Editorial

Irvine H. Page, MD

In this last issue of our journal’s 20th anniversary celebration, we honor Irvine H. Page, MD, the founder of the Council for High Blood Pressure Research and one of the forces behind the common goal and commitment of all of ourreadership, the better understanding of the underlying mechanisms of blood pressure control, and the causes and treatment of hypertensive diseases. It was Dr Page’s drive and commitment to these problems that brought him to the Cleveland Clinic and stimulated the business community of that city to support and nurture the early organization that became the Council. Because of his early leadership in the American Heart Association, the Council for High Blood Pressure Research was one of the first scientific councils of the association.

After making countless contributions to our field, Page died in 1991 in his 90th year. Perhaps his most outstanding contributions were the (1) discovery and characterization of angiotensin; (2) identification and characterization of serotonin; (3) description of a neurogenic mechanism in renal hypertension; (4) demonstration of baroreceptor resetting in experimental and clinical hypertension; and (5) elucidation of the mosaic theory of hypertension. Any one of these contributions by any of our contributors would be a landmark achievement in the history of hypertension research, but through his tireless work he did much to strengthen the National Institutes of Health after the Second World War; create a scientific basis for the American Heart Association; participate in forming the International Society of Hypertension (of which he was the first president); and initiate a “full court press” on the pages of Modern Medicine as its editor to create a National Academy of Medicine which was finally established as the Institute of Medicine.

During this year of our journal’s 20th anniversary, we have honored those leaders in hypertension whose efforts were successful in establishing Hypertension as the first journal in its field. We have saluted the authors of the scientific papers that have received the greatest number of citations in each of the four editors’ five-year tenures of the journal. We have also recognized those special workers in our field who were first identified by the Council for special awards, lectureships and other means of recognition, and who, at a later date, were honored by the Nobel Committee with the Nobel Prize in Medicine. It is appropriate and fitting that we salute Irvine H. Page in this final issue of our year of celebration for his lasting service to our field of commitment and study.

As an example of the iconoclastic leadership that Page exerted in science, in general, and in the field of hypertension, the editors received the permission from Modern Medicine to reprint the following editorial from June 25, 1962. A member of our editorial board, Ervin G. Erdős, MD, who organized the meeting of the New York Academy of Sciences to which Page referred, forwarded this to the editors for our interest. We thought it appropriate to share it with our readers.

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Peptide Probes

Irvine H. Page, MD, Editor; Walter C. Alvarez, MD, Editor Emeritus

Not long ago I attended a symposium at the New York Academy of Sciences on the structure and function of biologically active peptides. The odd thing about it was that the only really widely useful peptides are insulin, vasopressin, oxytocin, and these were not discussed.

Attending the symposium were men from all over the world, and when you think that the symposium was concerned with substances such as bradykinin, kallidin, and angiotensin, none of which you may have heard of, perhaps it will be a little clearer why I think it worth a moment of your time.

We are said to be in an age of cultural decline; there are no giant novelists, musicians, artists, or philosophers. The great age of mediocrity and conformity is said to be on us. This may or may not be true, but, for science and medicine, it most decidedly is not. While it is true that no one stands out as an individual hero because there are so many, still our generation has more than its share of intellectual giants. And it is so good to see that, giants or not, scientists are in direct communication with physicians. This could hardly have happened twenty years ago, for many reasons.

I mean specifically that, at the symposium, organic chemists such as Boissonnas of Basel, Elliott of London, and Nicolaides of Detroit were matching wits with pharmacologists such as Roche é Silva of Ribeirão Prêto, Lewis of London, Croxatto of Santiago, and Collier of Middlesex and with physicians such as Forell of Munich and Ferrari of Cagliari—and with an appropriate sprinkling of Americans in

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all categories. The subjects ranged from the synthesis of polypeptides to the treatment of acute pancreatitis, all hung together by the peptide molecule. These were interesting people who kept your mind on a stretch sixteen hours a day for two and a half days. You know how good it feels to get on the plane after a martini and ignore your neighbor while pretending to read the newspaper, the print of which you can’t see!

I learned a lot. Ever since du Vigneaud synthesized oxytocin, there has been a rapidly growing interest in unscrambling the vast number of physiologically active peptides in the body. The next one synthesized was angiotensin, and you should be familiar with it if only for friendship’s sake. Besides raising blood pressure, it seems to control the secretion of aldosterone. According to Khairallah in our laboratory, it acts on the cell surface and exhibits a highly specific type of stimulation because of its helical structure.

Years ago, Frey, Werle, and Kraut came across a strange substance in the pancreas they thought was a “circulatory hormone.” It lowered blood pressure and caused peripheral vasodilation. You will remember it as padutin or kallikrein. It turns out that kallikrein, recently named kallidin, is really an enzyme that releases from a globulin substrate an active peptide containing 10 amino acids. You see the similarity with the formation of angiotensin from renin and renin-substrate where renin is a protein-splitting enzyme. If one amino acid, lysine, is split off of kallidin, a 9-amino acid peptide results. This one was discovered by Roche e Silva and was called bradykinin. The upshot of all this is that whole new groups of substances that might be called “kinin hormones” seem in the making. They all cause isolated smooth muscle, such as uterine and intestinal muscle, to contract.

Kallidin and bradykinin act powerfully to reduce blood pressure and dilate blood vessels. So it is thought that when the salivary glands secrete, the accompanying hyperemia is due to local liberation of bradykinin. Bradykinin-like substances are widely distributed in nature, as, for instance, in wasp venom. At the symposium at the New York Academy of Sciences, the synthesis of both bradykinin and kallidin was announced.

You see how quickly we are now moving along. I don’t suppose the organic chemists had ever heard of these substances five years ago, and now they are available for laboratory and clinical study.

On a little more clinical level, my friend, William Antopol, showed that small doses of bradykinin given just before the provocative dose of endotoxin to set off the Shwartzman phenomenon greatly intensify the local tissue response. Amidopyrine, a partial inhibitor of bradykinin, was shown to inhibit the Shwartzman phenomenon. Quite different was the use by Forell of Munich of an inhibitor of the parotid gland proteolytic enzymes called trasylol. Since acute pancreatitis is associated with the freeing of large amount of proteolytic enzymes, he used trasylol in the treatment of this tricky condition. You guessed it—that was quick loss of pain and rapid recovery. I cannot vouch for the results, but they look interesting.

Then there was one last peptide discussed called substance P, for no sufficient reason. It was discussed by my old and warm friend, Ulf V. Euler of Stockholm. We first met many years ago in Bayliss’ laboratory in London. At any rate, substance P has been isolated, possibly in pure state, from horse intestine. It is also found in the brain and peripheral nerves and it, too, stimulates smooth muscle. Its synthesis, like spring, cannot be far behind. This peptide is new enough to allow every possible function to be claimed for it. Some think it causes motility of the intestine, and others think that it is a transmitter substance in the brain. Thus, it has constipation—physical or intellectual—in common.

So here is a whole series of peptides that are all over the place, and they are now being corralled, identified, and synthesized. The search is on for antagonists. It is interesting and significant that the pharmaceutical firms are leading the field, though they did not open it up. Perhaps this is as it should be.

Hold your hats, because, despite how it may seem, discovery these days is not limited to missiles, outer space, or how pretty is the first lady of the land.—I.H.P.