

Mechanisms of Hypertension

Proceedings of an International Workshop Conference
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Editor

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Preface

This volume is a compilation of 40 papers presented and discussed at a Workshop Conference on Mechanisms of Hypertension in March, 1973 at Los Angeles. The invited presentations were deliberately chosen to provide an entire spectrum on the subject. The contributions range from authoritative syntheses of the current state-of-the-art to entirely new research data and include critical commentaries on the controversial thoughts, working hypotheses and sanctioned speculations dealing with topics of current interest in the field.

For the sake of organizational clarity, the 12 sessions of the workshop have been grouped under 7 chapters in the volume. No attempt was made to cover these topics completely or exhaustively but, rather, to present selected areas of current interest under each heading. Particular effort was invested in the arduous, if not impossible, task of presenting to the reader many of the valuable aspects of abundant interchange of ideas and opinions that occurred during the discussion periods. We have tried to tread the hazardous path of achieving a balance between verbatim quotation of spoken remarks and a summary of the intent of the discussants in paraphrased language. To the extent we have succeeded in this task, the credit goes to the sub-editors of each session, who have the editor's gratitude for performing this Herculean task. Our failures and shortcomings in this regard are attributable solely to the functions of this editor.

The editor is indebted to each of the session chairmen, who expertly guided the discussions and provided the valuable opening and closing remarks. It is my great pleasure, and indeed privilege, to express my appreciation for the generous cooperation of all who made the conference and the publication possible: all the participants, all those who provided the necessary funds from the pharmaceutical industry, everyone who worked at various levels in the organization of the conference, and those involved in the publication of this volume. My special thanks go to Ms. Florence Forman, the executive secretary of the conference.

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Introduction

It is my great pleasure to welcome you to the International Workshop Conference on Mechanisms of Hypertension organized by the Hypertension Division of the Department of Medicine of the Sepulveda VA Hospital and the U.C.L.A. School of Medicine.

In societies of every socio-cultural level, roughly 10% of adults, both men and women, have high blood pressure. The available figures are even higher in this country.

The past 4 decades have seen unparalleled advances in our understanding of hypertensive cardiovascular disease, and many of you have been intimately involved in expanding these horizons. It is now established that long-term effective treatment of hypertension does successfully reduce the target organ damage and markedly lower the incidence of eventual complications. It has also become clear that the achievement of the important objectives of early detection and adequate treatment of this disorder is going to represent a major and difficult public health challenge.

Another crucial approach in conquering this immense problem is the advancement of our understanding of the fundamental mechanisms of hypertensive disease, so that future roads can be paved for development of more specific modes of therapy. Our goal should be to circumvent the life-long commitment to taking antihypertensive drugs, as is required today in most cases. It is the desire to take progressive steps in this direction that brings all of you together and I am confident your efforts will be eminently rewarded, sooner or later. To the extent we have played a part in bringing you together, we feel gratified and delighted. We bid you a very warm welcome.

David H. Solomon

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A review of experimental studies on hypertensive cardiovascular disease*

A. Grollman**

The concept of the renal origin of hypertensive cardiovascular disease began with Richard Bright (1827) who noted that patients with a 'full pulse', reflecting a high blood pressure, were found at autopsy to have cardiac hypertrophy and renal disease. Bright interpreted the cardiac hypertrophy as a compensation for the increased force necessary for propelling the blood through the diseased kidney. Subsequent workers, particularly Sir George Johnson and Traube elaborated on Bright's findings while Mahomed and Allbutt first showed that hypertension of the so-called 'essential type' occurred in the absence of renal disease (Ruskin, 1956).

The earliest experimental studies were devoted primarily to determine the effect of nephrectomy and other manipulations of the kidney on the blood pressure. Grawitz and Israel (1879), for example, induced hypertrophy of the heart by partial nephrectomy of rabbits, which they attributed to the development of hypertension. Päsler and Heineke (1905) oblivious of the earlier work, demonstrated the production of an increase in blood pressure by the procedure in dogs. Katzenstein (1905) made the first observation on the effect of partial constriction of the main renal arteries on the blood pressure but his period of observation was short and the results either negative or equivocal, as were the numerous other attempts to induce hypertension by manipulation of the kidney or its circulation. The most successful of these experiments were those of Chanutin and Ferris (1932) who induced chronic hypertension in rats by partial nephrectomy.

The great impetus to the modern study of hypertension was the demonstration by Goldblatt, Hanzal and Summerfield (1934) that the application of a clamp to the renal artery of a dog with the subsequent removal of the opposite kidney resulted in chronic elevation of the blood pressure. Goldblatt's experiment was based on the assumption that hypertension was a result of ischemia of the kidney and that the application of the clamp was comparable to the reduction of the blood flow through the kidney by nephrosclerosis. This concept of the pathogenesis of hypertension was opposed by the observations of Bell (1951), Smithwick and Castleman (1951) and others but Goldblatt's procedure for the first time offered a practical method for experimentally inducing a condition analogous to that of essential

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hypertension, namely, the induction of an elevation in blood pressure without appreciably affecting renal excretory function.

EXPERIMENTAL INDUCTION OF HYPERTENSION

Numerous procedures are available for inducing an elevation in blood pressure in experimental animals. In some of these, the hypertension is acute in onset and transient; in others, it develops more slowly and is chronic. The disease as induced in the rat and in other laboratory animals is identical to that occurring spontaneously in the human being in its clinical, hemodynamic and pathologic features. Despite the refusal of some to accept observations on animals as applicable to the human being, the results indicate that we are dealing with the same disease in the experimental animal as occurs in man. To deny, on the basis of demographic data, existence of essential hypertension as a clinical entity or to consider the disease as indefinable is to ignore a mass of incontrovertible experimental and clinical data.

Most of the experimental procedures used for inducing hypertension involve some manipulation of the kidney or renal artery. Instead of applying a clamp and removing the contralateral kidney as in the Goldblatt procedure, results are obtained more easily and consistently by applying some form of compression to the kidney (e.g., by a figure-of-eight ligature) or a clip to the renal artery. A number of other procedures have been used, such as the removal of one kidney and the administration of desoxycorticosterone or other steroids (Grollman et al., 1940a), enucleation of the adrenals with unilateral nephrectomy (Skelton, 1955), the use of choline or potassium-free diets (Grollman and White, 1958) infarction of the kidney (Loomis, 1946), etc.

Analogues of essential hypertension as it occurs in the human being have also been produced by selective inbreeding in mice and in strains of spontaneously hypertensive rats (Smirk and Hall, 1958; Okamoto and Kyuzo, 1963). Like its human counterpart, the disorder in the rodent is inherited and genetic in origin and is not accompanied by obvious renal lesions or evidence of renal excretory deficiency. A similar form of hypertension may be induced by the treatment of pregnant rats (Grollman and Grollman, 1962). Like their human analogues, the off-spring of such animals are normotensive at birth but their blood pressure increases gradually and reaches hypertensive levels.

So-called renovascular or surgically remediable hypertension is also reproducible in the experimental animal. Drastic restriction of the renal artery or infarction of a kidney results in the production of acute hypertension which like its human counterpart is remediable by removal of the constriction or by nephrectomy. This form of hypertension may develop ultimately in some cases into chronic hypertension particularly if the contralateral kidney is removed.

Ogden et al. (1946) first noted a difference in the mechanism responsible for the elevation in blood pressure during the acute stage following application of a clamp to the renal artery and its subsequent elevation, a difference ignored in many experimental studies. The development of lesions in the untouched kidney have been attributed to the effect of the elevated blood pressure but are also due, in part, to the liberation from the kidney of a circulating pressor agent and possibly also to an autoimmune reaction (White and Grollman, 1964).

The function of an organ is most readily determined by noting the effect of its ablation. Insofar as the role of the kidney in the pathogenesis of hypertension is concerned, the debilitating effects of loss of renal excretory function renders this approach difficult as was first pointed out by Allbutt (1915). With recognition of the importance of utilizing an electrolyte and protein-free diet and the introduction of such procedures as the artificial kidney and intermittent peritoneal lavage, the determination of the effect of nephrectomy on the blood pressure became possible. The results of such studies on a variety of laboratory animals (frog, rat, dog and opossum) as well as on the human being (Grollman, 1970;