W.H. BIRKENHÄGER and J.L. REID

HANDBOOK OF HYPERTENSION

Volume 3

PHARMACOLOGY OF ANTIHYPERTENSIVE DRUGS

Editor: P.A. van ZWIETEN

ELSEVIER

Handbook of Hypertension

Series Editors: W.H. BIRKENHÄGER and J.L. REID

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Pharmacology of Antihypertensive Drugs

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Foreword

Hypertension has developed rapidly over the last 30 years from the study and care of end-stage renal disease, heart failure and stroke in a small number of patients with severely elevated blood pressure, to a major community-health problem involving a substantial proportion of the population. Over the past 10 years several well-written 'textbooks' on hypertension have appeared. Some of these undoubtedly appealed to those looking for a systematic approach with compact, concise and comprehensive presentation. We shared a common feeling with our Publisher, that the vast accumulation of biological and clinical knowledge in the field of hypertension has outgrown the limitations of the classical textbook or monograph. Moreover, the subject of hypertension by its very nature is a multidisciplinary one, attracting such diverse professionals as biochemists and public health workers. When one tries to envisage what would happen to a single all-encompassing book, it is clear that it could never satisfy the active workers in the different fields. It would be so unwieldy as to be physically unbalancing to the reader. Some sections would become outdated rapidly whilst others would remain adequate. An alternative option was to escape from the constraints of a single textbook and to reconcile the interests of both generalists and specialists by choosing the format of a serial handbook.

The present work has resulted from lengthy deliberations and discussions with many clinicians and scientists. Six volumes have been or are currently under preparation which we believe will be of interest to many different groups including clinicians, clinical investigators, house officers, general practitioners, medical students, pharmacologists, pharmacists, biological scientists, physiologists and epidemiologists.
The volumes will appear in the following sequence:

1. Clinical aspects of essential hypertension
   (Editor: J.I.S. Robertson)
2. Clinical aspects of secondary hypertension
   (Editor: J.I.S. Robertson)
3. Pharmacology of antihypertensive drugs
   (Editor: P.A. van Zwieten)
4. Experimental and genetic models of hypertension
   (Editor: W. de Jong)
5. Clinical pharmacology of antihypertensive drugs
   (Editor: A.E. Doyle) and
6. Epidemiology of hypertension
   (Editor: C.J. Bulpitt)

Although further volumes are planned, they are at a preliminary stage of development. On this framework, we hope to cater to the needs of the majority of physicians and scientists interested in high blood pressure.

Each volume will be complete and separate in its own right, and not dependent on other volumes in the series. Although it is likely that there will be some degree of overlap between volumes, this is unavoidable and in our view even desirable in such a broad field. Operationally, these 6 volumes will become available in a time course of two years. After that, the matrix will be expanded or partly recycled as the demands

arise. We are fortunate to have been able to persuade a distinguished group of individuals to undertake the role of Volume Editors. They have a range of clinical and experimental backgrounds and have tackled their respective volumes with energy and enthusiasm. They have organized their individual volumes and enlisted an impressive array of international specialists as authors. Our role has been limited to that of providing invited comments and overall co-ordination. It has been a great privilege to work with these gifted and able colleagues.

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Preface

Drug treatment is an important aspect of the management of hypertension and hypertensive diseases. This is particularly so for essential hypertension. The *Handbook of Hypertension* would be incomplete if it did not address fully the subject of treatment. The present volume emphasizes the basic pharmacology of antihypertensive drugs, although a certain overlap with their clinical pharmacology cannot and should not be avoided. A further volume in the series will be devoted to clinical pharmacology, the application of antihypertensive drugs in clinical practice, and another to overall management including drug treatment. The present volume aims to discuss aspects of the most important groups of drugs in use at present emphasizing their modes of action and hemodynamic profiles. Several groups, such as the diuretics and the β-blockers, not only are used in the treatment of hypertension but also contribute to other areas of therapeutics. Emphasis will be laid upon the mechanisms of the blood-pressure-lowering action, although for the sake of completeness other applications are usually mentioned briefly.

Apart from covering new developments and recently introduced drugs such as calcium antagonists and angiotensin-converting enzyme inhibitors, the present volume includes reviews on classical antihypertensive drugs like direct-acting vasodilators, α-methyldopa, peripheral adrenergic neuron blockers and ganglionic blocking agents. Although some of these groups of drugs are less widely used in the first-line treatment of hypertension today, they remain of importance and interest not only in the treatment of resistant hypertension but also for the insights they allow into basic mechanisms of blood pressure control. I have tried, therefore, to prepare a nearly complete listing of antihypertensive drugs, which have been or still are of therapeutic relevance.

Apart from the discussion of the pharmacology of various groups of drugs in different sections and chapters, it was thought of interest to add an introductory chapter on the regulation of blood pressure, including the modification of these regulatory processes in hypertensive disease and the interference with these compensatory mechanisms by different types of antihypertensive drugs.

There is also a separate chapter on experimental hypertension, the effects of antihypertensive drugs in animal models and the relevance of these models and responses to human hypertension. Volume 4 of the *Handbook of Hypertension* considers in full 'Experimental Hypertension'.

The treatment of hypertension and developments of drug treatment have progressed rapidly over the last 20–30 years. It is unlikely that this progress will end in the foreseeable future. Although future developments may overtake some of the conclusions of this volume, this is the fate of any monograph on a rapidly developing subject. I hope, however, that the present volume will remain of use for some time as a review of the pharmacological basis for the drug treatment of hypertension.

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Handbook of Hypertension, Vol. 3: Pharmacology of Antihypertensive Drugs.
P.A. van Zwieten, editor.

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1. General introduction: the classification of antihypertensive drugs

P.A. van Zwieten

The treatment of arterial hypertension is based mainly on the administration of drugs, although other types of intervention such as reduction of sodium intake, normalization of body weight and, in very special cases, surgery may also be considered. The drug treatment of hypertension has only a short history: before the 1950s, virtually no therapy was possible at all. Ganglion-blocking agents and α-sympatholytic drugs were the first groups of compounds used to lower pathologically elevated blood pressure. In spite of the various disadvantages and side-effects of these drugs, this type of intervention, especially the ganglion-blocking agents, was recognized to be truly effective, in contrast to most other measures used in the attempt to lower blood pressure. Since the 1950s, various groups of effective antihypertensive drugs with acceptable side-effects have been introduced into current therapy. Their basic pharmacology is the subject of the present volume.

For most types of drugs, but not all, the mode of action and the mechanism of their side-effects is reasonably well understood. However, our deficient knowledge of the pathogenesis of essential hypertension — the most frequently occurring type of the disease — prevents a complete understanding of the influence of the drug on the hypertensive patient. Conversely, it should be realized that several of the newer antihypertensive drugs have proved to be most useful in unraveling the mechanisms of circulatory regulation and its pathological abnormalities as reflected by hypertensive disease.

In view of the wide variety of antihypertensive drugs available at present, a strict classification of the various subtypes is essential. The following categories of antihypertensive mechanisms of drugs should be distinguished:

1. *Drugs which depress the activity of the peripheral sympathetic nervous system*:
   ganglion-blocking agents
   peripheral adrenergic antagonists
   reserpine and other Rauwolfia alkaloids
   the Veratrum alkaloids.
2. *Centrally acting hypotensive drugs.*
3. *Drugs which block peripheral α- and/or β-adrenoceptors*:
   α-adrenoceptor antagonists (also to be considered as vasodilators)
   β-adrenoceptor antagonists
   (α + β)-adrenoceptor antagonists (viz. labetalol).
4. *Diuretic agents.*

5. *Vasodilator drugs with a direct action on vascular smooth muscle.*
6. *Calcium entry blockers (calcium antagonists).*
7. *Drugs interfering with the renin–angiotensin system:*
   angiotensin-II-receptor blocking agents (saralasin)
   inhibitors of angiotensin-converting enzyme (captopril, enalapril)
   inhibitors of renin.
8. *Ketanserin*

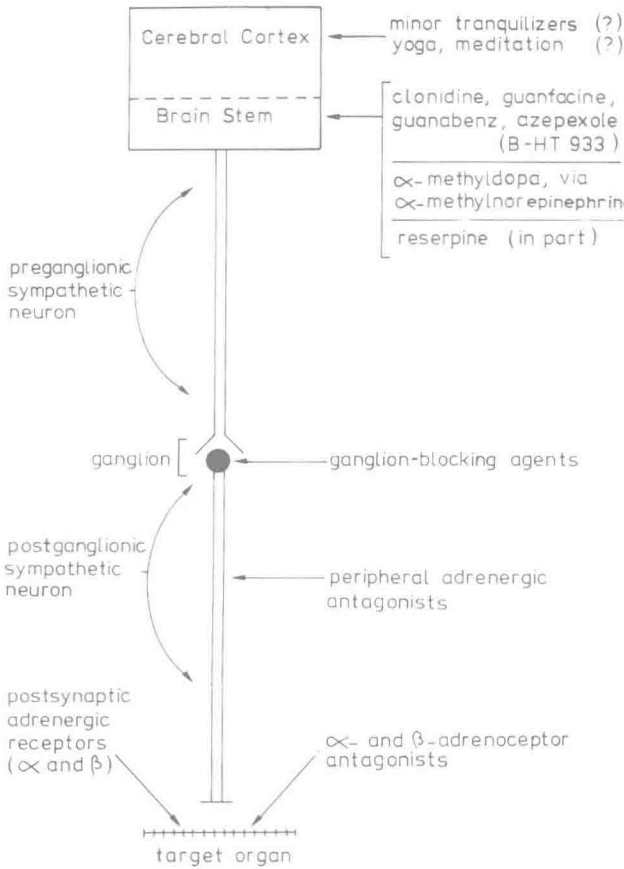

Fig. 1. Schematic representation of the influence of various antihypertensive drugs on the different structures in the central nervous system and the peripheral sympathetic system. Minor tranquilizers such as the benzodiazepines and measures such as transcendental meditation and yoga influence the cerebral cortex in a manner such that a modest decrease in blood pressure may occur. Various drugs like clonidine and related agents, but also α-methyldopa and, to a certain degree, reserpine, interfere with the central regulation of blood pressure at the level of the brainstem. The ganglion-blocking agents will interrupt sympathetic transmission at the ganglionic level. Various peripheral adrenergic antagonists, e.g. guanethidine and compounds with a similar pharmacological profile, interrupt sympathetic transmission at the postganglionic level. Various α- and β-adrenoceptor antagonists may lower arterial blood pressure since they diminish the activating influence of the sympathetic nervous system on the circulation.

TABLE 1. *Classification of the most important antihypertensive drugs, with some relevant examples of each subtype*

Class	Examples
1. Drugs which depress the activity of the peripheral sympathetic nervous system	
Centrally acting drugs	Clonidine Guanfacine Azepexole (B-HT933, exp. comp.) Guanabenz Lofexidine α-Methyldopa in part: Reserpine (mainly peripherally acting)
Ganglion-blocking agents	Mecamylamine Trimetaphan Hexamethonium Pentolonium Pempidine
Peripheral adrenergic antagonists	Reserpine, other Rauwolfia alkaloids Guanethidine Debrisoquine Bethanidine Cyclazenine Bretylium Guanacline
Rauwolfia alkaloids	Reserpine
Veratrum alkaloids	Protoveratrine A Protoveratrine B
2. Drugs which block peripheral α- and/or β-adrenoceptors	
α-Adrenoceptor antagonists	Prazosin Trimazosin Doxazosin Phentolamine Phenoxybenzamine Indoramin Thymoxamine
β-Adrenoceptor antagonists	Acebutolol Alprenolol Atenolol Metoprolol Nadolol Oxprenolol Penbutolol Pindolol Propranolol Sotalol Timolol
(α + β)-Adrenoceptor antagonists	Labetalol

TABLE 1. (*continued*)

Class	Examples
3. Diuretic agents	
Thiazide diuretics and analogs	Bendroflumethiazide Chlorthalidone Chlorthiazide Clopamide Cyclopenthiazide Hydrochlorothiazide Hydroflumethiazide Polythiazide Quinethazone
High-ceiling diuretics ('loop' diuretics)	Furosemide Mefruside Bumethanide Ethacrynic acid
4. Vasodilator drugs	
Vasodilator drugs with a direct relaxing action upon vascular smooth muscle (no mediation by the autonomic nervous system)	Hydralazine, dihydralazine, endralazine Minoxidil Nitroprusside sodium Diazoxide
5. Calcium antagonists	
	Verapamil, gallopamil (D-600) Nifedipine Diltiazem Nisoldipine
6. Drugs interfering with the renin–angiotensin system	
Angiotensin-II receptor blocking agents	Saralasin (P-113)
Inhibitors of angiotensin-converting enzyme	Captopril (SQ-14225) Enalapril (MK-421) and various experimental compounds
Inhibitors of renin	Pepstatin
7. Miscellaneous	
Blockers of 5-HT_2- and α_1-adrenoceptors	Ketanserin

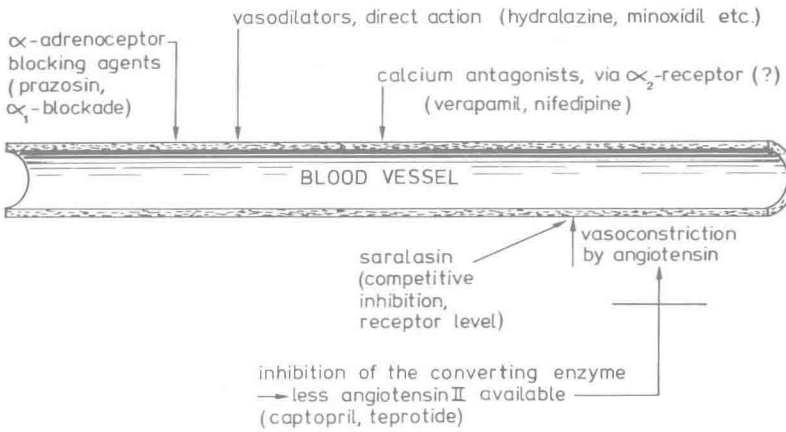

Fig. 2. Vasodilation induced by various types of drugs. α-Adrenoceptor antagonists, e.g. prazosin, cause vasodilation since they prevent the stimulatory influence of endogenous neurotransmitters. A direct action, independent of the autonomic nervous system, is induced by vasodilators of the hydralazine type. Calcium antagonists are vasodilators, which possibly owe part of their relaxing influence on resistance vessels to a complex interference with the stimulus induced by the α_2-receptor–agonist complex. Saralasin and related compounds are antagonists of angiotensin-II receptors; this inhibition explains their hypotensive activity. Inhibitors of angiotensin-converting enzyme, such as captopril, teprotide and MK-421, will reduce the concentration of angiotensin-II and hence lower blood pressure.

The major mechanisms of drug-induced reduction in arterial blood pressure are as follows:

a. drug-induced reduction of peripheral sympathetic activity. Such a mechanism can be brought about by a variety of mechanisms (see Fig. 1);
b. drug-induced relaxation of arteriolar vascular smooth muscle; this overall-mechanism can also be induced by different mechanisms (see Fig. 2).

All these categories of drugs are discussed in detail in separate chapters and sections of the present volume. Newer drugs such as ketanserin and agents with miscellaneous properties are also mentioned.

The various types of antihypertensive drugs are listed in Table 1. Some well-known examples of currently used antihypertensives are shown.

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2. Animal models in experimental hypertension: relevance to drug testing and discovery

P. Zandberg

Animal models of human disease are used to study the etiology and pathogenesis of human disease, to try to prevent disease or to find a therapy and identify risk factors contributing to the disease. Although hypertension can be induced in experimental animals relatively easily, evaluation of blood pressure changes in various models has been difficult.

Since the control of blood pressure is multifactorial, any of a number of these factors can cause the derangements involved in the development of hypertension (1, 2). Primarily, hypertension probably depends on hereditary factors, age and environmental conditions, the latter including a variety of dietary and social factors (3). As a consequence, one or more controls of cardiovascular homeostasis will change; it follows that as one regulatory factor changes, other homeostatic mechanisms will be modified secondarily.

Similar alterations in regulatory mechanisms may therefore occur despite possibly — or even probably — primary differences in etiology. It is therefore reassuring that experimental models share many features with human hypertension. Many of them have been developed by utilizing the etiological factors presumed for human hypertension such as excessive sodium intake, increase of mineralocorticoid production, hyperactivation of the renin–angiotensin system, alteration of baroreceptor sensitivity, and also by genetic expression. The experimental models can be subdivided into hereditary, renal, endocrine, neurogenic and dietary forms.

These various forms of experimental hypertension were primarily developed to obtain information on the etiology and pathogenesis of primary and secondary hypertension and were the subject of many review articles (4–10). As the major treatment of hypertension is pharmacotherapeutic, animal models are also used as a tool for investigating compounds with potential antihypertensive properties.

These hypertension models should fulfil the following criteria (see also Ref. 9):

a. simple to perform
b. uniformly reproducible
c. relatively inexpensive
d. feasible in small animals and use minimal quantities of compounds
e. able to predict therapeutic antihypertensive properties.

I. HYPERTENSION MODELS AND DRUG EFFECTIVENESS

Experimentally induced hypertension is now generally used in screening potential antihypertensive agents, although many antihypertensive agents are also effective in normotensive animals.

Occasionally, however, effectiveness can only be demonstrated when blood pressure is elevated. Moreover, blood-pressure-lowering effects are more pronounced in hypertensive animals than in normotensive animals, e.g. the sympathetic tone in a quietly resting normotensive dog is very low; under such conditions, sympatholytic drugs will have negligible effects on blood pressure and cardiac function.

Not all antihypertensive agents are effective in all models. Because antihypertensive agents can act through diverse mechanisms, effectiveness in one model does not necessarily mean that the mechanism of action of a given agent in a given model is related to the pathogenesis of elevated blood pressure.

Generally, antihypertensive agents can be classified into 4 major groups:

a. inhibitors of the renin–angiotensin–aldosterone system
b. diuretics
c. directly acting smooth-muscle relaxants
d. drugs interfering with the sympathetic nervous system, which can be subdivided into drugs acting centrally, and drugs acting peripherally either at the presynaptic level, influencing the synthesis and/or release of norepinephrine, or at the postsynaptic level at the α- and/or β-adrenoceptor sites and the effector organs (see Fig. 1).

These different classes of antihypertensive agents are discussed in this Volume. The purpose of this chapter is to give a concise description of the pathogenesis of currently used models for the screening of potential antihypertensive agents and to discuss how and by which classes of antihypertensive agents these models can be influenced.

II. METHODS OF MEASURING BLOOD PRESSURE

In screening antihypertensive agents in conscious animals, blood pressure can be determined directly by a chronically implanted cannula, or indirectly. For indirect measurement, an artery is occluded and the appearance or disappearance of the pulse distal to the occlusion sensed by a sensitive microphone, by sensing the changes in impulse volume with a plethysmograph, by the ultrasonic Doppler technique or by a pneumatic sensing bulb coupled with a piezoelectric transducer.

Indirect methods

In rabbits, the central ear artery can be used for indirect measurement. A cylinder with an elastic membrane is used, the membrane being placed over the central ear artery. Systolic and diastolic pressure can be determined by measuring the capsule pressure necessary to occlude the artery completely and the pressure to allow continuous flow through the ear artery (11).

In dogs, a method has been developed for measuring blood pressure by a cuff occluding the tibial artery on the anteromedial surface of the hindpaw (12). The radial artery of the forepaw can also be used (13). Another method is to exteriorize the common carotid artery in a skin flap (carotid loop).

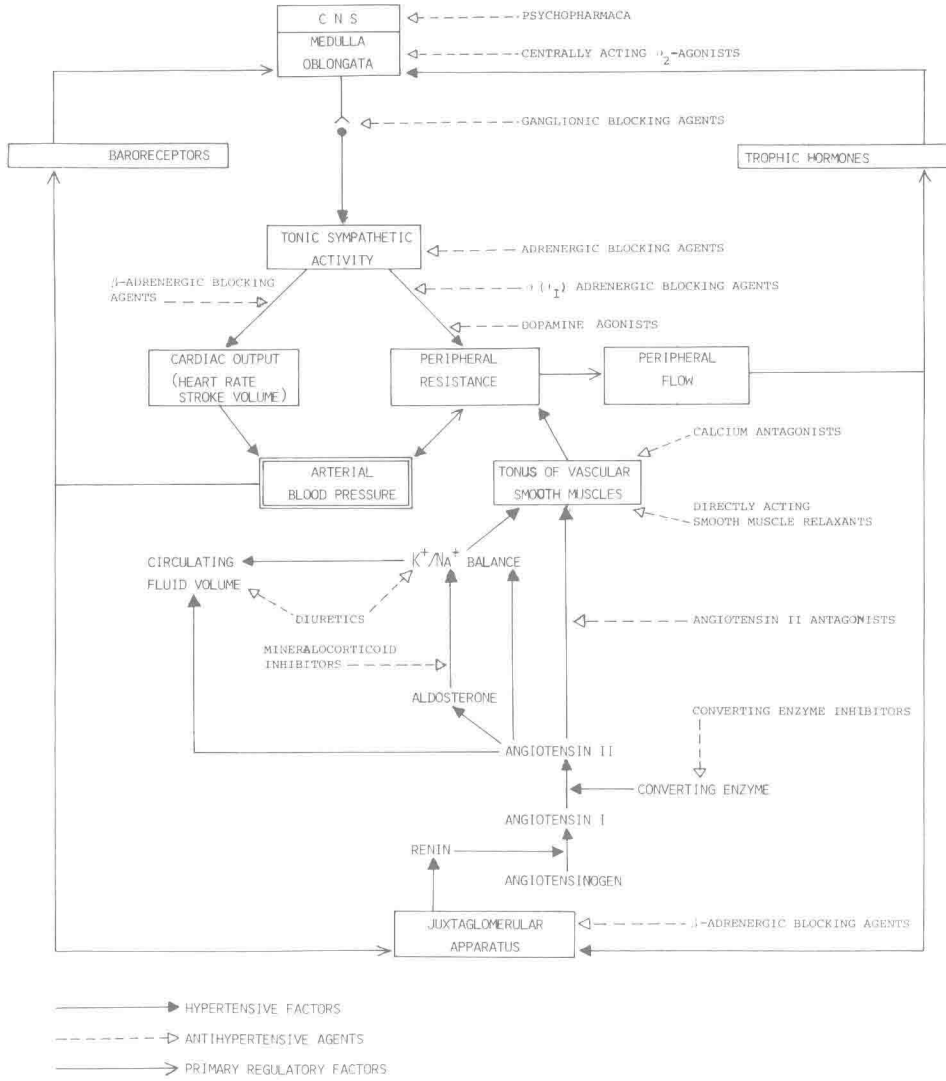

Fig. 1. Schematic representation of the site of action of the different classes of antihypertensive agents.

Systolic blood pressure in these dogs can be measured by an occlusive cuff applied to the carotid loop and connected to a sphygmomanometer. Systolic pressure measured in this way has been found to correlate well with intra-arterial systolic pressure (14).

Considering the anatomic locations of the arteries of the generally used laboratory animals (rat, rabbit and dog), the animal of choice for screening antihypertensive agents is the rat.

The rat tail allows blood pressure measurements to be made by indirect means utilizing a small inflatable tail cuff. Moreover, the rat is a very useful test model

because of its size, ease of handling and housing, and the relatively low costs involved.

In most systems, blood pressure is observed in the tail cuff manometrically and the appearance of the tail pulse oscillographically (15–17). Heart rate may be obtained with a cardiotachometer. Attention, however, should be paid to the conditions used: the values of systolic blood pressure recorded can vary with the ambient temperature (18, 19), with the size and position of the occluding cuff and with the rate of inflation and deflation of the cuff (20–22).

Moreover, training of the animals is a prerequisite to minimize artefacts caused by handling, movement, physical restraint and visual, auditory and tactile stimuli (22, 23).

Heating of the animal is also necessary because the tail arteries which are important in thermoregulation are often constricted at room temperature. Abrupt vasodilatation in the tails of rats are obtained at environmental temperatures of 28–30°C. In practice, a temperature of at least 32°C is necessary to obtain a tail pulse. If heat is applied to the tail, the recording improves (21). A drawback of the indirect measurement of blood pressure is local vasoconstriction (autoregulation) of the tail artery caused by compounds which lower arterial blood pressure, thus leading to a reduced arterial pulse and consequently in a systolic end-point. Moreover, the method is only useful for the measurement of systolic blood pressure, although recently a method has been described by which diastolic blood pressure can also be measured (17).

Direct methods

To obviate the difficulties of indirect measurements, methods have been developed which allow continuous recording of both diastolic and systolic blood pressure in conscious animals by inserting indwelling catheters into the common carotid artery which are passed subcutaneously to the back of the neck. This method has the disadvantage that it can interfere with the baroreceptor reflex regulation of blood pressure.

Other methods for rats have been described by Popovic and Popovic (24) and by Weeks and Jones (25) who inserted permanent cannulae into the abdominal aorta at the level of the renal arteries.

Buñag et al (26), later modified by Nijkamp et al (27), cannulated the iliac artery instead of the abdominal aorta.

Both methods have the disadvantage that a relatively large operation is required; laparotomy has to be performed.

Another direct method is cannulation of the caudal tail artery (28).

To measure blood pressure in conscious rats over a long period, the most consistent results are obtained with the method of Weeks and Jones (25). Some investigators were able to measure arterial blood pressure for more than 2 months by this method.

In awake rabbits the central ear artery can be punctured or cannulated using local anesthesia. A chronic indwelling cannula through the carotid artery into the thoracic aorta has also been used. With this last method arterial blood pressure could be measured for more than 6 months (personal observations).

In dogs a cannula can be introduced from the proximal stump of a cut left cranial thyroid branch through the common carotid artery down to the descending thoracic aorta. Other investigators have punctured the carotid loop for blood pressure measurements.