Mechanisms of Hypertension

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Editor

Mohinder P. Sambhi

Department of Medicine U.C.L.A., Division of Hypertension, Veterans Administration Hospital, Sepulveda, Calif., U.S.A.

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Organizing committee

Mohinder P. Sambhi, M.D., Ph.D., Chairman

Chief, Division of Hypertension, Sepulveda VA Hospital
Associate Professor of Medicine, U.C.L.A.

Peter Eggena, Ph.D.

Research Staff, Division of Hypertension, Sepulveda VA Hospital

Jack D. Barrett, Ph.D.

Research Staff, Division of Hypertension, Sepulveda VA Hospital

Consultants

David H. Solomon, M.D.

Professor and Chairman, Department of Medicine, U.C.L.A.

Michael C. Geokas, M.D., Ph.D.

Chief of Medicine, Sepulveda VA Hospital
Vice Chairman, Department of Medicine, U.C.L.A.

Anthony J. Brunse, M.D.

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Sepulveda VA Hospital

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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.

Participants

Dr. K. Arakawa, Research Institute of Angiocardiology & Cardiovascular Clinic, Kyushu University School of Medicine, 1276 Katakasu, Fukuoka 812, Japan

Dr. T. A. Assaykeen, Department of Surgery, Division of Urology, Stanford University Medical Center, Stanford, California 94305

Dr. H. Balikian, Department of Medicine, Division of Endocrinology and Metabolism, VA Hospital, 16111 Plummer Street, Sepulveda, California 91343

Dr. J. D. Barrett, Division of Hypertension, VA Hospital, 16111 Plummer Street, Sepulveda, California 91343

Dr. D. G. Beevers, MRC Blood Pressure Unit, Western Infirmary, Church Street, Glasgow G11 6NT, Scotland

Mr. Stanley L. Bernheim, Vice President, Excerpta Medica, Princeton, New Jersey 08540

Dr. L. B. Berman, Department of Nephrology, The Mt. Sinai Hospital of Cleveland, University Circle, Cleveland, Ohio 44106

Dr. J. R. Blair-West, Howard Florey Institute of Experimental Physiology and Medicine, University of Melbourne, Parkville, Victoria 3052, Australia

Dr. R. Boucher, Clinical Research Institute of Montreal, 110 Avenue des Pins Ouest, Montreal 130, P.Q., Canada

Dr. J. J. Brown, MRC Blood Pressure Unit, Western Infirmary, Church Street, Glasgow G11 6NT, Scotland

Dr. F. M. Bumpus, Division of Research, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, Ohio 44106

Dr. O. A. Carretero, Hypertension Research Laboratory, Henry Ford Hospital, 2799 West Grand Boulevard, Detroit, Michigan 48202

Dr. K. J. Catt, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland 20014

Dr. K. Crowshaw, Department of Pharmacology, The Medical College of Wisconsin, 561 North 15th Street, Milwaukee, Wisconsin 53233

Dr. J. O. Davis, Department of Physiology, University of Missouri-Columbia School of Medicine, Columbia, Missouri 65201

Dr. D. A. Denton, Department of Physiology, Howard Florey Laboratories of Experimental Physiology, University of Melbourne, Parkville, Victoria 3052, Australia

Dr. H. R. Dettelbach, Clinical Development Division, Hoechst Pharmaceutical Company, Route 202-206 North, Somerville, New Jersey 08876

Dr. C. T. Dollery, Department of Clinical Pharmacology, Royal Postgraduate Medical School, Hammersmith Hospital, London W12 OHS, England

Dr. A. E. Doyle, Department of Medicine, University of Melbourne, Austin Hospital, Heidelberg, Victoria 3084, Australia

Dr. P. Eggena, Division of Hypertension, VA Hospital, 16111 Plummer Street, Sepulveda, California 91343

Dr. E. D. Freis, Veterans Administration Hospital, 50 Irving Street, N.W., Washington, D.C. 20422

Dr. J. W. Funder, Hypertension Laboratory, Hospital Broussais, 96 Rue Didot, 75014 Paris, France

Dr. J. Genest, Clinical Research Institute of Montreal, 110 Avenue des Pins Ouest, Montreal 130, P.Q., Canada

Dr. M. C. Geokas, Department of Medicine UCLA, Medical Service VA Hospital, 16111 Plummer Street, Sepulveda, California 91343

Dr. T. L. Goodfriend, Departments of Internal Medicine & Pharmacology, School of Medicine, University of Wisconsin, Madison, Wisconsin 53706

Dr. A. Grollman, Department of Pathology, University of Texas, Southwestern Medical School, Dallas, Texas 75235

Dr. A. C. Guyton, Department of Physiology and Biophysics, University of Mississippi Medical Center, School of Medicine, 2500 North State Street, Jackson, Mississippi 39216

Dr. R. B. Hickler, Department of Medicine, University of Massachusetts Medical School, The Memorial Hospital, 119 Belmont Street, Worcester, Massachusetts 01605

Dr. S. W. Hoobler, Department of Internal Medicine, the University of Michigan Medical Center, R-6669 Kresge Medical Research Building, Ann Arbor, Michigan 48104

Dr. R. C. Hoppe, Clinical Services Division, Smith Kline & French Laboratories, 1500 Spring Garden Street, Philadelphia, Pennsylvania 19101

Dr. J. C. Hunt, Division of Education, Mayo Foundation, Rochester, Minnesota 55901

Dr. C. I. Johnston, Department of Medicine, Monash University, Prince Henry's Hospital, St. Kilda Road, Melbourne, Victoria 3004, Australia

Dr. O. Kuchel, Clinical Research Institute of Montreal, 110 Avenue des Pins Ouest, Montreal 130, P.Q., Canada

Dr. G. B. Lal, Science Editor, emeritus, San Francisco Examiner.

Dr. J. A. Luetscher, Department of Medicine, Division of Endocrinology, Stanford University School of Medicine, Stanford, California 94305

Dr. L. Lutwak, Department of Medicine UCLA, Division of Endocrinology and Metabolism, VA Hospital, 16111 Plummer Street, Sepulveda, California 91343

Dr. P. J. Mulrow, Department of Medicine, Yale University School of Medicine, New Haven, Connecticut

Dr. G. Onesti, Department of Medicine, Hahnemann Medical College & Hospital, 230 North Broad Street, Philadelphia, Pennsylvania 19102

Dr. W. S. Peart, Medical Unit, St. Mary's Hospital, London W2, England

Dr. K. Poulsen, Department of Cardiac Biochemistry Research, Massachusetts General Hospital, Boston, Massachusetts 02114

Dr. D. Regoli, Department of Pharmacology, Centre Hospitalier Universitaire, Université de Sherbrooke, Sherbrooke, Quebec, Canada

Dr. I. Reid, Physiology Department, University of California at San Francisco, San Francisco, California

Dr. R. Roberts, Ciba Pharmaceutical Company, Summit, New Jersey 07901

Dr. M. P. Sambhi, Department of Medicine U.C.L.A., Division of Hypertension, Veterans Administration Hospital, 16111 Plummer Street, Sepulveda, California 91343

Dr. M. Schambelan, Clinical Study Center, San Francisco General Hospital, San Francisco, California 94110

Dr. L. Schoenfeld, Department of Hypertension and Nephrology, VA Hospital, 16111 Plummer Street, Sepulveda, California 91343

Dr. D. H. Solomon, Department of Medicine, University of California at Los Angeles, Los Angeles, California 90024

Dr. C. G. Strong, Division of Nephrology, Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota 55901

Dr. K. Thurau, Department of Physiology, University of Munich, Pettenkoferstrasse 12, 8000 Munich 15, Germany

Dr. L. Tobian, Department of Medicine, Division of Internal Medicine, University of Minnesota Medical School, Minneapolis, Minnesota 55455

Dr. A. P. Truant, Research and Development Division, Pennwalt Corporation, Jefferson Road, Rochester, New York 14623

Dr. R. Veyrat, Department of Medicine, Division of Nephrology and Hypertension, Hôpital Cantonal, CH 1211, Geneva 4, Switzerland

Dr. E. F. Wamsteker, Division of Clinical Research, Schering Corporation, 60 Orange Street, Bloomfield, New Jersey 07003

Dr. M. H. Weinberger, Department of Medicine, Indiana University School of Medicine, 1100 West Michigan Street, Indianapolis, Indiana 46202

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

Chapter I Regulatory mechanisms of high blood pressure

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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

* Previously unpublished studies included in the present paper were supported by grants from the American Heart Association, the Lilien K. Christy Bequest, the National Institutes of Health of the U.S. Public Health Service, and the Vaughn Fund.

** Department of Pathology, University of Texas Southwestern Medical School, Dallas, Tex., U.S.A.

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., 1940*a*), 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;