CIBA FOUNDATION SYMPOSIUM
ON
HYPERTENSION
Humoral and Neurogenic Factors

Editors for the Ciba Foundation
and
MARGARET P. CAMERON, M.A., A.B.L.S.

Assisted by
JOAN ETHERINGTON

With 73 Illustrations

LONDON
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1954
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Humoral and Neurogenic Factors
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PREFACE

This symposium on Hypertension had its origin in a suggestion by the late Professor H. Rasmussen of Norway. Just before his untimely death he proposed that a conference should be organized for discussion of hypertension from the epidemiological point of view. As Professor Pickering mentions in his Opening Remarks, this project has not been abandoned, but it is proving difficult to arrange, and in the meanwhile, with Professor Pickering's invaluable help, the symposium of which this volume contains the proceedings has been held as a complementary discussion to the one in view.

A word about the Ciba Foundation must be added here by way of explanation to those to whom this book serves as an introduction to its activities. It is an international centre, established as an educational and scientific charity under the laws of England. It owes its inception and support to its founder, Ciba Ltd. of Switzerland, but is administered independently and exclusively by its distinguished British Trustees.

The Foundation provides accommodation for scientific workers who visit London from abroad, organizes and holds international symposia, conducts (in conjunction with the Institut National d'Hygiène) a post-graduate medical exchange scheme between England and France, arranges informal meetings for discussions, awards an annual lecture-ship, assists international congresses and other scientific societies, is building up a library service in special fields, and generally endeavours to give aid in all such matters as may promote international co-operation in scientific research.

Leading research workers from different countries and in different disciplines are invited to attend the symposia or colloquia. The size of the groups is, however, very strictly
limited in order to obtain a free conversational manner of discussion—although the basic timetable of the programme is strictly observed. The smallness of the groups necessarily means the exclusion of many other workers active and interested in the subjects discussed, and therefore the proceedings of these conferences are published and made available throughout the world.

It is hoped that the papers and discussions in this book will prove not only informative and stimulating, but will also give to readers a sense of participation in an informal and friendly occasion.
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in Hypertension”, 27th–30th July, 1953.

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CHAIRMAN'S OPENING REMARKS

G. W. PICKERING

I am sure that the first thing you would like me to do is to express our appreciation to the Ciba Foundation for arranging this meeting, and for allowing us to meet in this highly agreeable atmosphere to discuss these matters of common interest. But it is not only for that that I think we should thank its Director, Dr. Wolstenholme. He has arranged nearly all this Symposium, and I have been astonished at his remarkable and detailed knowledge of the whole field of the subject about which we are talking.

There is no need, I think, to stress the importance of the problem of hypertension and its effects on the cardio-vascular system. The problem could have been approached from two points of view: from the functional point of view, or, if you like, the point of view of applied physiology, which is the purpose of this Conference; or from the epidemiological point of view, and I have the Director's permission to mention that he has it in mind to have a future Symposium on this second aspect of the problem.

Twenty-two years ago, when I started to work on hypertension, having been trained as a physiologist and working in a laboratory which was given to the physiological approach, the laboratory of Lewis, it seemed to me that this would be a relatively simple problem to solve. All it needed was the application of the experimental method and physiological principles. It is rather sad to look at it again after twenty-two years, and see that I have to count myself amongst those who do not know the answers to most of the questions which we ask. We know, of course, that it is possible to produce hypertension in the experimental animal by a variety of means. But I think it is only in that particular variety which
is produced by section of the carotid sinus and depressor nerves that we have even the remotest appreciation of what the mechanism of the hypertension actually is. I believe it is still true to say that in the hypertension invented by Goldblatt, whom we are extremely sorry not to have with us here today, we do not know the answer, and I think perhaps the same is true concerning the hypertension that follows nephrectomy. I say this, speaking at 4.15 p.m. on the 27th of July. I hope that at a corresponding time on the 30th of July I shall be able to revise these opinions.

It is not surprising, if we know so little about the mechanism of hypertension in the animal, that we know even less about it in man, even in those relatively well-defined conditions in which the hypertension is associated with lesions in the kidney which can actually be seen under the microscope, and with certain disorders of the endocrine glands which again are perfectly obvious. Perhaps it is not so surprising that in that much more elusive and intangible phenomenon, essential hypertension, we should be even further in the dark. So that this problem of hypertension provides a challenge to clinicians, biochemists, pharmacologists and physiologists, and I take it that it is our purpose here and now to try and accept that challenge, to pool our ideas and knowledge, and see how far we can get.
NEURAL AND HUMORAL CONTROL OF BLOOD VESSELS

IRVINE H. PAGE

That an international conference has been called to discuss neural and humoral controls of the circulation is proof enough of the station this topic has attained. The field has developed in a truly international way; such names as Abell, Dale, Elliott, Fourneau and Cannon occur among the early workers in this fruitful vineyard. We who have come later have our reward now in the benefits of this present association and hospitality, for which we thank the Trustees of the Ciba Foundation and the scientific perceptiveness of Dr. Pickering and Dr. Wolstenholme.

I am told that I am not intended to document the topic, but rather to express the views, activities, current interests and aspirations of our group at the Cleveland Clinic. The aim, in brief, is to provide a setting for discussion rather than a manuscript to moulder in the archives.

Those aspects of cardiovascular regulation with which I am most concerned can best be set in their place by visualizing the problem as a whole. This I have tried to do by an octagonal diagram which indicates the controls of tissue perfusion function in a dynamic equilibrium. This concept I regard as important because it seems that the problems we face are more realistically soluble in terms of altered equilibria than by any one of a variety of monistic approaches.

For this reason we have been particularly occupied with the problem of vascular reactivity, i.e., of the response to a vasoactive agent and the factors which modify this response. This area of investigation has been too widely overlooked. The fact is that the response of the tissue to a drug or procedure is at least as important as the nature and quantity of the
stimulus. The technique used in most of our experiments consists in observing the changes which occur in an animal's arterial pressure after administration of a variety of vasoactive drugs. Obviously, various mechanisms can participate in these changes, such as cardiac output on the one hand or peripheral vasoconstriction on the other; when changes of reactivity can be shown to occur, specific and complex methods of analysis must be used to determine their nature.

Neural Factors

Neurogenic Hypertension. As has been shown by electrical stimulation, certain areas of the brain influence the level of arterial pressure. The significance of these acute responses remains obscure. Because of our interest in the problem of chronic hypertension, Dr. Taylor and I (1951) attempted for
some time to elicit chronic arterial hypertension by means of cerebral ischaemia in dogs. Each new induction of ischaemia caused only a transient episode of hypertension; eventually a point was reached where increased ischaemia was lethal. However, we went on to combine cerebral ischaemia with repetitive stimulation of the floor of the fourth ventricle—the latter was achieved by implanting a tantalum wire and subjecting the animal’s head to an inductotherm at intervals after the operation—and the result was a persistent neurogenic hypertension of moderate severity which was abolished by section of the spinal cord at C6.

The hypertension which follows section of the carotid sinus and aortic depressor nerves is similar. The blood pressures of these animals are often increased to levels of 300 mm. Hg. and over; the hypertension can be relieved by total sympathectomy or abolished by high spinal cord section. Increased cardiac output due to cardiac acceleration was once believed to be the major factor in causing this increase in arterial pressure. However, it now appears that the disequilibrium of sympathetic control extends to the arteries and arterioles, since the hypertension persists after cardiac denervation, when cardioacceleration is absent (McCubbin and Page, 1951).

The responses of these dogs to tetraethylammonium chloride (TEAC) are of particular interest to me; they demonstrate the concept of reactivity, validate the view that sino-aortic neurogenic hypertension is due to misplaced equilibrium of sympathetic vasomotor controls and may yield some insight into the problem of hypertension in human beings. Briefly stated, intravenous injection of standard test doses of TEAC causes in these animals deep, briefly sustained, repetitive depressor responses, whereas in normal dogs or in dogs with renal hypertension, initial moderate depressor responses are followed by pressor responses to successive injections (Page and McCubbin, 1951; 1952a). The drug itself acts primarily by blockade of transmission through sympathetic ganglia; the responses in the dog with neurogenic hypertension indicate, as might be predicted, that these
ganglia are transmitting a vast shower of vasopressor impulses; the responses are deep because these impulses have become the major determinants of the blood pressure level; they are repetitively obtained because these ganglia, supercharged as it were from above, resist the blockade which, in other animals, supervenes after repeated TEAC dosage. As concerns clinical hypertension, the point of interest lies in the fact that a minority of patients show repetitive deep depressor responses to TEAC, whereas the majority do not; the response pattern of those who do this corresponds to that of dogs with sino-aortic hypertension and suggests that hypertension in these patients is also primarily neurogenic. It is hoped that
this form of clinical hypertension, like the experimental disease, will respond to sympathectomy.

Reactivity and Neural Change. Destruction of the spinal cord from C6 caudally, if the animal or patient survives in relative well-being, sharply increases responses to test doses of noradrenaline, adrenaline and barium chloride; responsiveness to angiotonin is unaffected or only slightly enhanced; sensitivity of the vagal cardio-inhibitory reflex is greatly augmented. In brief, this form of neural ablation induces a definite pattern of reactivity change.

Section of buffer nerves induces a different series of changes. Thus, as McCubbin and I (1952) showed, section of the carotid sinus nerves, when preceded by section of the vagus-depressor trunk and administration of TEAC, greatly enhances the response to angiotonin; responsiveness to noradrenaline, serotonin and Pitressin are not proportionately increased; sympathectomy prevents this effect of buffer nerve section.
Curiously, the effect on angiotonin responsiveness is not as great when hexamethonium is substituted for TEAC.

Thus, under specific situations, discrete neural ablations result in highly characteristic changes in reactivity. But the complexity of the problem and the sensitivity of the mechanisms involved is illustrated by the fact that enhancement of angiotonin response by buffer nerve section is only observed when TEAC is given by a definite schedule of repeated doses; when either TEAC or hexamethonium is given by slow infusion, the augmentation which results resembles that seen after cord section regardless of the state of the buffer nerves. Thus it seems likely that we deal in these situations with the interaction of selective neural mechanisms of vascular regulation; their existence has only been visualized and their nature is not understood.

Another aspect of the neural control of reactivity is demonstrated by causing anaesthetized, curarized dogs to inhale 15–30 per cent CO$_2$ (Page and Olmsted, 1951). They respond by a moderate decrease of arterial pressure; at this point the ability to respond to adrenaline or noradrenaline is either greatly impaired or absent; responsiveness can be restored, or the onset of refractoriness prevented, by ganglionic blockade or by ablation of the paravertebral sympathetic ganglia.

These examples of altered responsiveness show that neural regulation of circulatory function is exercised in large part by mechanisms which control and inhibit and do not exclusively work, as we have been accustomed to think, by means of excitation. The limited data available prevent any very specific conclusion; they do suggest that those interested in circulatory controls should concern themselves with the inhibitory as well as the excitatory aspects of neural regulation; indeed, by analogy, it seems likely that circulatory neural controls, like other neural functions, act by a system of equilibrating "feed-backs".

One of the more attractive explanations of the sensitizing action of the blocking drugs has been that they somehow
depress amine oxidase activity, although this would not seem to apply to histamine, barium, or sodium nitroprusside. The hypothesis was tested by measuring responsiveness to noradrenaline, serotonin and angiotonin before and after administration of drugs which, in vivo or in vitro, were known to inhibit amine oxidase. Among these, ephedrine gave slight augmentation of response to noradrenaline; but, disappointingly, amphetamine had either no effect or even impaired the responses, and a third agent, Marsalid (1-isonicotinyl-2-isopropyl hydrazide phosphate) clearly decreased them.
Thus, inhibition of amine oxidase activity would not seem to be the reason for the post-TEAC augmentation.

The importance of autonomic nerve function in vascular response to a vasoactive agent, is exemplified dramatically in the case of serotonin. This drug has usually a biphasic depressor-pressor response in the dog; in the cat, the response is purely depressor, as it is also in the dog with neurogenic (sino-aortic) hypertension. Blockade of autonomic ganglia with TEAC or hexamethonium causes the drug to exert a

![Graph showing the effect of 30% carbon dioxide on vascular reactivity in a sympathectomized dog.](image)

Fig. 5. The effect of 30 per cent carbon dioxide on vascular reactivity in a sympathectomized dog (No. 1328).

purely pressor action (Page and McCubbin, 1953). Thus, response to serotonin is an index of vasoconstriction resulting from nervous activity.

The drugs which block the actions of the sympathetic nervous system more peripherally result in still another pattern of reactivity. Regitine, Priscoline, and the Benzo-dioxanes, are presumed to interfere with the humoral mediators, adrenaline and noradrenaline, at the myoneural junction. Such blockade again exemplifies the specificity and varied nature of changes in reactivity. These agents reverse the response to adrenaline and inhibit the pressor response to noradrenaline, but do not affect pressor responsiveness to angiotonin and Pitressin. Serotonin is affected irregularly by adrenergic block. Under certain conditions its action may be transiently reversed from pressor to depressor.

To sum up, a variety of neural activities influence not only the level of arterial pressure but also, and with some specificity, responsiveness to vasoactive agents (Page and Taylor, 1950). These effects may depend on one and the same action, variously exerted. The data at hand emphasize the importance of considering not only the amount and kind of vasoexcitor which may be present, but also the amount and kind of response which it will excite; the concept is proposed that the inhibitory as well as the excitatory properties of central nervous function must be considered in assessing the nature of drug action. In a world of cats and neurogenic hypertensive dogs, serotonin would be classed as vasodepressor; in the world of reality we find that its properties depend on the responsiveness of the recipient.

**Humoral Controls**

The relationship between the presence of humoral substances, the calibre of blood vessels, and their reactivity, has been under study for many years. The brilliant studies of von Euler, of several English physiologists, and Peter Holtz, adumbrated by Walter Cannon, have uncovered much of the mystery of adrenaline and noradrenaline. Nature’s experi-
ment in this field, the phaeochromocytoma, has demonstrated to the clinician the havoc that a disequilibrated humoral system can produce. In spite of the relative simplicity of the chemical structure of the adrenergic agents, progress in this field has taken a good many years. The structural complexity and small amounts of other potentially significant humoral agents probably account for the fact that we know so little about them. And, fortunately or not, Nature does not co-operate by establishing tumours which will secrete angiotonin, serotonin, cerebrotonin, either alone or in combination.

**Renin, Renin-Substrate, Angiotonin (Renin, Hypertensinogen, Hypertensin).** The study of the renal pressor system began when Tigerstedt and Bergmann showed that extracts of kidney were pressor when injected intravenously into dogs. The substance responsible for this effect was termed renin and considered to be a pressor substance with direct action. This concept was dispelled when, with Helmer, we found that initial purification of renin yielded a protein mixture which did not act directly on the blood vessels of isolated organs perfused with Ringer's solution (Page and Corcoran, 1948). These mixtures were then found to become vasoconstrictor when perfused in the presence of plasma. The substance in plasma which made the inactive renin active was tentatively called, "renin-activator" (Kohlstaedt et al., 1940; Page, 1940) until further studies showed that what had occurred was an enzymatic interaction of renin with a protein substrate and the formation of an ultrafiltrable pressor substance which was directly vasoconstrictor. The substrate was termed renin-substrate, and the pressor product of the reaction, angiotonin. Eduardo Braun-Menendez accomplished a similar demonstration at the same time, and he and his associates termed the substrate hypertensinogen, and the product of the reaction, hypertensin (Braun-Menendez et al., 1946).

At the time, we both probably had the notion that scientific nomenclature was an ordered system and that each in his
own way had fulfilled the rules and regulations, while the other had flouted them. We have both learned that the rules of nomenclature seem to be mostly self-made and although we now laugh at the tangle we created, we regret the difficulties experienced by medical students in assimilating this terminology. Unfortunately, the trivial names will persist, for, while it would be desirable to use chemical names, it is unlikely that anyone ever will; these materials are too complex. Even as concerns simpler compounds, while 5-hydroxytryptamine may replace serotonin and enteramine, neither adrenaline nor noradrenaline are referred to by their more informative structural names, and "Regitine" is more convenient than 2(N-p'-tolyl-N-m-hydroxyphenylamino-methyl) imidazoline.

The clue to the nature of the renal pressor system was the demonstration of renin-substrate. However, this material is not yet available in pure form. Some years ago with Plentl and Davis, we found (Plentl et al., 1943) that most of the renin-substrate of plasma occurred in the alpha-2 globulin. Green, in our laboratory, has since prepared a concentrate of this material by fractionation of plasma with ammonium sulphate at various pH's. One gram of this concentrate yields, on incubation with renin, 20 to 30 mg. of a peptide fraction which corresponds in activity to 6 mg. of the purest angiotonin yet prepared. This small yield testifies to the probability that the substrate content of the concentrate must still be relatively small in relation to the other proteins it contains. In brief, all we know is that renin-substrate is probably an alpha-2 globulin, that it is formed in the liver (Page et al., 1941) and, as Dr. Helmer will tell us, that its formation is influenced by the adrenal corticosteroids.

A significant advance has been made in the preparation of renin in that Haas, Lamfrom and Goldblatt (1953) have obtained a material of very great potency. Unfortunately, even after 34,000-fold purification, electrophoretic analysis reveals two components and the estimated purity of the material is about 65 per cent. This material, however, is
much more homogeneous than any which has hitherto been available. Thus, the studies done to date on renin and renin-substrate, on their interaction and concentrations in blood and tissues, have all ultimately to be re-examined by modern enzymatic methods as purer reactants come into our hands. Many early claims and counter-claims can be put aside and judgement suspended until confirmation by exact means is possible.

Thus, with an impure substrate and an impure enzyme, it is no wonder that the isolation of the complex product of their interaction has not gone on apace. Angiotonin has been much in my thoughts for the past fourteen years, as, under another name, but just as elusive, it has been in those of Dr. Braun-Menendez. Our group, including my former associates, Helmer and Plentl, made great advances in its purification, only to be outstripped by Edman in Sweden, but Edman seems to have lost interest in the problem. Our present colleague, Bumpus, has recently prepared an angiotonin that is, as nearly as the comparison can be made, more than twice as active per milligram nitrogen as Edman’s best.

The fascination of angiotonin lies partly in its ability to mimic most of the haemodynamic changes of essential hypertension. Unfortunately, pending better methods, the most that can be said is that it seems to be present in increased concentrations in the blood of some renal hypertensive animals and of some patients with advanced hypertensive disease. However, in this connection, one should keep in mind the point made above, that under appropriate conditions of altered neural function, responsiveness to angiotonin is greatly increased. Consequently, it is possible to envisage a situation in which normal or presently unmeasurable concentrations of this agent might effect a large and persistent increase in arterial pressure. And, once the new equilibrium of arterial pressure had become established, the enhanced sensitivity to angiotonin which set the process in motion might very well disappear. Admittedly, the situation I envisage here is complex and hypothetical; I point it out