FRONTIERS IN HYPERTENSION RESEARCH

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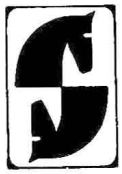

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Dedication
Sir George Pickering—A Tribute

When Sir George Pickering died in Oxford on September 3, 1980, cardiovascular medicine lost one of its most creative and influential personalities of the last fifty years. The present volume records his still penetrating contributions to what was, regrettably, the last major meeting he was to attend.

George Pickering's career was greatly stimulated by his association with Sir Thomas Lewis at University College Hospital, London, in the late 1920s and early 1930s. It was then that he developed fully the method of applying quantitatively basic physiologic principles to clinical medicine, an approach which was to pervade his subsequent work. Withal, he retained a warm and sympathetic bedside manner and was always conscious of the psychologic impact of doctors ("the doctor must never frighten his patient").

The pertinacity with which he strove for precise quantification of clinical and experimental results underlay all his major contributions to medicine. His interests were

wide, including peptic ulceration, headache, and temperature regulation, but his greatest achievements were in the field of hypertension.

In the 1930s, following Goldblatt's experiment, he was one of those responsible with Prinzmetal for the rediscovery of renin, which had first been described by Tigerstedt and Bergman in 1898. It was a source of lasting regret to him that he did not at that time establish an international renin standard, and he continually deplored the failure of subsequent workers in this field to express their results quantitatively. He perceived that the renin-angiotensin system was ideally suited to maintain arterial pressure over hours and days, and he pioneered the experiments–technically very difficult with the apparatus then available–which demonstrated that the continuous intravenous infusion of renin into animals could sustain blood pressure elevation for up to 18 days. With Cook, he demonstrated that renin is located in the vascular pole of the glomerulus, and he encouraged and supported Peart in the isolation of angiotensin and the subsequent determination of its amino acid sequence. Pickering showed that removal of the sole remaining kidney lowered blood pressure in the early stages of Goldblatt hypertension in the rabbit, but was ineffective later. Thus he argued that while the renin-angiotensin system might be responsible for the hypertension initially, it was unlikely to be so later. He favored structural changes in the resistance vessels for this latter role and thus foreshadowed the approach which Folkow was later to develop so penetratingly.

The quantitative approach led him to support the proposal that the malignant phase of hypertension is not a separate disease entity, but simply the pathologic expression of very severe blood pressure elevation–a compound of the absolute height of the arterial pressure and the rapidity with which this has been attained. Thus the malignant phase can supervene in hypertension of varied etiology and, most importantly, can be expected to resolve with adequate blood pressure reduction. This latter prediction has since been demonstrated both by the surgical correction of various forms of secondary hypertension and by the use in essential hypertension of antihypertensive drugs. The papilledema and retinal edema of the malignant phase were, he reasoned, the expressions of increased cerebrospinal fluid pressure, and he supported this contention with relevant pressure measurements, which he was always concerned to make personally. Pickering's lumbar puncture technique, given his persistence combined with a marked hereditary tremor, was invariably a source of anxious fascination for the onlooker.

Pickering and his colleagues demonstrated that blood pressure values are continuously distributed within populations and thus that so-called essential hypertension is incapable of other than an arbitrary definition. This discovery, which he described as "though a veil had been lifted," has since been repeatedly confirmed by numerous workers, but was not initially accepted by all. Robert Platt in particular entered the lists, and there followed the famous Pickering-Platt debates of the 1950s. Platt thought that the distribution of blood pressures in the general population was not unimodal. He believed that a single gene, with incomplete dominance, was responsible for the development of high blood pressure with increasing age in some persons. Pickering demonstrated convincingly that the distribution was in fact unimodal, that the tendency to develop high blood pressure was almost certainly inherited in a polygenic fashion and, most importantly, that it was impossible to draw a dividing line between a "normotensive" and a "hypertensive" subset. He summarized his case in "The Nature of Essential Hypertension" in 1961, a book which is a model of cogent, lucid scientific writing.

Pickering went on to emphasize the continuous, quantitative relationship between blood pressure and the incidence of vascular complications—close for stroke, where arterial pressure and age are the predominant pathogenic influences; less close for

ischemic heart disease, where blood pressure is but one of several important risk factors. It is often now forgotten how central these concepts are to preventive antihypertensive therapy today.

This work progressed naturally into another fruitful scientific field as he pioneered, together with younger colleagues in Oxford, devices for the continuous measurement of arterial pressure. These revealed the very large fluctuations of pressure which occur during normal daily activities. He was so delighted with the findings that he chose as a cover design for the second edition of his book *High Blood Pressure* a record of arterial pressure during coitus.

As his contributions to the present volume show, he remained to the end unconvinced that moderate dietary salt restriction is effective in reducing arterial pressure. In this view he was greatly influenced by the detailed Medical Research Council Study of 1950, which showed that while severely hypertensive patients in hospital did respond to very strict salt restriction (down to 10–20 mEq/day), a regime that could be tolerated only briefly, blood pressure rose again when salt intake was allowed to rise only to the range 35–50 mEq/day. We remain uncertain whether Pickering's views on this topic will eventually be vindicated; what is sure is that his criticisms will inspire further accurate and definitive studies of the problem.

George Pickering's clarity of thought was evident in both his speech and his writing, which were invariably models of lucidity and style. He deplored clumsiness of expression as betraying confusion of reason. In sharp contrast, his manner of dress seemed of little concern to him. He combined great personal charm with an often ribald and occasionally caustic sense of humor. While never, to my knowledge, unwittingly offensive, he suffered fools not at all. He thrived on controversy and revelled in debate in which he could take, as well as give, hard blows. He was always concerned to distinguish scientific argument from personal animosity; nevertheless, his critique of a paper was often accompanied by a finely wrought vignette of the author's personality, a practice which invariably illuminated insight into the work under consideration.

For me, and I am sure for many others, a day in George Pickering's company always sharpened the wits and warmed the heart. My last memory of him, just a few weeks before his death, is happy and appropriate. We dined together in a Paris restaurant, with George charming my small daughter, recounting slightly bawdy tales, relishing the food and wine, complaining of a deficiency of garlic, and calling loudly for the salt cellar. We shall not, sadly, see his like again.

J.I.S. Robertson

Prologue

The creation of this symposium to discuss, analyze, and then publish the frontiers in hypertension research occurred partly by accident and partly by intent. It could be viewed as another example of chance and prepared minds.

I had in mind to have a modest one-day meeting on hypertension at my home base, The New York Hospital/Cornell Medical Center in New York City. I wanted, in particular, to invite Don Seldin to participate. He had graciously invited me and a number of my research group to Dallas two years ago to exchange views with his faculty on the high blood pressure problem. I was especially anxious to do it again because in my long association with Don I have enjoyed and cherished his passion for knowledge in general and his special interest in renal physiology and hypertensive phenomena. He is the ideal sounding board and critic. He brings to a conference table the broader perspective of a professor of medicine not particularly committed or involved in hypertension research but at the same time extremely interested in its products and their relevance. As is indicated by some of his comments in this volume his ability to interpret data and synthesize their meaning provides another helpful dimension. Don was particularly intrigued, as I was, with Roger Palmer's experiments in the turkey model showing that the form of the pulse wave and the force of cardiac contraction are more important than the absolute pressure level for producing vascular damage.

While I was thinking about arranging my next meeting with Seldin, I met with Fritz Bühler at a symposium in Berne, Switzerland. He expressed interest in having an international symposium where some of the recent clinical trials in hypertension might be discussed along with other selected issues, with the idea of producing a book containing not only the formal presentations but also transcripts of the discussions, and this as quickly as possible so that none of the freshness of the issues would be lost. Don Seldin was also at the meeting in Berne and the three of us agreed that we would like to be involved in such a venture. Fritz Bühler's expertise in the areas of beta receptor blocking drug action, sympathetic nervous system theory and in the conduct and analysis of clinical trials was especially valuable for arranging a number of the scientific sessions. His own pioneering research linking neurogenic activity to the activity of the renin system also served as a springboard in several of the scientific sessions.

It was apparent to all of us that the International Symposium on Hypertension to be held in New Orleans in the Spring of 1980 created an opportunity for us to bring together a large group of distinguished scientists, who might not otherwise be available. Accordingly, we began to construct an agenda and a slate.

Not surprisingly, the size and scope of the project grew overnight. We recognized the possibilities for a working meeting involving the world's most distinguished investigators in the many disciplines of basic or clinical science that compose the field of hypertension research. The opportunity was mouth-watering. We set about to identify at least one scientist from every major laboratory in the world and involve him in this scientific exchange. The responses to our invitations were uniformly enthusiastic, with over 120 scientists participating, most arriving with manuscripts and data in hand.

We foresaw great possibilities for such a meeting. We would bring together under one roof the full range of scientific disciplines involved in hypertension research, ranging from epidemiologists to clinical investigators, to animal physiologists, pharma-

cologists, cell biologists and biochemists. It would be an opportunity for interdisciplinary cross-fertilization on critical issues. For example, we proposed to look anew at the growing epidemiologic evidence on the value, or lack of value, and the risks of various types of drug therapy. We also wanted to re-examine the value or lack of value of manipulating dietary salt and consider the key issue of whether such interventions were useful or harmful to various subsets of patients.

Within this epidemiologic reference framework the meeting was designed to consider fundamental cellular mechanisms of sodium transport and of vascular tone and their mediation by local chemical transmitters or circulating hormones. The orchestration of these phenomena by control systems involving the nervous system and the renin system and possibly other control systems would also be considered.

In dealing with pathogenesis we decided to re-examine the obviously subtle and still elusive role of the sympathetic nervous system and also to reconsider the role of the renin-angiotensin-aldosterone system as a primary, sustaining, or reactive factor in the spectrum that composes essential hypertension. In particular the question would be examined of the meaning and the role of renin and of volume factors in the pathogenesis of hypertension where renin values are low or normal. We would consider, in the light of new evidence, the possible role of intravascular renin production.

We also would probe the question of the pathogenesis of hypertensive vascular and organ damage and the possibly important role of renin and other vasoconstrictions. The role of blood pressure and blood flow, the role of renin, the role of neither one, but rather of some complex interaction between cardiac output, pulse wave form and resistance vessel activity determined by renin or other vasoconstrictors would be discussed. And finally we would consider the action and relevance and the promise of therapeutic modalities including of course the latest anti-renin drug types as exemplified by the prototype teprotide and captopril.

Operationally, the plan was to have three working days with the discussions to be transcribed and published in entirety. The meeting would be divided into 18 frontier "topics," each of which would be introduced by a position paper of 20 minutes or less followed by a series of short papers of 10 minutes or less on particular aspects of the problem, and then by the discussion period. Our goal was to openly discuss even the most tender areas of dispute while maintaining decorum and friendship in an atmosphere where maximum disagreement could be encouraged with the common goal of sharpening the issues and answers.

The symposium was an incredible success. The staying power of the participants was beyond belief. The discussions were comprehensive and constructive, at times bristling with disagreement. There was some acerbity but the mood was mostly one of friendship and respect built on a commonality of interest, as you will find upon reading these discussions.

The 18 topics covered represent the final choice of what the three editors consider to be the important frontiers in hypertension research. Within this volume they are presented in entirety as they occurred. Unfortunately, however, everything could not be covered. For example, I have a personal regret that time did not allow us to have a session on the factors involved in aldosterone secretion. Moreover, there was no time for discussing the biobehavioral approaches to hypertension. These we can save for another time. Inevitably, too, there were a few scientists who unavoidably could not attend. In these instances, we tried to ensure that their work and viewpoints were recognized.

This symposium never could have become a reality without the marvelous and unqualified support of USV Laboratories Division of the Revlon Health Care Group. No detail was overlooked for making the symposium a success and for maintaining the highest standards of science without any intrusion from commercial interests.

The three full days' sessions were held at the Metropolitan Club. Attendance was by invitation and the press was specifically excluded. Indeed, our sponsors at USV Laboratories insisted that we have total freedom to criticize or discuss their own or any other drug company product, and that the meeting be a forum for absolutely free expression of current thinking on the part of working scientists the world over who are concerned with the high blood pressure problem. All this, I think, is reflected in this present volume.

I did not have to mention more than once the plans for our symposium to Chuck Smith and Herb McDade at Revlon Health Care Group before they evinced great enthusiasm for it. Indeed they jumped at the opportunity to support it. Their enthusiasm was even amplified after they discussed it with John Roelker, the President and Group Executive of Revlon Health Care Group, and with Michel Bergerac, Chairman and Chief Executive of Revlon, Inc. These people not only made the symposium possible, they created a setting where distinguished scientists participated actively with a large pool of their peers for three days and enjoyed their companionship as well in the off-hours and at meals with almost no extraneous distractions. This volume serves as a lasting testimony of what was achieved. Hopefully it will be helpful for research scientists and other people interested in the high blood pressure problem.

The organization of the meeting and all of the attendant details which made it not only scientifically successful but a distinct pleasure for all of the participating scientists were accomplished by my longtime associate, Joan Banes, with the help of Howard Mason, Director of Product Management, USV Laboratories. Mrs. Banes also was responsible for the faithful transcription of all of the discussions and for organizing the entire text into book form. It was a Herculean task well done.

Finally, the scientists of our field were greatly saddened by the death of Sir George Pickering, shortly after he participated in his usual lively manner in the Frontiers meeting. We have lost a leader whose contributions speak for themselves. Fortunately, a piece of his personal integrity and force is captured in this volume in his paper and in his telling comments throughout the regular sessions and during the special evening section transcribed at the end of this book. George was my friend and I will miss him. We are pleased to dedicate this volume to him. I am especially grateful to Bob Robertson for the discerning resume of George's career.

John Laragh

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