Hypertension: A Complex Disease with Complex Causes

Hypertension, which afflicts 24 million people in the United States, is the most common of the chronic diseases. It is a major health problem because people with high blood pressure are more likely to have strokes, heart disease, or kidney failure than are people with lower blood pressure. The bright side of all this is that when high blood pressure is lowered by appropriate therapy—and the therapy is effective in the vast majority of cases—the risk of heart or kidney failure and stroke falls along with it.

This is the fourth in a series of Research News articles examining recent developments in research on heart disease.

Until recently, however, finding the therapy to control a patient's high blood pressure was more of an art than a science. Physicians tried various drugs or drug combinations until they hit on one that worked. That was because 90 percent of the patients have what the medical profession calls "essential" hypertension. "Essential" means that no one knows what causes the condition. The situation is now changing as a result of research into the mechanisms that regulate blood pressure.

One of the conclusions of the research is that hypertension is actually a complex of diseases in which different defects produce the same result—the elevated blood pressure. Therefore drugs that work for some persons may not work for others who have different defects. Investigators think that the research may provide a basis for predicting which agents will work for a given patient.

The idea that hypertension could have more than one cause should not be too surprising. Although the blood pressure depends mainly on two factors—the resistance of the circulatory system to the flow of blood through it and the volume of fluid contained within the blood vessels—regulation of the two factors requires a complex set of interactions between the circulatory, nervous, endocrine, and excretory systems. A disturbance in any one could upset the balance required to maintain normal blood pressure.

For the past 10 to 15 years investigators have focused much of their attention on the role of renin, an enzyme produced by the kidney, in regulating blood pressure. Renin catalyzes the splitting of angiotensinogen, a protein found in blood, to form angiotensin I, a peptide containing ten amino acid residues. Another enzyme removes two of the residues from angiotensin I to yield angiotensin II. The heptapetide angiotensin III is a third member of the angiotensin family.

The angiotensins act to increase blood pressure by influencing both peripheral resistance to blood flow and blood volume. At one time, all the actions were attributed to angiotensin II. Angiotensins I and III were thought to be physiologically inactive precursor and breakdown products, respectively, of the octapeptide. Recent evidence indicates that each angiotensin may be active, although in different ways.

Angiotensin II causes the constriction of the arterioles. These are small arteries that branch to form the capillaries, which are the smallest blood vessels and the sites where the blood exchanges nutrients and waste products with the tissues. The state of constriction or dilation of the arterioles is the most important determinant of the resistance to blood flow of the circulatory system and, therefore, of the amount of pressure required to force the blood through the circulatory system.

Stimulation of aldosterone secretion by the cortex or outer layer of the adrenal gland is a second consequence of angiotensin II formation. Aldosterone is a steroid hormone that acts on the kidney to increase retention of sodium ions and water. The resulting augmentation of the fluid content of the circulatory system elevates the blood pressure. Angiotensin II also acts directly on the kidney to increase sodium retention.

The third action of the angiotensins involves the nervous system. They stimulate the release of the neurotransmitter norepinephrine by the nerve terminals of the sympathetic nervous system and by the adrenal medulla (the inner portion of the adrenal gland), and potentiate the action of the norepinephrine. The sympathetic nervous system is the branch of the autonomic nervous system that helps the organism respond to stress. One of the effects of norepinephrine release is increased blood pressure caused by constriction of the arterioles.

A drop in the pressure of the blood flowing through the kidney is one stimulus for renin release. The normal signals that tell the kidney to stop releasing renin are an increase in blood pressure and angiotensin itself, which acts by a feedback mechanism to inhibit renin release. The result is that the pressure is not maintained above normal levels for long periods. But when these feedback mechanisms go awry chronic hypertension may result.

The known causes of hypertension include kidney damage and a narrowing of the arteries leading into one or both kidneys, with the result that the arterial pressure always appears low to the kidney. These conditions may be dangerous since the pressure may be very high but they can frequently be cured by removing the kidney or repairing the artery. Another known cause of hypertension is excess secretion of aldosterone, which may be due to the presence of a tumor of the adrenal cortex, for example. Again surgery will effect a cure of the hypertension. These causes account for only about 10 percent of all cases of hypertension.

At least some of the 90 percent of patients who have essential hypertension have elevated concentrations of renin in their blood even though they have no apparent sign of kidney damage. John Laragh and his colleagues, first at the Columbia-Presbyterian Medical Center and more recently at the Cornell University Medical Center in New York City, have been analyzing the amount of renin in the blood of hypertensive patients. The investigators find that 16 percent have high renin activity in the blood plasma and 27 percent have low activity. Renin values are normal in the remaining 57 percent. Laragh says that these differences show that hypertension is a heterogeneous disease in which not all patients present the same clinical picture. He thinks that classification according to plasma renin activity provides a guide to both the prognosis and therapy of a patient.

Laragh has found that patients with high plasma renin activity have the highest incidence of heart attacks, strokes, and kidney failure, whereas patients with low activity have lower risks of the serious consequence of high blood pressure. He thinks that the difference depends on whether increased vasoconstriction or increased blood volume is predominant in elevating a given patient's blood pressure.

In the first group, the problem would be vasoconstriction as a result of the activity of renin and the angiotensins. Although these patients also have high concentrations of aldosterone in their blood, many do not have increased blood volume because the hypertension, which was induced by the vasoconstriction, causes increased excretion of fluid; as a result the plasma volume may actually be reduced and the blood viscosity in-

creased. This combination of increased vasoconstriction and blood viscosity could put a great deal of stress on the blood vessels. Fortunately, therapy with the drug propanolol usually controls the blood pressure in these cases, possibly by decreasing renin secretion.

Laragh thinks that the condition of the second group is due mainly to an expanded arterial blood volume and that the increased pressure suppresses renin secretion. Thus, the organs and blood vessels of low-renin patients would be less subject to the extra stress imposed by renin vasoconstriction.

Among the possible causes of the expanded fluid volume would be decreased sodium excretion by the kidney or increased aldosterone secretion. Arthur Guyton and his colleagues at the University of Mississippi Medical Center have suggested that the kidneys of all hypertensive patients may be defective in their capacity to secrete sodium; at high blood pressures normal kidneys would secrete the ion in increased quantities and thus return the pressure to normal. In any event, Laragh thinks that diuretics, drugs that increase fluid excretion by the kidneys, are the best therapy for the low-renin patients.

The largest group of patients with essential hypertension are those with normal renin concentrations. These individuals have a risk of serious consequences almost as great as those with high renin activity. Even though their renin concentrations appear normal, Laragh thinks that they may actually be inappropriately high since the high pressures should suppress production of the enzyme. Also, in accord with Guyton's suggestion, the patients' kidneys may be defective in excreting salt with the result that the blood volume is increased. Laragh hypothesizes that subtle defects in the kidney may be responsible for the initiation of the normal-renin hypertension. Some of these patients respond to diuretics alone and some to drugs that combat renin production; others require both.

Accurate measurement of the renin activity can be difficult, because the results may be influenced by a variety of factors, including the salt intake of the patients. Another way to assess the contribution that elevated renin is making to a particular case of hypertension is the use of antagonists to angiotensin II (the production of angiotensin is determined by that of renin).

In order to produce its effects, angiotensin II must first combine with specific receptors on the target organs. Angiotensin antagonists are peptides that resemble the natural substance in that they bind to the receptors and prevent angiotensin from binding. The antagonists produce the same effects as the natural substance, but only when they are given in high concentrations; at low concentrations the antagonists block the action of angiotensin.

A number of investigators, including F. Merlin Bumpus of the Cleveland Clinic Foundation and Garland Marshall and Philip Needleman of Washington University Medical School have synthesized angiotensin antagonists. The general approach involves replacement of one or more of the amino acids of angiotensin II with different amino acids. At present, the most commonly used antagonist is the octapeptide Saralasin that was the first synthesized by Donald Pals and his colleagues at the Norwich Pharmacal Company.

Uses of Antagonists

When Saralasin is injected intravenously into a patient with hypertension, the blood pressure falls to normal if the elevation is totally due to the activity of angiotensin and, thus, renin. If angiotensin makes no contribution to the increase, the blood pressure will not decrease. Or if the elevation in blood pressure is partly caused by angiotensin, the drop will be proportional to the contribution made by the octapeptide.

This kind of information is useful to the clinician in designing appropriate drug therapies. An inhibitor of renin release, for example, would be of little value for a patient whose hypertension is not caused by inappropriately high concentrations of renin. Several investigators, including Laragh, William Pettinger of the University of Texas Southwestern Medical School, and David Streeten of the Upstate Medical Center of the State University of New York, are using Saralasin in this manner.

Although the design of more effective therapeutic agents is one of the goals of the investigators synthesizing angiotensin antagonists, the antagonists now available can only be used on a limited scale. Because they are peptides, they must be administered by intravenous injection and even then they are rapidly degraded in the blood. But, in addition to their diagnostic applications, the current angiotensin antagonists are useful for studying the mechanisms of hypertension and also the mechanisms by which other drugs act. This latter kind of information should be useful in designing new drugs.

The observation that renin release or blood volume or both are abnormal in patients with hypertension does not explain what causes the abnormalities. For example, they may be in the kidney itself, as Guyton has suggested. The nervous system is another possible location for the origin of the aberrations. The interaction between angiotensin and the sympathetic nervous system, in which the hormone increases the release of sympathetic neurotransmitters such as norepinephrine and potentiates their effects on target organs, has been known for some time. But the central nervous system also plays a role in regulating blood pressure and this too appears to involve the renin-angiotensin system.

In an early experiment in 1961, Joseph Buckley of the University of Houston showed that angiotensin II could act through the central nervous system to increase blood pressure in the dog. Since then a number of investigators have confirmed this observation in additional species. Buckley, for example, showed that injection of small amounts of angiotensin II into the brain of the cat caused rapid and significant increases in blood pressure. The effect could be blocked either by cutting through the spinal cord or by intravenous administration of an agent known to block the action of norepinephrine. Thus the investigators concluded that the central nervous system increases blood pressure by increasing the activity of the sympathetic nervous system.

Buckley and his colleagues have shown that destruction of a portion of the brain called the subnucleus medialis, which is located in the midbrain, abolishes the blood pressure response. Other investigators have shown this area to be involved in the control of peripheral resistance to blood flow.

According to Buckley, angiotensin I also increases the blood pressure when injected into the brain. He does not yet know whether this is a direct effect or whether the angiotensin I is first converted into the octapeptide.

Angiotensin II does not have to be injected directly into the brain in order to produce its effects; however, it is somewhat surprising that a peptide of this size would cross the blood-brain barrier, which prevents the movement of many substances from the circulatory system to the brain or spinal cord. Buckley, in his early experiment with dogs, injected the material into the circulatory system. And Carlos Ferrario of the Cleveland Clinic Foundation observed a significant increase in blood pressure in dogs when he injected the octapeptide into an artery leading directly to the brain.

Experiments in Ferrario's laboratory and those of other investigators indicate that another region of the brain, the area postrema, is also involved in regulating blood pressure. Destruction of this area,

which is located in the medulla at the base of the brain, prevents the increased blood pressure in response to angiotensin injection. The area postrema is located in a part of the brain that is devoid of a blood-brain barrier, and angiotensin II should have easy access to it. Moreover, there are connections between the area postrema and the nucleus tractus solitarii, a relay station through which pass the nerve fibers from the baroreceptors.

These receptors, which are present in certain major arteries are activated when blood pressure increases. Impulses from the baroreceptor neurons cause the sympathetic neurons that evoke vasoconstriction to stop or slow their firing and thus produce a decrease in blood pressure. Ferrario says that the area postrema may serve as a gate through which angiotensin reaches neurons in the solitary tract and modifies the signals in such a way that sympathetic neurons with which they connect fail to stop firing. The sympathetic neurons would continue to signal the arterioles to constrict even if this response were inappropriate.

Not everyone agrees that angiotensin can cross the blood-brain barrier, but it may not have to. Investigators, including Jacques Genest of the Clinical Research Institute of Montreal and Detlev Ganten of the University of Heidelberg, Germany, have evidence that suggests that angiotensin is synthesized in the brain. The organ contains angiotensins I and II, renin, and the precursor of the angiotensins. Renin is a protein and cannot pass from the blood to the brain.

Some of the evidence concerning the role of the nucleus tractus solitarii in controlling blood pressure comes from the work of Donald Reis and Nobutaka Doba at Cornell University Medical Col-

Hypertension and Patient Noncompliance

Hypertension is a condition in which the pressure of the blood in the arteries is higher than normal. The definition of what is normal depends on the age of the individual, with the normal value increasing with age. For a young adult it is about 120/80. The higher figure represents the pressure (in millimeters of mercury) during systole, that is, when the heart is contracting and forcing blood into the arteries. The lower figure is the diastolic blood pressure or the pressure between contractions.

Hypertension does not usually cause symptoms until the condition has progressed to the point where damage has occurred in the form of atherosclerosis, kidney impairment, heart disease, or stroke. The lack of symptoms undoubtedly contributes to what many clinicians think to be the number one problem in hypertension control—that is, the failure of patients to stick to the therapeutic regimen prescribed for them. According to a recent estimate from the National Heart, Lung, and Blood Institute (NHLBI), less than one-third of the hypertensive persons in the United States have their condition under adequate control, despite the availability of an easy, noninvasive technique for detecting high blood pressure and of effective therapies.

Therapy usually includes treatment with one or more drugs, often in conjunction with a weight-reducing diet if the patient is overweight. It may also be necessary for patients to restrict their salt intakes. Diets are rarely considered enjoyable, and many of the drugs are associated with side effects such as weakness or drowsiness and, in some cases, impotence. These usually diminish with time or can be overcome by adjusting the dosage or substituting one drug for another, but a patient may simply feel better when not taking the drugs and thus drop out of therapy before the optimum drug combination is found. This is one reason why investigators would like to develop more scientific methods for tailoring therapies to fit a given individual's needs. Other factors that may contribute to this problem of patient noncompliance are the complicated schedules that may be required when two or more drugs are prescribed and the fact that the treatment, which must often be continued for life, can cost a lot of money over long periods of time.

The following are among the drugs now used:

- Diuretics to increase the excretion of salt and water and thus deplete the blood volume. Some common diuretics are the sulfonamides, spironolactone, and furosemide.
- Agents that act directly on the blood vessels to produce dilation. These include hydralazine and minoxidil.
- Agents that produce vasodilation by counteracting the vasoconstricting action of the sympathetic nervous system. These include guanethidine, bethanidine, debrisoquine, and reserpine.
- Agents to decrease renin production by the kidney and thus decrease constriction of the blood vessels. Some of the drugs that are thought to decrease renin act in more than one way. This is true for reserpine, for example, and for methyldopa, which also acts through the nervous system. Propanolol may be given in combination with certain of the other drugs in order to counteract their side effects, and may have the additional effect of lowering renin output.

Physicians, who may fail to prescribe the effective drugs that are available now, often share the blame for inadequate control of a patient's hypertension, according to members of the National High Blood Pressure Coordinating Committee. Equally important is the need for the physician to communicate to the patient the necessity of continuing treatment, to follow up on the patient's condition, and to adjust the therapy in response to any problems that may arise.

There are a number of programs sponsored by the government and private organizations aimed at educating both the public and the medical profession about the importance of seeing that all patients receive adequate treatment for hypertension. One of these is the National High Blood Pressure Education Program. This program, which involves a number of federal and state agencies and private organizations, is coordinated by the NHLBI. Its functions include the collection of information about the current state of hypertension therapy, the dissemination of the information to health professionals, and then working with the professionals to set standards for treatment of the disease.

The American Heart Association, through its local chapters and in conjunction with civic groups, sponsors free clinics to screen for persons who have high blood pressure. Those with hypertension are urged to see their physicians or directed to appropriate clinics for treatment. When possible, volunteers check back with the persons to determine whether or not they are receiving treatment. High blood pressure is one major health problem that can be solved but only if the person who has it obtains treatment, and then sticks with it.—J.L.M.

lege. These investigators found that when this portion of the brain is destroyed, rats develop severe hypertension and die of congestive heart failure within a few hours of the operation. The investigators think that the hypertension is due to selective activation of sympathetic neurons that elicit vasoconstriction. They have shown that the blood vessels of the skin, muscles, and internal organs constrict but that other effects of the sympathetic nervous systems are absent in the animals. Destruction of the tract apparently prevents the inhibition of the sympathetic neurons by the baroreceptors, so that the sympathetic neurons continue firing even when the blood pressure is already elevated. But Reis says the effects of the central lesions are more severe than those produced by simple severing of the baroreceptor nerve fibers and thinks that additional inhibitory control mechanisms may be interrupted.

Because rats die so rapidly after destruction of the tract, they are not a good model for chronic hypertension. With Marc Nathan, also of Cornell University Medical College, Reis recently produced the lesions in the brains of cats. The animals survive with moderate, but persistent hypertension. Their blood pressures also fluctuate much more than those of normal animals in response to stimuli that elicit changes in blood pressure. The Cornell investigators produced similar changes in cats by using a chemical to selectively destroy certain neurons (those releasing norepinephrine) that innervate the nucleus tractus solitarii. Reis says that this result indicates that chemical imbalances in the brain can produce chronic hypertension.

One of the reasons for the interest in the relationship between the nervous system and hypertension is the widespread although unproven belief that stress causes chronic hypertension. Stress is known to evoke transient increases in blood pressure. But the question is whether that elevated pressure can become chronic if the stress is maintained over long periods of time. This could be the case if the elevated pressure produces biochemical or structural alterations in the blood vessels.

Some investigators, including Reis and M. Samir Amer of the Mead Johnson Research Center, have observed changes in the concentration of cyclic nucleotides in the aortas of rats with chronic hypertension. Certain neurotransmitters released by neurons of the autonomic nervous system in response to stress and other stimuli are thought to produce their effects by causing increases or decreases in the concentrations of these cyclic nucleotides in the target cells, including smooth muscle cells. The changes observed by the investigators are in the direction that would be expected if the smooth muscle of the vessel walls were becoming more rigid and more resistant to blood flow. If they were sustained, the result might be an increase in blood pressure.

Although the renin-angiotensin-aldosterone system may be getting the most attention from investigators of hypertension, they are not the only substances thought to be involved in the regulation of blood pressure. The prostaglandins, a family of lipid hormones that participate in a number of processes in the body, have also been implicated. The situation is complicated, however, because some prostaglandins act to decrease blood pressure whereas others increase it.

According to John McGiff of the University of Tennessee Center for the Health Sciences and John Vane of the Wellcome Research Laboratories in Bechenham, England, prostaglandin E_2 (PGE_2) tends to decrease blood pressure by counteracting the angiotensin-induced constriction of the arteries and arterioles. It has been known for some time that responses to angiotensin II diminish when it is administered repeatedly or for prolonged periods of time. McGiff and Vane think that this results because angiotensin stimulates the production of PGE_2.

Infusion of angiotensin II into anesthetized dogs at first decreases the flow of blood through the animals' kidneys, but the flow begins to return to normal even when the infusion is continued. The investigators showed that the production of PGE_2 by the kidney increases at the same time as does the blood flow. Inhibition of prostaglandin synthesis by the drug indomethacin prevented the increase. Moreover, indomethacin decreased renal blood flow in the absence of added angiotensin, and doses of angiotensin that were without effect before inhibition of prostaglandin synthesis decreased renal blood flow in the presence of the inhibitor.

McGiff and Vane suggest that maintenance of the rate of blood flow through the kidney when the animal is stressed depends partially on the continuous synthesis of PGE_2 and that in the absence of that synthesis, the activity of substances that constrict blood vessels is potentiated. A similar situation could be occurring in the arteries and arterioles, which also secrete PGE_2 in response to angiotensin. Thus, a decline in the synthesis of PGE_2 could contribute to the development of hypertension.

The next question that arises is what could cause such a decline. McGiff and his colleagues have evidence that the answer might be a deficiency of kinins. Kinins are small peptides that lower blood pressure by increasing secretion of water and sodium ions by the kidney and by causing the dilation of blood vessels. The best known kinins are bradykinin and lysyl-bradykinin. According to McGiff, bradykinin stimulates PGE_2, release by the kidney and the arteries, and the prostaglandin appears to mediate some effects of the kinin.

The enzyme kallikrein produces the kinins by catalyzing the splitting of a large peptide found in blood. Harry Margolius, now at the Medical College of South Carolina, Ronald Geller of the National Heart, Lung, and Blood Institute and their colleagues have found that patients with hypertension secrete less kallikrein in their urine than do persons with normal blood pressure. A deficiency of the enzyme should result in a lack of kinins. Another pertinent observation in this regard is that mean urinary kallikrein concentrations are lower for black than for white children, according to Margolius and his colleagues, even though the black children had normal blood pressures. The incidence of high blood pressure is much higher in the black population than among whites. Moreover, the investigators found that the mean blood pressure scores of the families with low mean kallikrein concentrations in urine were significantly higher than those for families with high kallikrein concentrations. These results suggest that a biochemical defect, possibly of genetic origin, may predispose to the development of hypertension.

Whereas PGE_2 appears to decrease blood pressure, $PGF_{2\alpha}$ increases it. The latter compound does this by constricting the veins and thus enhancing the return of blood to the heart. This in turn increases cardiac output. Consequently more blood is pumped into the arteries and the arterial pressure increases. $PGF_{2\alpha}$ may also stimulate cardiac output by a direct effect on the heart.

The net effect of the prostaglandins on blood pressure would appear to depend on which one is predominant at a given time. And this could depend on their relative rates of synthesis. McGiff points out that $PGF_{2\alpha}$ may be synthesized from PGE_2 as a result of the activity of the enzyme PGE 9-ketoreductase. He suggests that this enzyme could play a regulatory role, with an increase in its activity favoring an increase in blood pressure and a decrease disposing to a decline in blood pressure.

Whether inhibiting prostaglandin pro-

duction by administering indomethacin to the intact animal will increase or decrease blood pressure is unclear. Indomethacin is sometimes used as a substitute for aspirin, but McGiff says that there is no evidence that it increases the blood pressure of individuals taking it. McGiff and his colleagues found that the drug did increase the blood pressure of rabbits and dogs.

On the other hand, Jürgen Frölich, John Oates, and their colleagues at Vanderbilt University, found that indomethacin decreased blood pressure in a small number of hypertensive patients and in normal individuals. They gave the drug to human volunteers because they and other investigators had evidence that prostaglandins stimulate the release of renin by the kidneys. This would favor angiotensin production and should increase blood pressure. But angiotensin increases PGE_2 production by the kidney and this should decrease blood pressure. This situation will obviously require further clarification.

Part of the problem may be that several systems are interacting to control blood pressure, and they are all influenced not just by each other but by such experimental conditions as the water and salt balance of the subjects. In other words, investigators of the mechanisms controlling blood pressure still have some problems to solve.

—JEAN L. MARX

The 1976 Nobel Prize in Physics

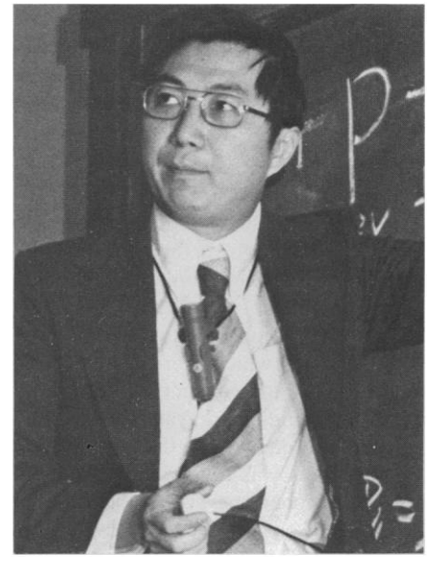
On 11 November 1974, the world of high energy physics was electrified by the news of the discovery of a new particle with remarkable properties. Just as remarkable was the fact that two groups had found it—one a group from Massachusetts Institute of Technology and Brookhaven National Laboratory led by Samuel C. C. Ting, and the other a Stanford Linear Accelerator Center–Lawrence Berkeley Laboratory (SLAC-LBL) collaboration led by Burton Richter. The sudden but permanent impact of that discovery on the field has been recognized by the award of this year's Nobel Prize in Physics to Richter and Ting, only 2 years after the great discovery.

Ting's group was studying production of an electron in conjunction with its antiparticle—the positron—in proton-nucleon collisions at Brookhaven. They found (*1*) a remarkable yield of electron-positron pairs of rest energy 3.1 Gev, indicating the production of a new particle, which they named J. Richter's collaboration was studying the process in reverse: what is formed when beams of electrons and positrons are made to collide head-on and annihilate to produce other forms of matter. Data taken near a total electron-positron energy of 3.1 Gev had shown erratic, irreproducible behavior, convincing the SLAC-LBL experimentalists to go back and explore that region again more carefully. During their next running period it only took a few days to find (*2*) that at precisely 3.098 Gev the rate of annihilation increased more than a hundredfold, indicating resonant production of a new particle, which they named ψ.

By chance, Ting was on his way to SLAC to attend a committee meeting when the SLAC-LBL discovery occurred. Both results were presented in a memorable session at SLAC, attended by a huge crowd that included not only the usual physicists but many staff people swept up in the excitement. The euphoria spread worldwide, and in my experience not since the discovery of parity nonconservation (including the perhaps more profound discovery in 1964 of the violation of CP invariance) has an experiment had such a sudden and revolutionary psychological impact. This immediate recognition of the importance of J/ψ came about because of its relatively large rest mass, more than three times that of the proton, its relatively long lifetime, and the ease of formation by the colliding electron-positron beams. The intervening 2 years have confirmed the original expectation: the ψ (*3*) had led to the apparent discovery of a new property of matter called charm.

Richter, after obtaining his degree at MIT, went to Stanford in 1956 determined to carry out experiments testing the foundations of quantum electrodynamics—the marriage of the Maxwell theory to the Dirac electron theory and to quantum mechanics. Richter first made measurements of the production of electron-positron pairs by 100-Mev gamma-rays, under conditions designed to strain the theory to the utmost. The results agreed with quantum electrodynamics. Around this time, G. K. O'Neill of Princeton made the audacious suggestion that intense electron beams could be stored and made to collide with each other at rates so high that processes of interest to high energy physics would be observable. Ordinary scattering of electrons at large momentum transfer would provide a quite sensitive test of electrodynamics at small distances. Richter, along with W. C. Barber and B. Gittelman, joined with O'Neill and built at Stanford a pair of electron storage rings with the 550-Mev linear electron accelerator as injector, and they successfully observed the electron-electron collisions. Again quantum electrodynamics was verified, this time on a distance scale small compared to the size of the proton.

Burton Richter



Samuel C. C. Ting