Renal Hypertension

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IN the last decade an enormous amount of investigation has been performed and rapid strides have been made in the understanding of renal hypertension. This monograph provides a summary of what has been accomplished and points out the gaps in our present knowledge. It constitutes at the present time an all important source of information on the subject. A resume at the end of each chapter will be useful to those not familiar with the subject. The techniques devised by the authors are described in an appendix. There is a complete bibliography.

THIS is not a line-for-line translation but is presented by Dr. Dexter in an easily understandable and readable fashion adequately conveying the writers' views. The extensive first-hand experience of the authors permits them to describe their own valuable contributions and to discuss the problems in a critical fashion. Their members represent the physiological, chemical and clinical fields.

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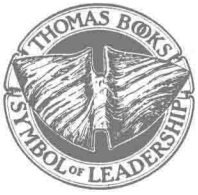

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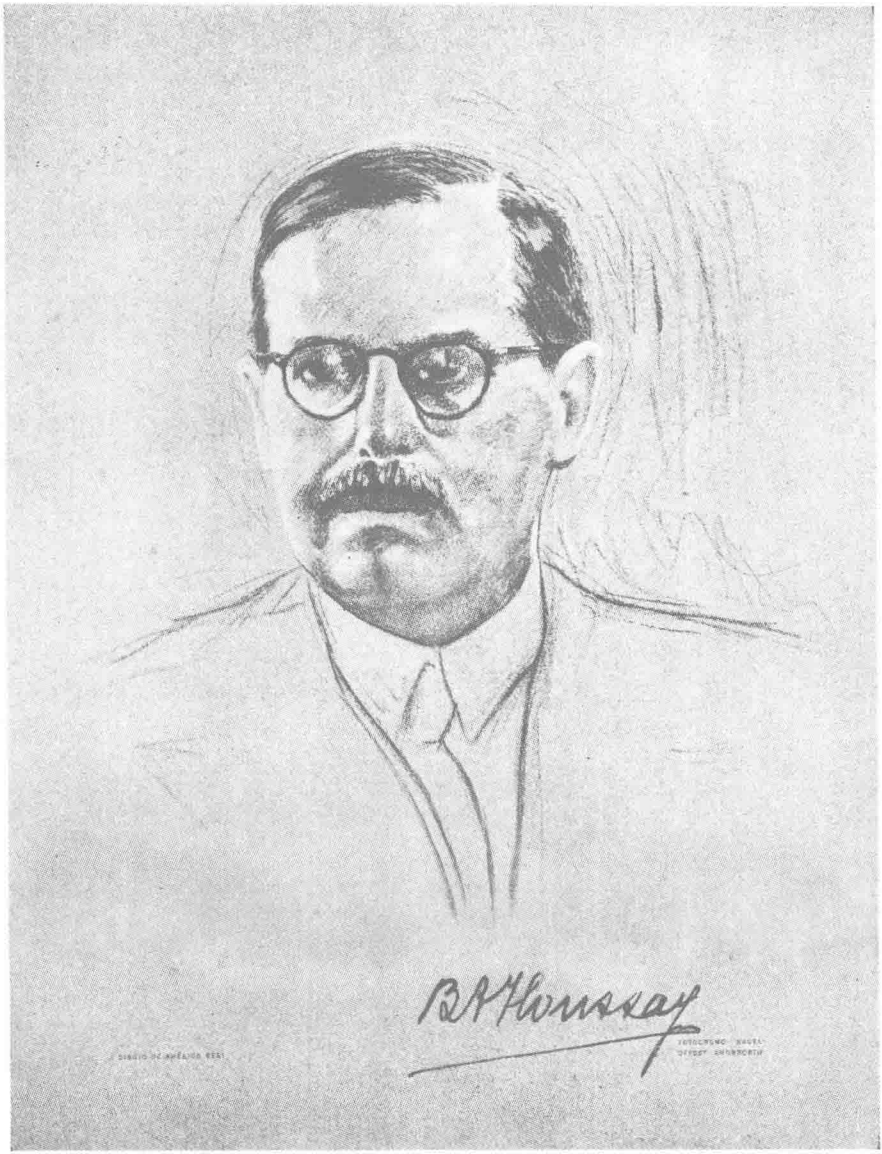

PROFESSOR BERNARDO A. HOUSSAY

PROLOGUE

Recent advances in our knowledge of renal hypertension represent an outstanding accomplishment in experimental medicine. An insight has been given into its pathology, an important field of investigation has been opened, and the hope of being able to prevent and cure one of the gravest of human diseases has been renewed.

The first real knowledge concerning renal hypertension began with Bright's accurate observation that hypertrophy of the heart frequently accompanies diseases of the kidneys. Later, on discovering methods of measuring arterial blood pressure, it was easy to demonstrate that such diseases were associated with hypertension and that the cardiac hypertrophy was a consequence of the hypertension.

No new important advances were made in our knowledge of the rôle of the kidney until Tigerstedt and Bergman demonstrated, in 1898, that extracts of the kidney possess a hypertensive action. They gave the name, renin, to the impure substance which produced this effect.

In that period the vasoconstrictor action of extracts of three organs had been demonstrated: the adrenal medulla, the hypophysis, and the kidney.

The discovery of adrenalin led to the hypothesis that its hypersecretion was the cause of hypertension. The adrenal theory, or more exactly that of hyperadrenalism, was formulated almost immediately after its discovery, first by Josué, and subsequently by many other clinicians. This theory transferred interest from the kidney to the adrenal medulla.

Much credit is due the indefatigable investigations of Volhard who was convinced that a vasospastic factor existed in the so-called pale hypertension, as was indicated by ocular and cerebral symptoms and by blanching of the vessels of the skin. Since he believed that the exaggerated contraction of these vessels was due to a substance circulating in plasma, he devoted himself with the help of his students to a search for its presence. He first showed the impossibility of demonstrating the presence of an excess of adrenalin in the circulating blood, although later some of his students, such as Bohn (1931), described the presence of specific vasoconstrictor substances in the

blood of hypertensives. This was subsequently disproven by numerous investigators.

In our Institute, plans for the study of this problem began when we had the misfortune of losing Juan Guglielmetti, in 1923, who died of malignant hypertension at the age of 33. Among those who have worked with us, he ranks as one of the most capable and talented. An attempt was made to produce experimental hypertension of renal origin in dogs by subtotal nephrectomy with limited success (Biasotti, 1927). New attempts were made by constricting the renal vein, but the hypertension was inconstant and transient (Braun-Menéndez, 1932).

Shortly after the discovery that permanent hypertension might be produced by section of the four pressor receptor nerves, attention was directed toward nervous factors which for some time had been considered as possible causes of arterial hypertension.

The modern period is due entirely to Goldblatt who, in 1932, and in a classical report of 1934, gave investigators an easy and sure method of producing permanent hypertension of renal origin. This procedure simply consists of reducing the diameter of the renal artery, and is referred to, with dubious correctness, as producing a partial ischemia or incomplete ischemia, which are terms now established by usage. In the skilled hands of this trained investigator and with the contributions of many other investigators from different countries, it was shown that this hypertension was not due to a nervous mechanism such as a reflex of renal origin or hyper-reactivity of the vasoconstrictor nerves. New investigations were carried out principally in the United States, Belgium, Argentina, and England.

In 1936, we renewed our studies with Fasciolo who energetically overcame innumerable initial difficulties. After confirming previous studies we were able to show, in 1937, that the incompletely ischemic kidney of a hypertensive dog produced and liberated into the blood a hypertensive substance which today we know as renin. This was demonstrated by grafting a kidney by vascular anastomosis of its artery to the carotid and of its vein to the jugular into the neck of a dog recently nephrectomized. The following year, with Taquini, we showed that the citrated plasma of venous blood of an ischemic kidney contained a vasconstrictor substance which did not exist in the plasma of normal venous blood.

At that point the subject passed into the hands of a team of investigators at the Institute of Physiology, whose combined efforts led to important discoveries. This group consisted of E. Braun-Menéndez, J. C. Fasciolo, L. F. Leloir, J. M. Muñoz, and A. C. Taquini, while important contributions over shorter periods of time were made by J. W. Bean, R. Dell'Oro, L. Dexter, V. G. Foglia, M. Gaudino, F. Huidobro, F. P. Ludueña, and J. M. Moglia.

In 1939, an important discovery was made almost simultaneously in Argentina and in the United States. Braun-Menéndez, Fasciolo, Leloir and Muñoz extracted a substance which they called hypertensin from the venous blood of ischemic kidneys, which was produced by the action of renin on a plasma globulin called hypertensinogen or precursor of hypertensin. They showed that this same hypertensin was produced by incubating renin with hypertensinogen *in vitro*. It was demonstrated, furthermore, that the kidney secreted renin which, though not of itself vasoconstrictor, rapidly produced the vasoconstrictor substance, hypertensin, upon coming in contact with the hypertensinogen of plasma. Evidence was presented that the reaction was enzymatic in nature.

Attacking the problem from a different angle, Page and his collaborators reached similar conclusions. They showed that renin did not possess a vasoconstrictor action when it was perfused in saline solution through an isolated surviving vascular system. When serum or plasma was added, vasoconstrictor properties appeared. They at first believed that the plasma contained an activator of renin but later showed that the appearance of the vasoconstrictor action was due to the formation of a new substance which they called angiotonin. Unfortunately, the numerous publications of Page and his school, although making important contributions and advances, included many assertions not always well demonstrated, affirmed the existence of many substances which are doubtful, and formulated numerous hypotheses and concepts which were not always in accord. Fortunately, their conclusions have gradually become similar to our own. Today the principal discrepancy is one of terminology. All agree that renin through its action on a plasma globulin (hypertensinogen, renin-activator, renin-substrate or prehypertensin) produces a vasoconstrictor substance (hypertensin or angiotonin).

In the clinic, the existence of hypertension from renal ischemia

similar to experimental renal hypertension, has not only been demonstrated but the hypertension has been cured by removal of the diseased kidney in some cases of unilateral renal disease. There are no definite proofs, however, that all hypertensions have a renal origin. Nervous factors appear to participate in variable degree in the genesis and maintenance of human hypertension.

Finally, endocrine and other metabolic factors are recognized as playing a rôle in certain instances. Whatever may be the respective importance of these various factors and whatever may be the course of future investigation, there is no doubt but that experimental studies on renal hypertension have strongly influenced current ideas and have stimulated numerous investigations. These have furthermore been facilitated by recent outstanding advances in the physiology of the kidney and in the development of renal function techniques. It is important, however, to recognize clearly the obscure and badly demonstrated points in order to undertake new investigations.

Although numerous medical and surgical therapeutic attempts have given variable results and as yet can not be considered to be satisfactory, we have the advantage of new knowledge which allows us to test experimentally the action of various therapeutic agents on renal or neurogenic hypertension in animals before testing them on man. We should not be alarmed if it takes considerable time to attain success since advances are always slow in biology. It only suffices to recall that thirty-three years elapsed between the demonstration of experimental pancreatic diabetes and the discovery of insulin.

The secretion of renin is one more example of a homeostatic substance produced by the organism. It is a true internal secretion which does not exist or is only of slight importance under normal conditions. In the presence of severe hypotension, it constitutes one of the numerous mechanisms at the disposal of the body for aiding in the recuperation of blood pressure. Under pathologic conditions of renal ischemia this secretion unfortunately acquires a hypertensive character.

A regulatory mechanism of blood pressure has thus been discovered, and has been clearly demonstrated in birds and mammals. Since it appears only in pathologic conditions which affect the

kidney, it is presumably an advantageous mechanism. It is easy to postulate, for example, the attractive but uncertain teleologic hypothesis that the hypertension thus produced is useful in increasing the renal blood flow or the glomerular filtration.

A curious fact is that the action of renin is indirect. Itself inert, it acts upon the hypertensinogen of plasma to produce the constrictor substance, hypertensin, whose action is ephemeral since it is rapidly destroyed in the body.

This monograph is a study of renal hypertension only and summarizes the present state of our knowledge. The enormous amount of work done on this subject is reflected by an abundant literature. Conclusions have sometimes been contradictory and sometimes excessive. The authors have an extensive firsthand experience which permits them to describe their own valuable contributions and to discuss the problem in critical fashion. This book, in addition to its original contribution wherein lies its true value, constitutes at the present time the most important source of information on the subject. I think that its reading will not only be instructive but will suggest new ideas and new subjects of study and investigation. An appendix describes the methods which have not as yet been published in detail. It is hoped that it will facilitate the work of future investigations.

B. A. Houssay

INTRODUCTION

Study of hypertension has experienced a remarkable impetus in recent years thanks to the efforts of both physiologists and clinicians. It has at times been considered by those unfamiliar with research that investigations by clinicians and by physiologists have no common ground. Both are actually sources of mutual information which help in the interpretation and discovery of natural phenomena. Evolution in our knowledge of arterial hypertension is a clear-cut example of this. The clinical-pathologic approach led to the discovery of the rôle of the kidney in hypertension, and the physiologic approach to the reproduction of this disease and to the study of its pathogenesis. Knowledge acquired experimentally made it possible for the clinician to discover new renal disorders capable of producing hypertension which had passed unnoticed until that time, and to develop methods of unquestioned value for the investigation of the function of the kidney.

As Professor Houssay stated in the prologue, the subject of renal hypertension has been intensively studied at the Institute of Physiology of the Faculty of Medical Sciences of Buenos Aires. Investigations performed up to the year 1938 had demonstrated that the ischemic kidney of a hypertensive dog liberated a pressor and vasoconstrictor substance into the blood stream. At the end of that year, at the suggestion of Professor Houssay, we joined forces with the object of isolating this substance. Such collaboration is a necessity in modern investigation when one aspires to solve a problem of considerable magnitude. The use of many available resources demands the distribution of responsibility and the help of specialists.

We have worked together for five years, each one contributing his measure in a common effort to elucidate the problem of hypertension which is so deleterious to the health of mankind and for which there is so great a need of solution. We have depended on other colleagues for their help, knowledge and ingenuity. We have counted above all on the inspiration, stimulus, and disinterested help of our teacher, Professor Houssay. The Institute of Cardiology, Foundation, V. F. Grego, which one of us (A.C.T.) directs, was founded in 1941. As members of this and as guests of the Institute of Physiology, two

of us (A.C.T. and J.C.F.) have worked for the last two years. May we express our deep appreciation to the members of each institution.

We have believed that it would be useful at this stage of our efforts to unite in writing a monograph concerning our present knowledge of renal hypertension. Several excellent articles on this subject have been written by investigators with wide personal experience,[1] but these articles by their nature have not been able to embrace the subject in all its ramifications. Our main purpose has been to explain as clearly as possible the present status of the problem, mentioning what is definitely known, indicating the gaps in our knowledge, and pointing out new lines of attack. Since our own endeavors have been mainly concerned with experimental renal hypertension, we have given particular attention to this aspect of the subject.

Although it has not been shown that human hypertension is due to the same mechanism as that produced by experimental renal ischemia, considerable evidence exists to suggest that the mechanism of each is closely related. Although our personal contribution in respect to human hypertension is limited, we have felt that it is necessary to discuss the *pros* and *cons* of the rôle of the kidney in human hypertension and to point out the similarities and differences which exist between human and experimental renal hypertension. Only incidentally will we refer to other aspects of the wide field of human hypertension which have been well analyzed in several pathological monographs.

We have endeavored to make our bibliography complete. Since causes of error in biologic investigation are numerous and may well escape even a careful critique, we have in each case cited the authors on whose shoulders falls the responsibility of a given statement. The reported results have at times been contradictory. In our interpretation, we have depended mainly upon the scientific accuracy of the investigation. In addition, however, we have taken into account the authority of the investigator presenting a given statement as judged by the calibre, integrity, and critique of his writings.

Finally, we wish to explain certain features of this book. Since

[1] Blalock, 1940; Fasciolo, 1939; Goldblatt, 1938b, 1940; Goldblatt, Kahn and Lewis, 1942; Goldblatt, Lewis and Kahn, 1942; Grimson, 1942; Houssay, 1940, 1941, Houssay and Braun-Menéndez, 1942; Lewis and Goldblatt, 1942; Page, 1940c, 1941b, 1943b; Page and Corcoran, 1942; Smith, Goldring and Chasis, 1943; Goldring and Chassis, 1944.

some of the fundamental concepts may not be sufficiently clear to the reader due to the abundance of bibliographical data, we have written a résumé at the end of each chapter for those who are not familiar with the subject. In the appendix, some of the techniques which we have devised are described. These we have used in the majority of our experiments. Our object in describing them here is to facilitate confirmation and continuation of our work by other investigators.

TRANSLATOR'S PREFACE

It has been a little more than a decade since the discovery of a satisfactory method for the experimental production of renal hypertension in animals. During this period, an enormous amount of investigation has been performed and rapid strides in the understanding of this disorder made. Although much remains to be accomplished both in the experimental and in clinical fields, it is appropriate that a summary of the work performed to date should appear at this time not only to describe what has been accomplished but to point out the gaps in our present knowledge.

The authors are particularly qualified to do this. Their members represent the physiological, chemical, and clinical fields working together in the laboratory of Professor Bernardo A. Houssay. Their method of presentation consists of critically reviewing practically all pertinent literature concerned with renal hypertension and of offering their interpretation in the light of available evidence. In any field as controversial as this, the reader may well disagree with the authors' interpretation since many problems, as they point out, are unsettled. The reader has the advantage, however, of becoming acquainted with the views of those who have perhaps been responsible more than any other group for the clarification of the renal humoral pressor mechanism.

The first edition of this book was published in 1943. Advances made since then have been incorporated in this English edition. The translator has not attempted to produce a line for line translation but has tried to present a version which would convey the authors' views to readers in this country. In difficult passages he has been aided by Dr. Luis F. Leloir and Dr. Juan Reforzo-Membrives. Preparation of the illustrations for reproduction was performed by Mr. James Ufford of the Photographic Department of the Fogg Art Museum. In preparing the manuscript and illustrations, the translator is indebted to Dr. Florence W. Haynes, Mrs. Wiley F. Barker, Miss Ann Fitz-Gibbon, and to his wife. He especially wishes to express his thanks to Miss Frances J. Cushman for her untiring effort in typing and checking the manuscript.

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