease in hypothalamic norepinephrine concentration (*Winternitz* et al. 1981) and a decrease in peripheral sympathetic tone (*Katholi* et al. 1981). These data indicate that renal denervation with interruption of renal afferent fibers can modulate central nervous system sympathetic activity, leading to a decrease in peripheral sympathetic tone and arterial pressure.

Kline and colleagues (1980) have shown that renal denervation prevented the increase in arterial pressure that follows cutting of the aortic depressor nerve and cervical sympathetic trunk in the rat; this effect may be mediated through changes in activity of the renin-angiotensin system (*Kline* and *Mercer* 1980b). These observations are in general agreement with studies demonstrating a generalized increase in sympathetic nervous system activity in SHRs (e.g., *Judy* and *Farrell* 1979) and DOCA-salt hypertension (reviewed in *Katholi* et al. 1980a).

Although recordings of efferent RSNA have not been made in DOCA-salt hypertension, those that have been made in SHRs have given discordant results. *Judy* and *Farrell* (reviewed in 1979), using multifiber or whole nerve recording techniques in conscious and anesthetized rats, demonstrated that basal levels of efferent RSNA were higher in SHRS than in age-matched genetic control normotensive Wistar Kyoto (WKY) rats. *Thoren* and *Ricksten* (1979), using single fiber recording techniques in anesthetized rats, showed that basal levels of efferent RSNA were 3.3 ± 0.45 Hz in SHRs and 1.6 ± 0.23 Hz in WKYs. *Francisco* et al. (1981), using whole nerve recording techniques in anesthetized rats, found basal levels of efferent RSNA to be similar in SHRs and WKYs. *Ricksten* et al. (1981), using whole nerve recording techniques in conscious unanesthetized rats, found basal levels of efferent RSNA to be slightly but not significantly greater in SHRs than in WKYs. The nerve recording studies showing no difference in basal levels of efferent RSNA between SHRs and WKYs are in agreement with the functional observations of *Touw* et al. (1980), who could not demonstrate any increased neural contribution to the heightened renal vascular tone in SHR as compared with WKYs.

In the case of renal hypertension, *Brody* and colleagues (1980) have provided evidence that the afferent renal nerves, via connections to the anterior hypothalamus, may play an important role in intiating the complex alterations in blood pressure regulation that result in this form of hypertension. The area of interest in the anterior hypothalamus is the anterior portion of the ventral third cerebral ventricle (AV3V). Electrical stimulation within the AV3V and the periventricular tissue produces renal and mesenteric vasoconstriction and hindquarters vasodilation; arterial pressure decreases with AV3V stimulation, but is unchanged with periventricular trissue stimulation. The renal and mesenteric vasoconstrictor responses were abolished by ganglionic blockade with hexamethonium and surgical denervation of the organ, but were unaffected by adrenalectomy. The active hindquarters vasodilator response involves β-adrenoceptor-mediated vasodilation which is produced, in part, by release of epinephrine from nerve terminals and the adrenals (*Berecek* et al. 1980). Stimulation of the afferent renal nerves produced an increase in arterial pressure, renal and mesenteric vasoconstriction, and hindquarters vaso-

dilation; the responses were abolished by hexamethonium, whereas bilateral adrenalectomy had no effect. The hemodynamic responses to AV3V stimulation were similar to those occurring after afferent renal nerve stimulation. Further evidence that the afferent renal nerves projected to be AV3V was provided when it was shown that an acute AV3V lesion essentially abolished the arterial pressure and vascular resistance changes produced by afferent renal nerve stimulation. Thus, it appeared that renal deafferentiation might interrupt the same neural loop that is blocked by an AV3V lesion and led to the hypothesis that renal deafferentiation might block or attenuate the development of renal hypertension. In rats with single autotransplanted (i.e., denervated kidneys, the onset of hypertension in response to figure-eight wrapping of the kidney (Grollman procedure) was delayed for 8–10 weeks. These several observations indicate that the afferent renal nerves ascend to the AV3V and synapse with descending efferent pathways which are distributed to several regional vascular beds. These pathways connecting the kidney to the central nervous system may play an important role in overall cardiovascular regulation in the development of renal hypertension.

The phenomenon of exaggerated natriuresis characterizes many forms of experimental hypertension. It has been described as being present (*DiBona* and *Rios* 1978) or absent (*Vandewalle* et al.1978; *Arendhorst* and *Beierwaltes* 1979) in studies conducted in anesthetiezd SHRs, a finding which might be explained by the nonuniformity of renal excretory responses to isotonic saline volume expansion in SHRs obtained from different sources (*Mullins* and *Banks* 1976). On the other hand, studies in conscious animals clearly demonstrate that SHRs have an exaggerated natriuretic response to intravenous isotonic saline volume expansion (*Struyker-Boudier* et al. 1979, 1980; *Ricksten* et al. 1981). Since volume expansion decreases efferent RSNA, which in turn is capable of directly reducing renal tubular sodium reabsorption, the relationship between volume expansion, exaggerated natriuresis, and efferent RSNA was examined in SHRs. In anesthetized rats with laparotomy, *Francisco* et al. (1981) demonstrated that isotonic saline volume expansion produced a similar degree of inhibition of efferent RSNA in SHRs and WKYs, while the SHRs had an exaggerated natriuretic response. In light of the compounding influences of anesthesia and surgical stress, these studies were repeated in conscious unanesthetized SHRs. *Ricksten* et al. (1981) found that isotonic saline volume expansion produced a greater inhibition of efferent RSNA and an exaggerated natriuretic response in SHRs as compared with WKYs. These latter observations suggest that the greater inhibition of efferent RSNA in SHRs may contribute to the exaggerated natriuretic response by directly reducing renal tubular sodium reabsorption. These studies confirm and extend the observations of *Thoren, Ricksten,* and

colleagues (*Thoren* and *Ricksten* 1979; *Ricksten* et al. 1979; *Noresson* et al. 1979; *Thoren* et al. 1979a, b; *Ricksten* and *Thoren* 1980; *Ricksten* 1980) which indicate that an intravenous volume load administered to SHRs is preferentially distributed centrally, resulting in a greater rise in left atrial pressure as compared with WKYs. The left atrial receptors are reset in SHRs so that a higher left atrial pressure is required for a similar degree of inhibition of efferent RSNA. Thus, volume expansion in SHRs leads to a greater rise in left atrial pressure, which is greater than that required to offset the upward resetting of left atrial receptors in SHRs, and to a greater inhibition of efferent RSNA as compared to WKYs similarly volume expanded. It is possible that this greater degree of inhibition of efferent RSNA plays an important role in the exaggerated natriuresis characteristic of this and perhaps other forms of experimental hypertension characterized by increased activity of the sympathetic nervous system (*Friedman* et al. 1955; *Ben-Ishay* et al. 1973; *Takeshita* et al. 1978, 1979; *Fink* et al. 1980).

Thus, several lines of evidence indicate an increase in sympathetic neural activity in hypertension and a relationship betwen efferent RSNA, sodium retention, and the development of hypertension in different animal experimental models of hypertension which are characterized by an exaggerated natriuretic response to volume expansion. In addition, afferent renal nerves are coupled to the central nervous system as part of an integrated cardiovascular control system which may participate in the development of renal and other forms of hypertension. The importance of enhanced efferent RSNA in human essential hypertension is reflected by the work of *Hollenberg* et al. (1975), who showed that renal arterial infusion of phentolamine, an α-adrenoceptor antagonist, increased renal blood flow significantly in six of nine patients with mild essential hypertension but in none of 15 normal subjects.

4.6 Summary

The renal nerves serve as an important efferent control system for the reflex regulation of several renal functions. A variety of reflex mechanisms, operating singly or in concert, can produce major alterations in renal blood flow, renal tubular solute and water transport, and renal release of physiologically significant vasoactive substances. Studies in conscious unanesthetized animals demonstrate the presence of low resting levels of efferent RSNA which, even after moderate increases as observed during carotid baroreceptor reflex stimulation, do not produce renal vasoconstriction, but which, after marked increases as observed during emotionally stressful auditory stimuli, produce pronounced renal vasoconstriction.

There is no functional evidence for sympathetic cholinergic vasodilator fibers in the kidney. Decreases or increases in efferent RSNA, produced directly or reflexly, result in parallel changes in renal tubular solute (e.g., sodium) and water reabsorption which are directly mediated by adrenergic nerve terminals containing α-adrenoceptors in contact with renal tubular epithelial cells. Renal hemodynamic factors, peritubular physical forces, and circulating humoral substances are not involved. The proximal tubule has been identified as one site for this neural control mechanism. Efferent RSNA is a participant in the efferent limb(s) of the mechanism(s) involved in the avid renal sodium retention of certain edema-forming conditions as well as the normal physiological response to dietary sodium deprivation. This neural control mechanism is operative in the conscious unanesthetized animal. The renin release response to increases in efferent RSNA is the result of a complex interaction of several mechanisms. One part derives from stimulation of β-1 adrenoceptors on the juxtaglomerular granular cells. The remaining portion is prostaglandin dependent and derives from α-adrenoceptor-mediated renal vasoconstriction with activation of the baroreceptor and macula densa receptor mechanisms. Renin release in response to direct neural stimulation of the juxtaglomerular granular cells is not mediated by α-adrenoceptors. Subthreshold levels of efferent RSNA can significantly augment the renin release response to nonneural stimuli, and this appears to be dependent on an intact macula densa receptor mechanism. Renal nerve stimulation increases the renal secretion of prostaglandin and kallikrein. Renorenal reflexes can participate in physiological regulation of renal function as well as mediate the compensatory adaptive responses of renal function in the kidney contralateral to a kidney whose function has been altered. Both afferent and efferent renal nerves are involved in the control of cardiovascular and renal functions which contribute to the regulation of body fluid and electrolyte balance, arterial pressure, and the devlopment and/or maintenance of hypertension.

5 Concluding Remarks

The functions of the renal nerves are multiple. Efferent renal sympathetic nerve activity participates in the regulation of the renal circulation, as well as in the filtration, reabsorptive, and secretory processes involved in the renal handling of solutes and water and the renal release of vasoactive substances which have important roles in cardiovascular function, the regulation of arterial pressure, and the development and/or maintenance of hypertension. Afferent renal nerves participate in renorenal reflexes which mediate the compensatory adaptive functional response of the kidney

contralateral to the kidney whose function has been acutely altered. In addition, via their connections to specialized centers in the brain, the afferent renal nerves are part of an integrated neurohumoral system which is involved in the regulation of body fluid and electrolyte balance, arterial pressure, and the development and/or maintenance of hypertension.

In 1970, *Norvell* queried: "Renal nerves: are they essential?" In view of the evidence that spontaneous or induced renal denervation in man and animals impairs the ability of the kidney to adapt normally to dietary sodium restriction and leads to the development of clinically symptomatic total body sodium deficits, the answer must be an unqualified yes. While an essential role for the renal nerves can be demonstrated in this and other circumstances of modest physiological stress, further experimental work is required to define more precisely the functional role of the renal nerves in normal homeostatic regulation.

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