research progress report

In reporting the progress of hypertension research assisted by research grants of the Public Health Service, Dr. William H. Stewart prepared for the National Advisory Heart Council, and for limited distribution, a detailed and documented account describing these studies and their relation to the origin, process, and treatment of hypertension. This brief summary of the investigations was drawn from Dr. Stewart's original report.

At the time of documenting the studies, Dr. Stewart was with the Grants and Training Branch, National Heart Institute. He is presently chief of the Heart Disease Control Program, Division of Special Health Services.

High Blood Pressure

IN THE PAST 5 years, approximately 2.5 million dollars from National Heart Institute appropriations has been granted for 30 research projects on high blood pressure and related fields. About 2 million dollars of this amount is employed by 21 still active projects.

The work pursued by these investigations has been a major influence in (*a*) encouraging additional extensive and intensive study in what was 5 years ago a peculiarly neglected field; (*b*) helping to bring about a change of attitude from one of near-hopelessness to one of optimism that hypertension can be managed; and (*c*) developing better treatment for more patients.

Investigators working on the problems of hypertension are pursuing many avenues in their research, motivated by certain general concepts. The following comments offer a crude frame into which to fit the pattern of NHI-supported research in this field as one element in the total picture.

High blood pressure, or hypertension, is the result of a disease—possibly systemic—directly affecting the blood vessels, from which the heart may ultimately suffer.

Arterial high blood pressure can be caused by or associated with a variety of disorders, but the full causes of essential hypertension, which constitutes the bulk of cases, are unknown. This type of high blood pressure is defined by many investigators as a persistent abnormal elevation of diastolic blood pressure (the blood measure while the heart is filling) secondary to increased resistance in the peripheral vascular system—the body's bed of small and minute arterial vessels. Since it is generally believed that the abnormal elevation of diastolic blood pressure represents an effect instead of a cause, the core of the problem is the mechanism of increased peripheral resistance.

The following facts illustrate the importance of high blood pressure:

Thirteen percent of the deaths from cardiovascular disease in the United States are definitely due to high blood pressure. Many more deaths which cannot be strictly classified are attributable to hypertensive causes. An additional 30 percent of heart disease deaths cannot be accurately classified as due to arteriosclerosis or hypertension, respectively, but they are due to one of the two, or both.

Of the estimated 10 million persons with some form of cardiovascular disease, fully 4,600,000 have high blood pressure. Of the young men examined by Selective Service during the years 1940–44, 165,000 were rejected because of high blood pressure.

Hypertension is far more common in women than in men, by a ratio of about 2 to 1. On the other hand, hypertension is less frequently fatal for women.

High blood pressure causes a progressively increasing amount of disability after middle life.

The majority of the research grants projects have been aimed toward finding the process by which the peripheral resistance is increased or toward finding a means of nullifying the increased peripheral resistance as therapy for this disease. Currently, several possible processes are under investigation. The studies can be classified roughly as therapy of hypertension, experimental hypertension, and clinical hypertension.

Therapy of Hypertension

Studies supported by the National Heart Institute on the therapy of hypertension chiefly have examined three general techniques: drugs, surgery, and diet.

An increasing variety of both new and old drugs has been under study in the past 4 or 5 years. The rapidly increasing use of some of these drugs by physicians reflects the progress of the research which found the drugs, screened and tested them, and developed their clinical use.

In view of the fact that as recently as 5 years ago there were no drugs especially satisfactory for treatment of hypertension, it is not surprising that the ideal agent has not yet been found. It is even too early to determine fully the benefits from drugs presently in use. High blood pressure is in many cases a 20-year to 25-year disease. The newer drugs, such as the Rauwolfias, have been in use less than 5 years. It can be said that many patients have been greatly helped, symptoms relieved, and useful living restored for some length of time. But a drug is not yet available which affects only the mechanism causing an elevated blood pressure, which remains effective for a long time in a given dose, and which has no bad side effects or reactions.

Surgical and dietary therapies are being improved and are continuing to be used, though perhaps not as much as in the past. At no time, however, has surgery been employed as extensively as diet therapy, which continues to be useful.

Contemporary surgical treatment consists of removal of a diseased kidney suspected of being the cause of hypertension, removal of an endocrine tumor, correction of coarctation of the aorta, or sympathectomy. Sympathectomies—operations on the sympathetic nerves designed to reduce blood pressure—are of two types: the total sympathectomy, which aims to remove functionally as many sympathetic ganglia as feasible (those nerves adjacent to the spinal column which are linked to and control the diameter of blood vessels), and partial sympathectomy, which restricts the surgery to specific nerve areas. Each denervation differs in procedure, area, and response.

Diet therapy usually falls into 1 of 5 groups: (*a*) low salt diets, (*b*) low protein diets, (*c*) low cholesterol diet, (*d*) low caloric diet, (*e*) rice diet.

Experimental Hypertension

The study of any disease is greatly facilitated if the disorder can be produced easily in experimental animals and then manipulated more or less at will. Consequently, much work is done in experimental hypertension, the production and study of this disorder in animals. This work includes studies of the factors which will modify the "experimental" disease once it has been produced and studies of its origin and development in experimental hypertension caused by kidney damage. Much attention is concentrated on the role of the sodium ion and on the activity of renin, an enzyme produced by the kidney. The sodium ion appears to have a central position in the genesis of vascular lesions.

In summary, studies have demonstrated that, by certain manipulations of the kidneys, hypertension in animals can be produced with a fair degree of predictability. Examples of such manipulation include wrapping the kidney with silk, administration of drugs or hormones, introducing infectious organisms, or substituting saturated salt solutions for drinking water. Although reports indicate considerable progress, the exact organic action of the kidney in this experimental animal hypertension is still undetermined.

Extensive investigation of the exact role of the secretions of internal glands in the production of hypertension and their relationship to

other mechanisms also have been productive of much useful knowledge, although it is not as yet decisive.

In particular, research has directed attention to secretions of the adrenal cortex and an anterior pituitary preparation. Removal of the adrenal glands had a striking effect on hypertension in nephritic rats injected with cortisone, if they were well nourished.

Grant-supported investigations of the role of nervous and psychological mechanisms in the origin and development of experimental hypertension have been directed mainly to human subjects because investigations of these stresses in experimental animals have yielded too little useful information. Even in man such studies are extremely difficult because they are affected by a multitude of variable factors. Nevertheless the few studies reported under grant support indicate that nervous and psychological factors must be considered in the complex process of hypertension.

Limited evidence indicates that persons prone to hypertension induced by nerves tend to give a positive skin reaction to injections of histamine. Such a test may help to distinguish such patients from those affected more by glandular or kidney action. Psychological tests and psychiatric interviews also may prove useful for this purpose, in view of results obtained from a study of college women.

Clinical Hypertension

Clinical investigations have been directed at discovering changes in function and composition of the body occurring in humans during the course of hypertension. In these studies several substances found in the blood are investigated as possible factors causing or maintaining elevations in blood pressure. Among these are:

Serotonin. A material normally found in the blood and taking part in the mechanism of blood clotting, but also a powerful constrictor of blood vessels.

Pherentasin. A highly active constrictor substance rarely present in the blood of mammals but isolated in the blood of hypertensive patients.

VEM (vasoexcitor material). A substance produced by the kidney to maintain blood pressure during shock.

Corticotrophin (ACTH) and cortisone. Hormones produced by special glands of the body that help regulate body function.

Epinephrine and nor-epinephrine. Hormones produced by the adrenal glands that act in controlling heart rate and blood vessel tone.

Dr. Hugh Rodman Leavell

Hugh Rodman Leavell, M.D., Dr.P.H., was chosen president-elect of the National Health Council by its board of directors in December 1954. He takes the place of T. Duckett Jones, M.D., who died on November 22, 1954.

Dr. Leavell, recently the president of the American Public Health Association, has been professor and head of the department of public health practice of the Harvard School of Public Health since 1946. He will succeed to the presidency of the council at its annual meeting in March 1955.