An Appraisal of Endocrinology (1936)

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AN APPRAISAL OF ENDOCRINOLOGY

I. INTRODUCTION

Endocrinology is concerned with a special phase of physiology, pathology and medicine. It is the science which has to do with the activities of the *endocrine organs.* These are a group of special glands which have the function of supplying the organism with special chemical regulatory substances, the *hormones* or *internal secretions.*

The endocrine organs share in many of the characteristics of glands in general, such as the tear glands that keep the eyes moist or those which supply the digestive juices. Each gland is a special living laboratory in which materials supplied by the blood are made over into peculiar substances, the *secretions.* In ordinary glands the secretions are poured through ducts to exert influences in their local spheres of action. Unlike the ordinary glands, however, the endocrine structures discharge their secretions directly into the blood stream—hence they are sometimes referred to as the *ductless glands.* After being discharged into the blood stream the hormones are carried throughout the body to arouse or to allay activities, as circumstances demand.

The internal secretions or hormones derive their importance from the part they play in the *control* of the body. In man and the higher animals the organism is made up of many complex units and these have to be kept functioning in harmony if the individual is to remain in health. Any significant disharmony results in disordered functions, and serious disharmony results in death.

For centuries the general principles of *nervous control* in the body have been known. The various sense organs on the

surface and within the body constantly pick up messages and these are transmitted by telegraph, as it were, over the nerve fibers to the central nervous system. Here the messages are received and interpreted and orders are telegraphed by other nerve paths to the various parts of the body as the necessities of the occasion demand. The classical illustration of this sort of control is that of the boy who touched a piece of hot iron and, before he had time for thought, hastily removed his finger.

For *rapid* and *episodic* purposes the nerve telegrams afford the most useful system of control. Thus if a man sees a golf ball approaching his head, just the right muscles must be set into quick action simultaneously to make the proper movements to avoid the danger. On the other hand, there are many functions of the body that are in the nature of *general policies* and for the control of these, general messages can be utilized. Such messages are conveyed by the hormones, or "chemical messengers." Hormone control is largely utilized in such processes as growth, digestion and sexual development.

The chief endocrine glands are: the *hypophysis* or *pituitary* which lies in the center of the head; the *thyroid* gland which straddles the trachea or "wind-pipe" at the base of the neck; the *parathyroids* which lie in or near the thyroid; the *adrenal glands* which cap the kidneys; the *pancreas* in the midabdominal region; and the sex glands—the *ovaries* situated in the pelvis of females or the *testes* which are contained in a special extension of the body cavity, the scrotum, of males.

The method of chemical control, although even more primitive than that of nervous control, has only recently come into scientific recognition. While the importance of the principle is now indisputable and while we know many things about the operation of the principle, the major part of the work necessary to a clear understanding remains to be done. Literally many issues of life and death are involved.

II. MAJOR ACCOMPLISHMENTS OF THE PAST

> "Since the development of the bacterial theory of infection there is probably no concept of disease that has latterly so dominated modern medicine as the doctrine of the internal secretions. . . . We are what we are, bodily, mentally, sexually, emotionally, facially, largely through the balance or imbalance of certain secretions discharged in minute quantities into the blood by the ductless glands." (*Garrison.*)

The Thyroid and Thyroxin

The thyroid gland was well known to the ancients because of their familiarity with the swelling of the gland known as *goiter.* Long ago Juvenal wrote, "Who wonders at goiter in the Alps?" The presence of the thyroid as a distinct structure was recognized by Galen of ancient Rome and it was described in the gross by Vesalius in 1543. Our first knowledge of its functions was obtained from clinicians. As early as 1786 an English practitioner, Caleb Perry, had recognized a new disease marked by protrusion of the eye-balls, palpitation of the heart and swelling of the thyroid gland—a serious and often fatal disease now well-known as *exophthalmic goiter.* A report on eight cases of the disorder was published posthumously by Perry in 1825. The disease was further studied by Graves (1835) and independently by Basedow (1840). The symptoms of Graves' disease—extreme nervousness and wasting away—we now know to be due to overactivity of the thyroid gland.

Our knowledge of the results of lack of thyroid secretion began with the discovery by Curling in 1850 that defective thyroid development is accompanied by "symmetrical swellings of fat tissues at the sides of the neck, connected with defective brain development." The first to make an experimental attack upon the problem of thyroid deficiency was Schiff of Geneva who reported in 1858 the fatal results of removing the gland in animals. Schiff's work, however, made

little impression upon contemporary scientists. For reawakening interest in the problem we are again indebted to clinicians. In 1873, Sir William Gull reported the cases of five middle-aged women whose puffy faces, bulky forms and physical lethargy indicated the presence of a common disease. Five years later, Ord had opportunity to make a post mortem examination of a victim of this disorder. He noted that the thyroid gland was deficient (atrophic) and that the general puffy appearance of the face and body was due to the accumulation of mucilaginous material beneath the skin. Because of this characteristic he named the disorder, *myxedema*. With the introduction of the principle of antisepsis by Lister, the treatment of goiters by radical operation became feasible. The first results of the operation were gratifying to the patients in ridding them of the unsightly protuberances of the neck but it soon became apparent that this was not an unmixed blessing for disturbances in nutrition soon developed. Clinical interest in the thyroid rapidly grew and Schiff was encouraged to resume his experimental studies. He found, in brief, that destroying the thyroid in dogs led to a train of symptoms similar to those following the surgical removal of the gland in man. Another important step was then taken by Bruns who had noted in the literature a report of a case of a boy from whom a goitrous thyroid had been perilously removed ten years before the advent of the antiseptic era. The lad had managed to survive the operation but at 40 years of age resembled in size and appearance a mentally and physically backward boy; in short, he had a typical case of myxedema (cretinism).

This is the condition of which Osler wrote: "No type of human transformation is more distressing to look at than an aggravated case of cretinism. It recalls Milton's description of the Shape at the Gates:

"If shape it might be called, that shape had none
Distinguishable in member, joint or limb,"

or those hideous transformations of the fairy prince into some frightful monster. The stunted nature, the semi-bestial aspect, the blubber lips, retroussé nose sunken at the root, the wide-open mouth, the lolling tongue, the small eyes, half closed with swollen lids: the stolid expressionless face, the squat figure, the muddy, dry skin, combine to make the picture of what has been well-termed 'the pariah of nature.'" In 1891 Murray had shown that the missing thyroid secretion can be artificially restored by the administration of thyroid tissue. Murray's first patient died in 1919 at the age of 74—her health having been maintained on thyroid medication for 28 years, during which time she had consumed the thyroid glands of several hundred sheep. Osler was thus in position to complete his allusion to cretinism: "Not the magic wand of Prospero or the brave kiss of the daughter of Hippocrates ever effected such a change as that which we are now enabled to make in these unfortunate victims, doomed heretofore to live in hopeless imbecility, an unspeakable affliction to their parents and to their relatives."

The discoveries epitomized in the foregoing paragraphs mark one of the most signal triumphs in the entire history of medicine. Of the mechanisms whereby the thyroid hormone, ***thyroxin,*** exerts its manifold influences in the body, much has been learned which space does not permit us to recount. The last major step in investigations was the isolation of a highly active crystalline thyroid derivative by Kendall. This was thought for several years to be the true hormone but Harington later obtained a more authentic product and in 1927 finally proved its composition by synthesizing it.

The Adrenals

The adrenal, or suprarenal, glands were described by Eustachius in 1563, and they were named by Riolanus in 1628. The adrenal consists of two independent parts, a *medulla* and, surrounding it, a *cortex.* In 1855 Addison rightly associated

these glands with what has since been called *Addison's disease.* Almost at once the young physiologist, Brown-Séquard, began experiments which showed that the removal of the adrenals from experimental animals inevitably results in death. The outstanding symptoms, like those of Addison's disease, are increasing feebleness of the circulation, bodily weakness and prostration ending in fatal coma. The cause of the prostration for years remained unknown. It was in 1894 that Oliver and Schäfer apparently solved the problem. They discovered that extracts of the adrenal medulla, when injected by vein, have a remarkable stimulating effect upon the circulation. The heart beats more forcefully and the blood vessels are markedly "toned up." The function of the glands, therefore, it was thought, must be to keep the body supplied with an invigorating tipple, lacking which, the characteristic prostration of adrenal deficiency ensues. Put to further test, however, the "beautiful theory was slain by an ugly fact." Despite the temporary improvement in circulation that ensued, the victim of adrenal deficiency, whether an Addisonian patient or an experimental animal, died as promptly with as without the injections—and the mystery remained as deep as before. To make another long story short, it was found that the fatal results of destroying the adrenals are due, not to lack of the *medulla,* but to lack of the *cortex* of the gland.

Nevertheless, medullary extract—the *adrenalin* of commerce—is a remarkable substance. It dilates the pupils, opens the air passages to the lungs, causes the hair to stand on end, brings forth stored sugar from the liver, causes the blood to clot more promptly, shifts the circulating blood to the brain and muscles at the expense of the skin and internal organs and stops the digestive processes. What could this mélange of apparently unrelated effects signify? Several years of researches by Cannon and his collaborators afforded the explanation. They are all changes that would serve to adapt the animal for the vigorous activity of contest or flight. The

medulla of the adrenal, therefore, seems to be an accessory device for integrating the individual to meet emergencies. It is doubtful whether, under conditions of quiet existence, it has any significant function.

This avenue having been closed, attention turned again to the cortex of the gland. The probability was high that it exercises its indispensable function by producing a hormone but the possibility remained open that it serves merely as a special structure for the "detoxifying" of bodily wastes. Numerous investigators tried without success to obtain a potent cortical extract. It was not until 1928 that Hartman, as well as Stewart and Rogoff, succeeded in the production of cortical extracts that would significantly prolong the lives of animals deprived of their adrenals. Subsequent workers have aided in further concentration and purification of the life-sustaining active principle but it has not yet been obtained in pure form.

The Testes and the Male Hormone

The earliest beginnings of our knowledge of endocrinology actually derive from observations on the sexual functions. Castration has been practiced by husbandmen from time immemorial, as a means to induce docility in animals. The same operation has been practiced upon human beings from motives of revenge, as a religious rite, to preserve the high-pitched voice of choir boys, or to safeguard the fidelity of harem attendants. The term "eunuch" has long had an opprobrious connotation, largely due, no doubt, to the uselessness of the castrate in the fundamental biologic purpose, the perpetuation of the species. The male gonads have always had a symbolic significance as tokens of personal worth. Virility, with all its appealing connotation, has long been believed to center in the sex glands. Their destruction has correspondingly been regarded as a major calamity to the individual, removing at one fell stroke all his capacity for romance and

the enrichments of life that grow directly or indirectly out of the love of man for woman.

The first to undertake a scientific study of the sex glands was the German, Berthold, who made the experiment of removing the testes from cocks but replacing them with small pieces implanted within the body. These grafts were found to make all the difference between the preservation of the normal masculine attributes such as comb and spurs, or pugnacity and crowing, on the one hand, and emasculate timidity on the other. In short, the animal deprived of his primary sex glands became an overgrown capon, whereas the recipient of the testis grafts developed as a normal cock. The experiment has often been confirmed. Thus an important fundamental biological fact was firmly established.

Berthold's results remained essentially without issue in human practice until a half century ago when Brown-Séquard, then an eminent French savant in his early seventies, reported a series of investigations which electrified the medical and biological world. Distressed with the growing enfeeblement incident to his years, he undertook to restore his waning virility by injecting into his own body simple extracts of the sex glands of animals. On May 31, 1889, he reported to the Société de Biologie of Paris that, after the injections, he found himself vastly rejuvenated as to general health, muscular power and mental activity. Unfortunately for human hopes, other investigators were unable to confirm his findings, and the long sought Fountain of Youth again had eluded quest. So great, however, was the prestige of the investigator and so startling were his claims that world-wide interest was at once evoked and serious attention to experimental endocrinology thus received a great impetus.

Within the next generation further important work on the influence of the sex glands was carried out by Steinach and others. This investigator removed the ovaries from female guinea pigs and replaced them with testes from their twin

brothers. The artificial males thereafter outgrew their normal sisters and showed the skeletal features, the coarser hair growth and the pugnacity suitable to their brevet masculine status. The reverse experiment of grafting ovaries into castrated males had a converse feminizing influence. These artificial females simulated their sisters in development: their breasts enlarged and these, by special treatment, were made to produce milk. Thus the astonishing phenomenon was set up of guinea pigs which had begun existence as males actually nursing adopted offspring. It thus became convincingly clear that males are masculine and females are feminine primarily because of their sex hormones.

The next major step in the development of our knowledge of these hormones was obviously to obtain them in a pure form and determine their chemical and biological properties. The first reliably potent male sex-gland extract was obtained from bull testes by McGee in 1927. The earlier preparations were relatively crude but were further refined by Gallagher and Koch (1929-30). Shortly afterward, various investigators succeeded in obtaining an active masculinizing product from the urine of younger men and demonstrating that it was absent in that of boys and elderly men. Recently the problem has been subjected to brilliant chemical study by Butenandt, Laqueur, Ruzicka and others. There are now available at least three different pure, crystalline substances having masculinizing properties; they are obtainable from testis substance, from human urine and by artificial synthesis, using the common substance, cholesterol, as a base. Throughout all this period of physiological advancement the psychologists have remained largely oblivious to the fundamental problems thus presented for study.

The Ovaries and Their Hormones

Folk knowledge of the female sex glands as determiners of body functions and behavior was much less adequate than

in case of the male. Although spaying has long been practiced in farm animals, the operation in women was so formidable as to have been beyond the competence of our forbears. The first surgical investigation of the physiology of the human ovaries was made by the gynecologist, Robert Battey, of Georgia who, in 1872, removed these organs from a woman for the relief of a neurotic condition. The feasibility of the operation having been demonstrated, it had a disastrous vogue among surgeons of a generation ago. Women galore were deprived of their ovaries—often for reasons that we now know to have been grossly inadequate. This is perhaps the darkest chapter in the evolution of modern surgery. The results of the operation are to bring on quickly the conditions of the normal menopause. When the endocrine balance is thus brusquely upset, the woman commonly undergoes a distressing period of nervousness and irritability with "hot flashes," headaches and insomnia among the more trying manifestations. She is, of course, no longer able to produce ova but, in addition to this deficit, suffers a marked regression in the secondary sexual characteristics. Menstruation ceases, the breasts atrophy and she not infrequently develops obesity and more or less of the hirsute adornments of the male. Erotic desire may or may not be lost. The results of the operation upon personality and temperament have not received adequate psychological investigation, but from the studies of Rowe, it would seem that the woman often suffers substantial diminution of the composure and graciousness with which she was previously endowed. Several investigators have shown that transplantation of ovarian tissue into previously ovariectomized women sometimes serves to reestablish menstruation, sexual desire and general sense of well-being.

The quest for the active principle of the ovaries was begun. The outstanding earliest work was done by Iscovesco (1912) who succeeded in preparing ovarian extracts that were capable of causing growth in the uterus and mammary glands of ani-

mals and awakening the erotic behavior pattern. The work was corroborated by others, including Frank of New York. A marked impetus was given to investigations in this field when Allen and Doisy (1923-24) discovered that raw fluid taken from follicular cavities in the ovary is, in itself, a potent feminizing agent. Another major step toward the unravelling of the problems in this field was the application by Long and Evans of California of a discovery that the cell content of the lubricating fluid of the vagina undergoes characteristic changes in the different phases of the sex cycle. The sequences of changes are easily seen under a microscope and serve to furnish accurate orientation as to the quiescence or activity of the sex functions in experimental animals. It thus became possible easily to determine the potency of ovarian extracts, using spayed mice or rats as test objects. The ovarian extract was finally made to yield two potent crystalline bodies, *estrone* and *estriol,* both of which have marked influence in restoring the feminine functions. Estrone was soon found in the blood of women by Loewe (1925) as well as by Frank, and in 1927 Aschheim and Zondek found it in huge amounts in the urine of pregnant women. The estrogenic (sex-stimulating) material having been obtained in crystalline form, it soon yielded to accurate chemical analysis and then to synthesis. At the present time at least seven naturally occurring estrogenic substances or estrogens have been isolated in crystalline form and their chemical structure has been established. The precise effects of each throughout the body remain largely for future determination. It is important that these influences be known because the materials are coming into wide use in practical medicine and, without further knowledge, considerable harm may unwittingly be done. Too, the materials may have other important beneficial effects in addition to the estrogenic.

Each month when a woman discharges a ripened ovum (egg) a cavity is left in the ovary which fills up with a blood

clot. This is soon replaced by an organized body, the *corpus luteum,* which has been shown to have an independent hormone function. Hisaw (1928), and Corner and Allen (1928-29) have been able to obtain the active corpus luteum principle, *progestin.* They and others have shown that it has a marked influence in preparing the uterus for the reception of the fertilized ovum and in bringing about various of the uterine and other changes characteristic of pregnancy. Butenandt (1934), Wintersteiner and Allen (1934) and others have determined the chemical structure of this active substance which is now known as *progesterone.*

The Hypophysis or Pituitary Gland

Another of the indispensable glands is the hypophysis. Its existence was known from the time of Galen. It was described by the Renaissance anatomists. As a *raison d'etre* it was long supposed to furnish a lubricating secretion (pituita) for the nasal passages. Robbed of this office by Schneider in 1660, it remained merely as a stimulus to speculation for another century.

Dimly then it began to be apprehended that the pituitary is in some way concerned with growth. In retrospect we can find the earliest beginnings of our knowledge in primitive legendary lore. Giants and dwarfs—walking exemplars of over-activity and under-activity, respectively, of the pituitary gland—have always engaged the folk imagination. In the book of Deuteronomy we read: "For only Og, King of Bashan, remained of the remnant of giants; behold his bedstead was a bedstead of iron; nine cubits was the length thereof, and four cubits the breadth of it, after the cubit of a man." The description implies that the king was approximately eleven feet tall. Goliath of Gath is another gigantic figure of popular lore. At the other extreme, we have Will-o'-the-Wisp, King of the Pixies, the attenuated legendary dwarf

who sported with his followers in the evening twilight on the rocky hillsides of Dartmoor.

Actually, our authentic knowledge of the relationship of the pituitary to body growth began with the appreciation of the connection between an enlargement of the pituitary and the modified type of gigantism known as *acromegaly*. In this disorder the victim becomes a gorilla-like, horse-faced caricature of his former self. The condition had been recognized as a distinct anomaly by Verga in 1864 and he noted that the pituitary in the patient he studied was abnormal. Thirty years later, Klebs published a monographic study on acromegaly; he emphasized the fact that the pituitary gland was excessively large but he was unable to decide whether this abnormality was the cause of, or merely a part of, the patient's general overgrowth. To Pierre Marie (1886) is usually given the credit for finally determining that acromegaly is due to over-activity of the pituitary.

The first experimental (surgical) attacks upon the physiology of the pituitary were made independently by Aschner and by Cushing early in the present century. They discovered that puppies deprived of this gland were unable to grow or to develop sexually. The brilliant researches of Smith, first upon tadpoles in 1917 and later upon rats, brought out the fact that the growth disturbances are due, not to the destruction of the whole gland, but only to that part derived from the primitive digestive system, the *anterior lobe*.

In 1921, Evans and Long found that the injection of anterior pituitary extracts (thought to contain a specific *"growth" hormone*) will produce gigantism in rats; and such extracts have since been found to induce growth in other animals and in some types of human dwarfism. In 1926-27 Smith and Engle, simultaneously with Zondek and Aschheim, found that this gland produces a hormone (*gonad-stimulating*) with unique capacity to hasten the growth and maturity of the testes and ovaries of animals. A failure in its production leads to

a lifetime of "over-grown babyhood" physically, and an existence robbed of romance and emotional maturity. In 1932 Riddle and Bates isolated still another pituitary hormone (*prolactin*), shown at once to cause the secretion of milk, and now shown by Riddle also to stimulate (and repair) the adrenal cortex. This latter function had previously been ascribed to an independent hormone, the *adrenotropic.* From 1925 onward facts obtained by several workers have indicated that the pituitary produces still another hormone (*thyrotropic*) capable of stimulating the thyroid gland, and—though the thyrotropic hormone has not yet been separated from the gonad-stimulating principle—the evidence for its individuality became conclusive about 1934. Since 1933 various other organs or functions of the body have been found to be greatly affected by one or another type of anterior pituitary extract.

Other Glands

Of other important endocrine glands only passing mention will be made. From the posterior lobe of the pituitary have been derived *pitocin* and *pitressin* (Abel, Rouiller and Geiling, 1923; Kamm et al, 1928) that have a striking influence upon the control of water and salt excretion and upon a variety of functions subserved by smooth muscle, throughout the body. These include the blood pressure, intestinal movements and contractions of the uterus and bladder.

A landmark in the history of medicine was the final isolation from the pancreas of *insulin* (Banting, Best, Macleod and Collip, 1921-22; crystallized by Abel, 1926). These accomplishments marked the culmination of a long series of preceding researches. Insulin is often a life-saving agent and it has removed the spectre of slow starvation from the lives of thousands of people. If endocrinology had no other triumph to its credit than the discovery of insulin, that alone would be a sufficient reward for all of the labors that have brought the science to its present state.

The *parathyroid glands* were first differentiated as independent functional structures by Gley in 1881. Upon these, too, are we fatally dependent for health and happiness. Their destruction results in excruciating cramps and early death. Deficiency in their secretion causes prolonged tenseness with frequent cramps, and also rickets of the bones. Their overfunction riddles the skeleton and ruins the kidneys. Their active principle, *parathormone,* has been obtained in fairly high concentration by Collip, Hanson and Berman, independently (1922-23).

The importance of the *pineal* and the *thymus* has been dimly apprehended in the past but the more significant researches on these structures are of such recent date as to be more appropriately treated in another section of this report.

Final mention may be made of the discovery of *sympathin* by Cannon in 1931. This agent has been shown to mediate the impulses of the sympathetic nervous system and has thus aided in putting on a firm basis an important new principle in modern neurology.

The establishment of such facts and relationships as those partially and briefly noted above have made it certain that the internal secretions are required for the normal growth and development of our bodies, that their normal functioning is essential to the maintenance of health, and that further knowledge of these secretions is essential alike to an understanding of the normal human body and to the development of a scientific conception of the cause and cure of many of its diseases.

A sure foundation has been laid and literally hundreds of problems of fundamental importance to human welfare have been opened up. Of some of the researches devoted to the solution of these problems the next section will treat.

III. CURRENT RESEARCH ACTIVITIES

(*In the United States and Canada*)

The evidence is now conclusive that every organ of the body and practically every function is subject in greater or less degree to hormone influences. The field of endocrinology is thus essentially coextensive with the fields of *physiology and pathology*. Since hormone factors are known to influence behavior, mental processes and emotional reactions, it seems obvious that the *psychology* of the future will also have to take substantial cognizance of the hormones. There is no field of *clinical* medicine in which the endocrine factors are not of importance. In consonance with these facts, endocrine investigations of the present day extend over a very large terrain.

Types of Research

Researches in endocrinology fall into three groups: (1) study of the influence of hormone factors in the normal structures and functions of laboratory animals; (2) the applications of the animal findings to clinical medicine; and (3) the direct study of endocrine perturbations as manifested in man.

Group 1. First are the basic problems which, because of their newness and complexity, must be studied on suitable laboratory animals. These animals must be of standard types, relatively inexpensive and available in considerable numbers. The primary aim of such studies is the discovery of fundamental principles. A large number of such experiments are made each year by young investigators. Though the results are often not widely significant they justify themselves as experience on a training and proving ground. In testing, quantitatively or qualitatively, various natural or derived preparations having endocrine properties, great numbers of the small laboratory animals are used. Here the rat or the mouse is merely the test animal of the physiologist and chemist. The problems presented are frequently of the type which may be

called basic, even when material to be analyzed is from human sources. It is this type of endocrine research which is most accurate and the methods and results of which may be best controlled.

Group 2 comprises studies having as their aim the adaptation of the principles derived from studies of Group 1 to clinical uses. Often such studies are also made on animals but with practical goals in view. The animals used are frequently higher in the scale of life, and more nearly similar to man. The monkey has been found to be the animal of choice for these experimental purposes except that it is relatively expensive. In rare instances the chimpanzee has been used. The experiments in this category are more directly aimed at preparing materials and evolving techniques and methods for clinical application.

Group 3. The third category in which we may discuss endocrine research is the clinical. The use of experimental test animals is frequently implied, but the object of interest is the patient and not the rat. Research in this group is less satisfactory from the scientific standpoint than it is in either of the other groups. With a rat one may cause a single endocrine disturbance. With a patient this is rarely the case. A monkey may be put in a cage and many details of his physical life analyzed. Most endocrine patients are ambulatory. The endocrine patient all too frequently has mental or emotional problems which influence and complicate the endocrine status; rats and monkeys are less, if at all, prone to "complexes." Finally the endocrinologist who is conducting clinical experiments rarely sees the often very informative autopsy results as does the animal investigator. With the exception of Addison's disease, diabetes, and a few other endocrine disorders, most cases do not come to death as a direct result of the endocrine disturbance. While this type of research is the most unsatisfactory from the experimental point of view, it

represents the last and essential step to take with any project. It is the real point at which all other research is aimed.

Sex Endocrinology and the Anterior Pituitary

In the first section of this report the evolution of our knowledge of the female sex-hormones was sketched. Study of the endocrinology of the sex life of women and girls is now one of the most active fields of research. It exemplifies all the three types of research discussed in the preceding section and illustrates their relations, one to another.

Discovery of the presence of a potent hormone in human urine has proved to be an important step in the development of endocrinology. Chemically pure crystals of the female active principle, *estrone*, were prepared in 1929 by Doisy, Veler and Thayer. Crystalline preparations were independently isolated by Butenandt (1929) and Laqueur *et al* (1930). The second step in a knowledge of this hormone was thus achieved. Several other crystalline preparations of female sex-hormones (estrogens) have now been obtained from ovaries and human urine and from the blood of pregnant mares.

Before the active agent had been prepared in crystalline purity, Allen had been studying the effects of extracts of the female sex-hormone on the female monkey. This animal is especially well adapted to work on sex physiology because the female has a menstrual cycle similar in every known respect to that of women. These transition experiments on monkeys, started by Allen, were participated in by several workers (Hartman of Baltimore, Corner of Rochester, Hisaw of Wisconsin and Engle and Smith of Columbia) and prepared the way for studies on women.

Following the work of Engle and Smith on the experimental production of the menstrual cycle in the monkey, Kaufman of Berlin got similar results in women whose ovaries had been removed. Under Allen's guidance, Werner and Col-

lier (1933) had first studied the reaction of women to estrone; but as Kaufman showed, the dosage which they used was only about one-tenth of the amount needed to produce complete uterine change. Thus had commenced, but only commenced, the development of the third phase of our knowledge of the estrogens. They are now used clinically in certain cases of failure of sexual development and disturbances of the menstrual cycle. Their most satisfactory use, however, has been in ameliorating the disturbances of the menopause or climacteric; in this condition they are a real boon.

An unusual application of *estrone,* which has been proved quite successful, has been the treatment of gonorrheal vaginitis in little girls. A few treatments entirely eradicate the infection in a disease which has been one of the real bugbears of gynecology. The method is based simply on the fact that the hormone causes intense growth of the lining of the vagina, followed by its being cast off after treatment is stopped. The slough carries away the infecting bacteria. Unlike many therapeutic measures for chronic infections of this sort, the treatment is harmless to the patient (Lewis, 1933, *et al*).

The relation of the female sex-hormones to *cancer* is attracting wide attention. Estrone is chemically quite similar to certain coal-tar products that can be used to produce cancer. Its administration to susceptible strains of mice increases their liability to breast tumors. It frequently causes a reaction in the uterus of monkeys that is strongly suggestive of cancer. The relationship is obviously one of such poignant human interest as to demand exhaustive investigation.

As previously noted, after the ovary has produced estrone, causing certain changes in the genital tract, ovulation occurs, and a new structure, the *corpus luteum,* is formed. The rabbit is the test animal of choice in experiments on the corpus luteum hormone, the mouse and rat being quite unsatisfactory. The research groups of both Hisaw and Corner have made

from the corpus luteum a satisfactory extract which is now called *progestin.* Corner and his associate in chemistry, Willard Allen, have shown the necessity of its action in causing the essential changes in the uterus preparatory to the implantation of the fertilized egg and the growth of the embryo. Without its influence pregnancy is impossible. Progestin was obtained in chemically pure form by three different groups at about the same time. W. Allen and Wintersteiner were the American team which reported in 1934. The preparation was tried on monkeys with effects in the uterine cycle the same as in women (Corner, Hisaw and Fevold, and Engle and Smith). Kaufman applied it successfully in castrated women, after preliminary estrone treatment, and produced the characteristic changes in the uterus that take place early in pregnancy.

Clinically, progestin may prove to be important in the treatment of habitual abortion (Krohn *et al,* 1935). Certain other possibilities of its use in severe uterine bleeding are indicated but adequate clinical tests have not yet been reported. Relief from dysmenorrhea or painful menstruation has been reported by several investigators.

Though the preceding important functions of the sex-hormones—estrone and progestin—can now be cited, it is here perhaps of equal or greater pertinence to indicate that there is much reason to believe that several very significant actions of these substances are yet to be discovered.

The importance of the *pituitary gland* as a regulator of other hormone-producing structures was discussed in earlier paragraphs. In partial recapitulation it may be said that without the anterior pituitary several other glands of internal secretion either stop functioning or operate at an entirely inadequate level. While important work had been done previously, the dawn of the present era began when Smith of New York successfully removed the anterior pituitary in rats. Smith has continued to be a leader in this field due to

the technical excellence of his operative procedures and the precision of his experiments. In 1926, when he removed the pituitary and observed cessation of sex function in both male and females, checking of body growth, reduction in size of the thyroid gland and atrophy of the adrenals and gonads a new vista was opened to the fields of endocrine research. After the first few years of biological fact finding, progress became dependent on long, tedious efforts of the chemists. As the problem now stands, a variety of active glandular principles have been isolated but some of them not in pure form; these are practically certain to be found to control a wide range of functions.

By extensions of Smith's observations in many laboratories it now appears that there is a hormone, the *gonadotropic,* which controls the activity of the gonads—the ovary and the testis. Both the production of the specific sex-hormones and the elaboration of the germ cells are dependent on the *anterior pituitary* (hereafter referred to as the "A.P."). Many investigators hold that there are two A. P. hormones regulating the sex-glands; others, that a single hormone under varying conditions exercises diverse functions.

The A.P. has one hormone, *prolactin,* which seems specifically to control milk production but which operates only after the mammary gland has been properly "primed" by the sex hormones. Another A.P. hormone, the *thyrotropic,* controls thyroid function. It may be a distinct entity, or may be united with the one (*adrenotropic*) that controls the function of the adrenal cortex. Still another factor governing the parathyroid glands (*parathyrotropic*) is reported to have been separated but its individuality is not yet certain. The A.P. has an important relationship to diabetes. There is no doubt of the existence of a factor, the *diabetogenic,* which, acting against insulin, raises the blood sugar. There is also another and apparently distinct hormone, the *anti-*

ketogenic, which controls the burning of fat — a function that is deranged in diabetes. Another factor which controls protein metabolism, the *somatotropic,* is indicated.

The far-reaching effects of the A.P. have been made more interesting and complicated by the discovery of a number of new sex factors, the *gonadotropic,* in blood and urine. Aschheim and Zondek, shortly after Smith, had shown that the A.P. has gonad-stimulating powers. They followed this confirmation with the highly important announcement that a gonad-stimulating factor, in addition to that derived from the ovaries, is present in the urine of pregnant women. Another gonad-stimulating hormone from the blood and urine of women whose ovaries have been removed or who have passed the menopause has been shown to have important influences in the sex sphere. Since many women are exposed to the action of this substance throughout the body, it presents a problem demanding extensive further research. A brilliant and promising discovery was that of Cole and Hart who found a gonadotropic hormone in the blood-serum (but not the urine) of pregnant mares. This offers promise of being especially useful as a research tool because of the precision of its influence as an ovarian stimulator.

It has now become abundantly clear that the anterior pituitary plays a determining role in the regulation of numerous bodily processes and functions. It is astonishing that so many important influences emanate from a gland that weighs, in an adult man, no more than half a gram (0.017 ounce). The details of its functions remain largely yet to be determined. The solution of the problems presented will demand the most exacting efforts of chemists, physiologists and clinicians. The most fundamental of the problems, as now visualized, are the individualization of the factors and the relationships among them. Until the problems are solved, an important hiatus will remain in our understanding of the functions of the body in health and disease.

At the present time numerous efforts are being made to determine the clinical significance of the laboratory findings above sketched. The first and to-date the most important contribution is the practical application of Aschheim and Zondek's discovery of the presence of a gonadotropic substance in the urine of pregnant women. The procedure employed, or a modification of it by Friedman, is the basis for the widely used "pregnancy test." By means of the test the existence of pregnancy may be determined within two or three weeks after conception and thus the prospective mother may have the maximal amount of time to make her plans for the coming baby. This early knowledge often serves to forestall awkward situations. Early fetal death can also be revealed by the pregnancy test and then measures be promptly taken to empty the uterus. Differential diagnosis between other types of stoppage of the monthly flow and that normal to pregnancy is similarly made possible. Assistance in the diagnosis of tubal pregnancy and differential diagnosis between true pregnancy and the growth of pelvic tumors is afforded. In the male the same test method is routinely used in the differential diagnosis between two types of tumors of the testis—one, malignant, and the other relatively harmless.

Another important practical application of the new knowledge is in the treatment of undescended testes in boys. In 3 to 5 of every 1000 boys these organs fail to descend into the scrotum; the result, if uncorrected, is always sterility, and the liability to malignant tumors is increased. Thousands of operations for placing the testes in the scrotum have been performed, with results which have been none too gratifying. After the demonstration that extract of pregnancy urine hastens the normal descent of the testes of young male monkeys (Engle, 1932) a considerable number of boys in whom that process had not taken place have been treated with the same preparation. Success has been attained in about half

of the cases from the hormone treatment alone and it is used as a helpful adjunct to surgery in others. Most of the potentially significant influences of the pregnancy-urine principle on other bodily functions remain to be worked out.

At the present time much hope is justified that endocrinology will have important contributions to make to the treatment of inadequate sexual development in girls and young women, despite the fact that numerous disappointments have so far been experienced from the use of A.P. or similar preparations. The relationships involved are complex and it is only as these are elucidated that consistently favorable results can be expected. In cases of sterility due to depression of ovarian functions, little of clearly proved value has yet been obtained from the estrogens, in women or monkeys, though some success in rats and rabbits has been achieved. More research is needed.

Treatment of certain cases of sterility in men appears to offer much promise. In all these instances the greatest need is for preparations of greater chemical purity, and for the application of scientific methods of evaluating clinical results.

We now have available in known chemical form three substances having properties of the male sex hormones (*androgens*), all of which have been made synthetically. The known physiological differences between these substances are slight—all give the same type of response on test animals but show different degrees of potency.

Clinical application of the male sex hormones has hardly begun. The McCullaghs of Cleveland have treated certain cases of depressed masculinity and a few cases of sexual impotence. The field needs wider exploration to determine the best uses of these hormones. They may prove to be important agents in the treatment of certain of the neuroses and

psychoses. Preliminary results in the Worcester State Hospital are hopeful.

The Adrenal Cortex

The functions of this structure are probably as multifold as those of the A.P. Extracts of the adrenal cortex have been prepared, particularly by Hartman and by Swingle and Pfiffner, which were assayed on the basis of prolongation of life in dogs and cats after removal of the adrenal glands. The study of the functions of the adrenal cortex, either by removal experiments or by administration of various cortical extracts, has become most interesting and valuable in the field of general metabolism and blood chemistry. Since the dog and cat have been the appropriate test animals for this work, extensive chemical observations may be made which would be impossible if rats or mice were used. In the absence of the cortical hormone (cortin), blood-urea and plasma-proteins increase. The deficiency characteristics are loss of appetite, muscular weakness, a severe drop in blood pressure and blood flow. The body temperature sinks and the animals are very sensitive to temperature changes. These effects become cumulative and coma and death ensue. It now appears, from the work of Kendall and Zwemer, that these various manifestations may be due largely to disturbance of the sodium-potassium balance in the body. Here again progress is impeded because of the impurity of the extracts that are available. Recent work, especially by Kendall, appears to be rapidly filling this gap.

Addison's disease has long been associated with atrophy and failure of the adrenal cortex. Great hopes were raised for the cure of this disease by the cortical hormone (cortin) but they have not been very satisfactorily fulfilled. Further purification of the preparations will doubtless lead the way to greater clinical usefulness as well as more precise experimental observations. There are now available suggestions

that cortin may have important uses in the treatment of a frequently fatal condition of dehydration in infants and in the exhaustion associated with infectious diseases.

Two other clinical states involving the adrenal cortex are of interest. These are the phenomena of genital precocity in children and pronounced masculinization in women. The precocity in children affects primarily boys. A tumor of the cortex is accompanied by a premature development of body hair, an over-growth of the secondary genital organs and the arousal of adult sexual impulses. In older women, a cortical tumor may frequently cause cessation of menstruation and development of virilism, with marked growth of a masculine type of body hair and beard. Frequently these virilistic characters may be expected to regress after operative removal of the tumor. It is probable that the hormone involved in these sex anomalies is a principle different from cortin—one that might be designated "*gonadotropic.*" Kendall has recently obtained a crystalline product from adrenal cortex tissue that has masculinizing properties and is, chemically, quite similar to the androgens. The work of Hoskins and his collaborators indicates that the adrenal cortex may produce a third active principle that increases blood pressure and stabilizes the circulatory system.

Recent clinical publications suggest that adrenal cortex preparations may come to have important value in the treatment of pernicious vomiting of pregnancy and of hay fever. The latter is a special aspect of allergy, a condition that is of widespread clinical importance. Should the preliminary results be confirmed, a medicament of major clinical significance will have been found.

The clinical picture of virilism indicates a pituitary-cortical interrelationship which is not well understood. The great difficulty in this field has been the lack of an experimental animal in which these features may be studied. In many forms, most of the symptoms of Addison's disease are re-

produced by adrenalectomy, but no animal has yet been found which will react to experiments so that any part of the clinical picture of sex-precocity or virilism may be reproduced.

The Thymus Gland

Lying in the upper part of the chest cavity is an organ, the thymus, which has long presented a challenge to investigators. It is relatively large in infancy and childhood, but shrinks with age. It persists in the juvenile form into the adulthood of castrates and enlarges when, for any reason, the adrenal cortex becomes depressed. Gland-extirpation studies served to suggest that the thymus has some relationship to bodily development but physiologists remained dubious of the evidence.

The first clean-cut positive findings were those of Riddle who showed that birds suffering from thymus disease were unable to produce normal eggs and that treatment with thymus substance corrected the difficulty.

More recently Hanson has succeeded in deriving a thymus extract which, in the hands of Rowntree and his associates at Philadelphia, has yielded very striking results in hastening the development of young rats. The effect is reported to be cumulative if the treatment is kept up through several generations. Such a result, however, is so contrary to accepted biologic principles that more than the usual amount of confirmation will be necessary to establish the validity of the claims that are being made for the new extract. If the work is confirmed, a promising therapeutic agent will have been found for the treatment of retarded children.

The Pineal Gland

It has long been known that the occurrence of tumors in the pineal gland is sometimes associated with marked precocity of sexual and bodily development. Experimental re-

moval of the gland in animals had given equivocal results. Pineal extracts had been shown a generation ago to cause a marked change in the color of the skin of tadpoles and, more recently, to hasten the development of tadpoles into frogs. In the higher animals, mostly negative results had been secured by various investigators until recently Hanson produced an extract which is reported to be significantly potent. Its properties have been studied by Rowntree's group at Philadelphia. It is reported to produce a cumulative effect when given in succeeding generations. The results are described as precocity of sexual development with depression of body growth so that dwarfism results. If this work is confirmed the extract may prove to be of value in the treatment of adolescent children who fail to develop sexually and continue to grow to inordinate height, and who explicitly need to come under the influence of just such an agent as Rowntree describes.

Centers for Research in the Above Phases of Endocrinology

Of the extensions now being made to our knowledge of the glands above discussed, a few of the more outstanding may be mentioned.

On the West Coast the important investigations of Evans and his collaborators on the various gonadotropic hormones and the growth hormone are being continued.

Excellent work in borderline clinical-experimental problems is that of Fluhmann of Stanford University Medical School. Other able workers are in Cole's group at the California Agricultural College, and Markee at Stanford.

In Los Angeles, Shelton is doing cautious and able work on problems of clinical endocrinology.

At Denver, Gustavson and D'Amour and associates are working on chemico-biological problems with particular reference to the female sex-hormone.

At Nashville, Wolfe and associates are studying the anterior pituitary and Burch is engaged on endocrine problems of gynecology. At St. Louis, the veteran pathologist, Leo Loeb, with many students, concentrates on the pituitary-thyroid relationship and Werner on clinical problems. Here, also, Doisy and a very active group are continuing investigations on endocrine chemistry—partly of the sex hormones but also the gonadotropic factors from urine. At Columbia, Mo., Overholser is making progress on clinical-gynecological problems. At the Missouri Agricultural School Turner has done much on the hormonal factors in lactation and McKenzie on reproduction. At the Mayo Foundation in Minnesota, Kendall has continued to report surprising things on the chemistry, first of the thyroid and recently of the adrenal cortex.

Chicago has naturally become one of the great centers for work in endocrinology. Moore's studies on the testis, Koch's on the chemistry of sex hormones and Thompson's on clinical problems of the thyroid may be mentioned. Wallen-Lawrence has worked on anterior pituitary derivatives. Geiling is known for his work on both insulin and the posterior pituitary. Ivy has for several years given special attention to the hormonal factors important in the functions of the digestive organs.

At Wisconsin, E. L. Sevringhaus and associates continue their excellent work on clinical endocrinology. At Cleveland the McCullaghs are doing good clinical work on the endocrine relations of the male; Zuck is young but active and able in both experimental and clinical work. At Columbus, Ohio, the work of Frank Hartman and his colleagues on the adrenal cortex continues to be outstanding.

The University of Rochester has Corner, whose name is identified with the corpus luteum, and who, with F. Allen, has done distinguished work. Willier and others here constitute this an important center.

At Detroit, Pratt, Moehlig, Schaefer and others apply endocrine physiology to clinical problems.

At Philadelphia, Friedman is engaged with gonadotropic hormones, Mazer with gynecological endocrinology and Rowntree with the startling new experiments on pineal and thymus extracts. If these reports on pubertal acceleration in successive generations are confirmed, they will mark a milestone in endocrine progress. Dunn's work on the hormone treatment of migraine and of adrenal virilism offers promise.

Baltimore possesses an able interpreter of experimental work in the gynecologist, Novak; the imaginative and stimulating Carl Hartman; and Richter, whose interests include problems of behavior and of metabolism involving most of the endocrine glands.

Hamblen at Duke University has indicated how satisfactorily clinical studies with gonadotropic and sex hormones may be conducted.

New York has so many centers that they can only be mentioned. Frank's work on the gonadotropic and sex hormones in relation to clinical problems is known the world over. Webster is doing excellent clinical and experimental work, particularly on the thyroid. Reynolds is a brilliant young man who is studying the influences of hormonal factors on the uterus. Riddle, near by, at the Carnegie Institution, Cold Spring Harbor, has done outstanding work on several of the hormones; his work on prolactin is especially noteworthy. Wintersteiner has effectively brought microschemistry into the endocrine field. The National Committee on Maternal Health acts at present as a clearing house of information and as a unifying and stimulating agency in all fields related to woman. The group, headed by Smith, while known best for the gonadotropic hormones, has touched upon numerous phases of experimental endocrinology and act as advisers and collaborators in many types of clinical experiments.

At Princeton, Swingle continues his work on the adrenal cortex.

New Haven is another center of endocrine research. Particularly prominent is the group headed by Edgar Allen, who are especially interested in the exploitation of the female sex-hormone—more recently in its relation to cancer.

Collip and Selye and their many collaborators at Montreal constitute a real endocrinological institute where both experimental and clinical work on a variety of endocrine problems is accomplished with increasing tempo. Toronto is the home of Marrian whose chemical work on the estrogens is second to none.

In Boston the observations of Rock on the clinical value of the female sex-hormone are promising. Cannon's group are engaged in a variety of activities in experimental endocrine physiology. Albright is conducting excellent studies in clinical endocrinology; his brilliant results in parathyroid disorders are especially well known. Means has long been noted for his work on thyroid disorders. At Cambridge Hisaw and Fevold are continuing their important research on the pituitary-sex relationships previously prosecuted at the University of Wisconsin.

Hormone Factors in Metabolism

The work that is now being done on the endocrine factors in the basic chemical processes of the body may now be discussed. Attention will be directed especially to studies in the special fields of carbohydrate, fat, protein, water and mineral metabolism and temperature regulation. Certain specific effects of various endocrine glands and their hormones upon these special metabolisms of the body are now well known and have received much intensive research. Other direct and specific effects are being discovered and investigated continually. Furthermore, important aspects of indirect control of metabolic processes are now receiving wide attention.

In the past decade, researches on the control and regulation of individual endocrine glands have greatly broadened our conceptions of the body's special metabolic mechanisms. Interrelationships, hitherto unknown or only vaguely suspected, have been clearly demonstrated. The physiologist now envisages an integrated and interacting system of hormonal regulators of metabolic processes and is able to speak of many of these in factual rather than in theoretical terms. The confusion at first engendered by these widened concepts is passing away, and renewed and vigorous attack is being enthusiastically directed at fundamental problems which were beyond approach a few years ago.

Carbohydrate Metabolism

The direct source of most of the energy, with which our daily life activities are carried on, is sugar. Elaborate chemical mechanisms are involved in the replenishment, storage and utilization of this substance. The best known manifestation of disturbed carbohydrate metabolism is diabetes mellitus.

The work of Houssay in Argentina, begun several years ago, is stimulating many researches on the role of the ***hypophysis*** in carbohydrate metabolism. In this country and in Canada the problem is being studied in the laboratories, among others, of Evans, University of California; Carlson, University of Chicago; Soskin, Michael Reese Hospital, Chicago; Best, University of Toronto; Cannon, Harvard Medical School; Chambers, Cornell University Medical School; Chaikoff, University of California; and Long, Yale University. The work of Long is of particular significance in that the relations of the pituitary, adrenal, thyroid and pancreas glands to carbohydrate metabolism are being studied simultaneously.

It is increasingly evident that the discovery and isolation

of insulin, important as it was, has left still unsolved many of the problems of *pancreatic diabetes.* The fact that often the victim of diabetes has seemingly adequate supplies of insulin in his pancreas has led to research towards finding principles, particularly in the liver, which may be destructive of, or antagonistic to, insulin. Rabinowitch of the Montreal General Hospital is perhaps the most active worker on this problem. Newer ways of preparing and administering insulin to increase its practical effectiveness are being tried in several laboratories and clinics, and in cooperation with commercial manufacturers of insulin. Sporadic attempts are still being made to discover substitutes that may be taken orally. Some further success is to be expected. The Armour laboratories in Chicago are preparing a duodenal extract that offers promise of efficacy. Other experimental investigations on the pancreas and sugar metabolism are being conducted by Cori, Washington University; Macallum, University of Western Ontario; Himwich, Albany Medical College; Soskin, Michael Reese Hospital, Chicago; Bischoff, Santa Barbara Hospital, California; Chambers, Cornell University Medical School; and Murlin, University of Rochester. Several of these workers are studying other endocrine glands, as well as the pancreas, in relation to carbohydrate metabolism.

The *adrenal medulla* and its hormone, *epinephrin* (adrenin), are known to play a part in the management of carbohydrate metabolism. Recently evidence has accumulated which indicates that the adrenal cortex also functions in this respect. Work on these problems is being prosecuted in the laboratories of Long, Yale University; Britton, University of Virginia; Hartman, Ohio State University; Chambers, Cornell University; Cannon, Harvard Medical School; Carlson, University of Chicago; Soskin, Michael Reese Hospital, Chicago; Grollman, Johns Hopkins University; Zwemer, Columbia University; and Cori, Washington University.

It has been surmised that the *thyroid gland* and the *gonads*

play secondary roles in the control of carbohydrate metabolism and occasional papers on these aspects are appearing.

Many of the main features in the story of the regulation of carbohydrate metabolism are now well in hand. Probably the most of the others have been advanced to the stage of working hypotheses for investigation. While there are still many details to be elucidated, it is likely that we are now on the threshold of a comprehensive new understanding of the physiological mechanisms involved in the body's use of carbohydrate. Our knowledge of diabetes will remain far from complete until these various mechanisms are worked out. With increasing knowledge, the treatment of the disorder will probably be substantially improved.

Fat Metabolism

Fat is the most concentrated energy-giving substance in the body. It is twice as effective per unit of weight as is sugar. It is in this concentrated form that most of our energy material is stored. It can readily be formed from other energy food. An intricate variety of regulatory devices are involved in the control of the digestion, assimilation, storage and utilization of fat. The penalty of a breakdown of these devices may be emaciation or obesity. Fatty substances are also important structural materials; the brain and the vitally necessary adrenal cortex contain relatively large amounts of fat derivatives.

The problem of the hormonal regulation of fat metabolism has proved to be a particularly baffling one and is, indeed, still obscure. There is, however, no lack of interest in this field. Some of the workers and laboratories investigating this phase of metabolism are: Collip, McGill University; Deuel, University Southern California; Evans, University of California; Soskin, University of Chicago; Murlin, University of Rochester Medical School; Lee, Harvard Medical School; Chambers, Cornell University Medical School;

Goldzieher, New York City; Blottner, Peter Bent Brigham Hospital, Boston; and Best, University of Toronto.

Accumulating evidence produced by these and other workers has led to an increasing conviction that several endocrine glands, notably the pituitary, adrenal cortex, pancreas, and gonads, play important roles in the metabolism of fats. New methods of approach to this problem are being used and it is to be expected that within a few years much clearer conceptions will be formulated of endocrine involvement in the mobilization, synthesis and oxidation of fats. When this happens this particular field will probably prove to be a popular and fruitful one for investigation. The important clinical problem of the control of obesity can not be much further advanced until the endocrine factors in the condition are resolved.

Protein and Nitrogen Metabolism

The endocrine regulation and control of protein metabolism has been another baffling problem and has received relatively little attention except in a few special phases such as the relation of the thyroid to creatine and creatinine metabolism. Since our muscular system is constructed largely of protein, a variety of important issues are involved. The increasing evidence of late indicates that the pituitary, thyroid, adrenal and thymus glands, are intimately involved in this phase of metabolism. Work on these problems is being carried out by: Gaebler, Henry Ford Hospital, Detroit; Perla, Montefiore Hospital, New York; Palmer, University of Minnesota; Lee, Harvard Medical School; Bodansky, John Sealy Hospital, Galveston, Texas; Chanutin, University of Virginia; Chaikoff, University of California; Rowntree, University of Pennsylvania.

A special phase of protein metabolism, in the production of milk by the mammary gland, is now well known to be under endocrine control. Active work on this phase is being

done by Riddle, Carnegie Institution, Cold Spring Harbor; Collip, McGill University; Gardner and Nelson, Yale University.

It is expected that the work now in progress will define more sharply the roles of these glands in protein metabolism and open approaches to the problems of growth, of protein storage and wastage in the body, and to certain clinical conditions such as myasthenia gravis and muscular dystrophy.

The processes of addition to the body's stores of protein in growth and after depletion by certain diseases, of changing body composition with age and the so-called endogenous nitrogen metabolism (the indispensable breakdown of previously formed cellular proteins), will probably prove to be subject to endocrine control and regulation.

Mineral Metabolism

A number of phases of endocrine control of special mineral metabolisms are being investigated at the present time. The relation of the parathyroid glands to calcium and phosphorus is being studied both clinically and experimentally, among others, by Albright, Massachusetts General Hospital; Aub, Huntington Hospital, Boston; Collip, McGill University; Hastings, Harvard Medical School; Riddle, Cold Spring Harbor; Barr, Washington University; Richter, Baltimore.

Problems on the relation of the thyroid gland to iodin metabolism and the relation of iodin to goiter, myxedema and hyperthyroidism are being actively investigated in a number of laboratories and hospital clinics. Among the workers are: Means and his co-workers at the Massachusetts General Hospital; Thompson, University of Chicago; Friedgood, Harvard Medical School; Rapport, Tufts Medical School; McCullagh, Cleveland Clinic; Curtis, Ohio State University; McClendon, University of Minnesota; Marine, Montefiore

Hospital, New York; Watson, University of Western Ontario; and Loeb, Washington University, St. Louis.

The relation of the adrenals to mineral metabolism, especially as regards potassium and sodium salts, is being actively studied by Kendall, Mayo Foundation, Rochester, Minn.; R. F. Loeb, and Rogoff, University of Chicago; Grollman, Johns Hopkins University; and Zwemer, Columbia University.

An important practical aspect of this particular work is the possibility of treating cases of Addison's disease with salt therapy, with or without the addition of adrenal cortical hormone.

Water Metabolism

Since water is the solvent in which the multifarious chemical processes of the body are carried out, the importance of full knowledge of how the water content of the body is regulated is obvious. The problem of obesity is, to a considerable extent, one of water control. Under certain conditions sufficient water may be retained in the body to cause genuine intoxication; this may greatly exaggerate any tendency toward epilepsy that a given patient may have. "Dropsy" and other forms of edema represent breakdowns of water control.

How and why water is required, distributed and utilized in the body constitutes a set of physiological problems, the full importance of which has only recently been appreciated. The storage and liberation of water by body tissues depends upon a variety of physico-chemical and metabolic factors, many of which are directly or indirectly subject to endocrine control and regulation. The chief endocrine glands concerned are probably the pituitary and adrenals. Research on the relation of the adrenal glands to water metabolism is being done by Swingle, Princeton University; Hartman, Ohio State University; and Grollman, Johns Hopkins University; McQuarrie, University of Minnesota; Adolph, University of Rochester; and Geiling, University of Chicago.

Control of Endocrine Glands

In the above, little has been said of the indirect regulation and control of the special phases of metabolism through the mediation of the pituitary gland. The thyroid, parathyroid and adrenal glands and the gonads themselves are controlled, to greater or less extent, by anterior pituitary hormones. Hence their special metabolic functions are indirectly influenced by the pituitary.

This is probably the most active line of endocrine investigation at the present time. Many important results, both for clinical application and for the development of physiological knowledge, have already been forthcoming and many more are in prospect. Many American laboratories are directly participating in this work.

Centers in which such metabolic work is in progress are: Columbia University, Department of Anatomy; University of California, Departments of Physiology, Anatomy and Biochemistry; University of Chicago, Department of Physiology; University of Pennsylvania, George S. Cox Institute and Philadelphia Institute for Medical Research; Harvard Medical School, Department of Physiology; Cornell University Medical School, Department of Physiology; Massachusetts General Hospital, Boston; Michael Reese Hospital, Chicago; Montefiore Hospital, New York; McGill University, Department of Biochemistry; University of Toronto, Department of Physiology.

Temperature Regulation, Heat Production and General Metabolism. No more than a single attack of fever is needed to convince any one of the practical importance of bodily heat regulation. The internal factors which determine the production and conservation of body heat and the maintenance of constant body temperature, are partly endocrine in nature. Although much is already known as to the action of these endocrine factors, fruitful investigations in this field continue

to be made. Practically every metabolism laboratory and clinic concerns itself to some extent with endocrine factors. The succession of scientific papers from these laboratories and clinics attests the constant progress that is being made.

The adaption of the body's metabolic mechanisms to seasonal and climatic variations in temperature has been a rather neglected field of endocrine investigation. It is now receiving renewed attention and promises to yield important results. The researches at present center around the thyroid gland and the adrenal cortex. They are being carried on at the Cold Spring Harbor Laboratory of the Carnegie Institution; at the Nutrition Laboratory of the Carnegie Institution in Boston; at the Harvard Medical School; University of Buffalo; University of Rochester; Columbia University; University of Texas; and at the Carnegie Institution Laboratory in Baltimore.

It is to be expected that studies in this field will define more precisely the roles of the thyroid, adrenal and subsequently of other glands, in the adjustment of the body's heat economy to sudden changes in environmental temperature, to more gradual seasonal and climatic changes and possibly to the changing requirements with age.

Endocrine Factors in Behavior and Personality

That the hormones play a significant role in personality and behavior has been indicated in various earlier paragraphs. One has but to compare the condition of a victim of cretinism before and after treatment with thyroid substance to appreciate the sluggishness of brain and flatness of emotional life that we who are normal escape by the beneficence of our thyroid glands. The strutting, belligerent cock owes his virility to his sex hormones. The boy or girl deprived of the sex glands is doomed to perpetual childishness of form and to emotional immaturity. Several writers have recently

ascribed to pituitary deficiency in children an exaggeration of such unfortunate traits as egotism, stubbornness and irresponsibility. The psychological aspects of endocrinology have been sadly neglected by specialists trained to deal with problems of personality but enough is now known to assure us that personality without the hormones is scarcely personality at all.

The practice of medicine in America is undergoing a transition. The infectious diseases are being conquered and the treatment of metabolic disorders is becoming increasingly successful. The stresses of life, on the other hand, are increasing. Thus it comes about that more and more of the patients who come to the physician are those presenting functional or personality, as contrasted with organic, disturbances. More than half of all hospitalized patients in this country are in institutions for the nervously and mentally ill. The psychological aspects of medicine are therefore coming more and more to claim the attention of both general and special practitioners. The role of the hormones in personality is thus a topic of increasing practical importance.

The personality is dependent in part upon what we bring into the world and in part on what the world does to us after our arrival. Of the initial equipment the endocrine organs are important elements. The life experiences also impinge in substantial measure upon the glands. The hormones thus play a large role in the finished personality. Personality depends in part upon the mentality but more upon the instinctual trends and their accompanying emotions. All three are subject to endocrine influences.

Of the avenues which are open for research on personality, experiments on animal behavior offer considerable promise. From these, basic principles may be derived. Few experimental endocrinologists, however, record or report the effects of their various procedures on the reaction patterns in other

than a superficial way, if at all. On the other hand, psychologists who are technically better equipped than psysiologists to study such matters have been little attracted to the field of experimental endocrinology. The current rapid progress in the production of potent and reliable endocrine substances is rendering practicable the study of an increasing variety of problems in animal behavior. From such studies much could be learned of the instincts and their control. Riddle's recent work on prolactin in relation to the maternal behavior pattern illustrates the possibilities in this field. Collip's report of a wolf-hound puppy that was converted into a whimpering coward by the loss of his pituitary and restored to vigor and courage by pituitary extract also arrests our attention. Just enough is known of such matters to assure us that we need to know much more.

In principle, the administration of potent glandular products to human beings amounts to a special type of experimentation but with the advantage over experiments on lower animals that the mentality and the emotions, as well as the physiological changes, can be studied. Psychologists now have available numerous well-standardized methods for examining such matters. The effects of human glandular disorders on the personality factors also give scope for study.

Finally, productive work can be done by learning the endocrine conditions and the effects of hormone therapy in the various nervous disorders, including the psychoses.

Not only is the effect of hormones upon functions of the nervous system important but likewise the influence of the nervous system on hormone production. Cannon's evidence that emotional stress causes discharge of adrenine is well known. There is evidence, little, if at all, short of proof, that the thyroid is similarly stimulated to augmented function by such stress; in the background of case histories of patients having exophthalmic goiter "emotional trauma" is frequently

found. The work of Brooks indicates that the excitement of erotic situations stimulates the anterior pituitary and Friedgood's recent observations suggest that the effect is mediated, in part, by the sympathetic system.

Some of the hormone-nervous relationships suggested are now under study in various institutions.

1. *Endocrine Treatment of Psychotic Patients.* The possible value of glandular treatment of the psychoses, chiefly by the administration of *estrogens* is being investigated in a number of different clinics and state hospitals. It is of importance, not only for the immediate help which it has been reported to give certain patients, but also for the light it throws on the causes of these conditions. Werner and his collaborators in St. Louis are experimenting with estrone administration and report good results, particularly in involutional melancholia. Sevringhaus in Wisconsin is also using this treatment with some success.

The estrogen in untreated pregnancy urine had been found to have a very strong stimulative effect in rats deprived of their sex glands. Applying this discovery, Richter has recently treated sixteen patients with different types of psychoses in a State Hospital near Baltimore with dried pregnancy urine administered in capsules. Seven of the patients showed a marked improvement; two left the hospital after six weeks' treatment. After several months' treatment three patients menstruated for the first time in 1½, 2, and 2¼ years, respectively.

Hoskins and his associates at the Worcester State Hospital are studying the effects of thyroid, adrenal and male sex-hormone administration.

Muncie and Katzenelbogen of the Phipps Clinic Staff at the Spring Grove State Hospital are testing the insulin-shock treatment of schizophrenics. Thus far only a small number of

patients have been treated. However, two patients in a deep stupor have shown remarkable improvement. Cameron has also several patients under treatment at the Worcester State Hospital with promising results. Sakel and other investigators abroad have had more extensive experience than have the American psychiatrists; their results have been remarkably favorable.

Howard of the Medical Division of the Johns Hopkins Hospital has organized an endocrine clinic which serves as a central endocrine station for the Hospital and functions in conjunction particularly with the Departments of Psychiatry and Genito-Urinary Diseases. The latter clinic receives a variety of remarkable and interesting patients. In this Clinic the emphasis is put on the mental changes which accompany definite glandular alterations, rather than, as in previous studies, on the glandular changes present in psychotic conditions. Both points of view are obviously useful. The opportunities for clinical study of this set-up with its well-balanced collaboration seem to be excellent. Howard, himself, is working on a number of special problems but at present is most interested in mild forms of masculine hair-growth in women who are otherwise normal but are greatly distressed by their unfortunate appearance.

Research on the effects produced on behavior by removal of the different glands has been confined largely to studies of the factors involved in the control and regulation of spontaneous activity. This work has been done largely in Hoskins' laboratories in Ohio and in Boston and in Richter's laboratory at the Johns Hopkins Hospital. The method is to keep small animals in revolving "squirrel cages" and to record automatically the distance they run each day. The object of this research has been to determine the factors involved in the maintenance of the different levels of activity of normal animals; the different means by which animals may be made hyperactive (experimental mania); the different means by which

they can be made inactive (experimental depression); and finally how, by replacement therapy, they can be returned to their normal levels of activity.

Inasmuch as great differences in activity, alternations between periods of great activity and almost total inactivity, are the chief characteristics of one of the most common of mental illnesses, the manic depressive psychosis, the results of these experiments on animals should ultimately be helpful in determining the causes of that disorder. Thus far, the hypophysis, the thyroid, the adrenal, and the sex glands have been found to play the chief roles in the regulation and control of movement. It has been found that regular cycles of activity, comparable to those found in manic depressives, can be produced by sections of the pituitary stalk, by removal of the parathyroid glands, and by injuring the ovaries. Activity has been shown to be the most delicate means of measuring glandular replacement therapy.

Similar studies are being carried on in the Phipps Clinic at Johns Hopkins and in state hospitals on patients. The activity is measured by means of pedometers.

A study of the output of sex hormones by patients offers another means of investigating endocrine factors in the psychoses. A beginning of such investigations has been made by Harris at the New York Psychiatric Institute and Hospital and by Hoskins at the Worcester State Hospital.

The mental hospitals that are at present most active in studies bearing on the endocrinology of psychotics are the Phipps Clinic, the Worcester (Mass.) State Hospital and New York Psychiatric Institute and Hospital. Such institutions offer wonderful opportunity for research and only more adequate funds are needed to increase their output. Since psychiatrists, as a group, are overwhelmed with routine duties, the funds are especially needed to permit increase of personnel.

Recently Richter has found that the removal of various endocrine glands produces marked changes in *appetite*. For instance, adrenalectomized rats showed a tenfold increase in their voluntary salt intake. So also parathyroidectomized rats showed a large increase in their appetite for calcium. Of particular interest in these experiments was the fact that by virtue of these changed appetites the adrenalectomized and parathyroidectomized rats were able to keep themselves alive and free from symptoms of salt or calcium insufficiency. This work reveals a new approach to problems of metabolism. It is possible that our knowledge of glandular function may be increased by this method of letting the animals themselves disclose the needs created by the removal of the different glands.

Liddell and Hartman have recently published the results of a brilliant study in which cortin was shown to have a potent influence in the amelioration of experimental neuroses in sheep. Their methods could be extensively applied in the study of other hormones.

Innervation and Blood Supply of the Endocrine Glands

Work on the innervation of the endocrine glands is at present centered on the pituitary, particularly in relation to the effects produced on water metabolism by lesions of different parts of the innervating mechanisms. Ranson and his collaborators, Ingram, Harris, and Fisher, in Chicago, have contributed very actively to the solution of this problem. They have been able to trace the nervous pathways from a center in the brain, down to the pituitary stalk and into the posterior lobe of the gland. Their work has significance for the understanding of the nervous control not only of the pituitary gland, but of the other endocrine glands as well.

Mahoney of Yale, in collaboration with Sheehan, is also doing excellent work on the nervous control of the pituitary

gland and on the production of diabetes insipidus. He has shown that the maintenance of diabetes insipidus is dependent in part on the thyroid gland—an entirely new conception. He has shown also that stalk-section gives different results in different species of animals, thus indicating that other factors than mere destruction of the nervous pathway will have to be taken into account in explaining the cause of diabetes insipidus. Richter's laboratory has shown that the anterior lobe also plays a role in the maintenance of diabetes insipidus; and that the excessive output of urine resulting from hypophysectomy in stalk-section is antecedent to the increased thirst.

Wislocki has added to our knowledge of the blood supply of the hypophyseal region by means of a study of the distribution of different vital dyes. The work carried on with Geiling on the whale and other animals should add even more useful knowledge toward a fuller understanding of the sources of production of the secretions and their channels of transmission into the blood stream and central nervous system. Brooks, working in Bard's laboratory at Johns Hopkins is studying the degeneration of nervous pathways in the brain stem produced by different locations of lesions in the pituitary stalk. Friedgood at Harvard is working on the pituitary and ovarian changes produced by electrical stimulation of the cervical sympathetic nerves to the pituitary gland. The results of these experiments bring for the first time definite evidence of nervous control of the pituitary through the sympathetic nervous system.

In final reiteration it must be emphasized that the study of the endocrine factors in animal behavior and in human personality and its disorders, as well as study of the nervous system and the endocrine organs in their mutual relationships, has lagged far behind the studies in physiological and clinical endocrinology. Perhaps no field of investigation is more promising, in terms of human happiness, than this.

Organizations Interested in Endocrinology

In the foregoing paragraphs an attempt has been made to indicate the lines of research that are being most actively prosecuted and the chief institutions in which the work is being done. The individual investigators receive much stimulus and help from their connections with professional societies. The annual programs of the American Medical Association usually include a considerable number of papers on endocrine topics. The societies devoted to internal medicine and to some of the specialties such as gynecology also frequently include endocrine reports in their programs. Of recent years the meetings of the American Society of Anatomists and of the Federation of American Societies for Experimental Biology have been devoted in very substantial measure to reports on endocrine investigations. Special interest attaches to the Association for the Study of Internal Secretions. This organization was founded twenty years ago in an attempt to stimulate investigations and coordinate activities in the endocrine field. Although membership is not nationally restricted it is made up so largely of American investigators as to constitute it, in effect, an American institution. The Association customarily holds two all-day sessions a year for the hearing and discussion of papers reporting researches in laboratory and clinical endocrinology. It publishes a journal, *"Endocrinology,"* that is the leading scientific periodical in this field. In addition to the publication of original articles it furnishes an abstract service in which the essential content of the more significant endocrine articles published throughout the world is made easily accessible.

IV ENDOCRINOLOGY OF THE FUTURE

The endocrinology of the past and of the present has been largely opportunistic. The classical first experimental approach to the hormone functions of any gland is to remove it and note the effects either anatomical or functional. Any de-

fects thus set up are likely, though not necessarily, to be ascribable to an induced hormone deficiency. The next general step is to attempt to normalize the disturbed functions by the administration of gland products, either by mouth or by injection. Having proved the efficacy of the given glandular derivative the third stage is to isolate the "active principle" and to identify it chemically. The final stage is to reproduce the active agent by chemical means (synthetically). These general experimental procedures have been supplemented in various ways by observations on human patients showing spontaneous or surgically induced endocrine abnormalities. A great majority of researches hitherto carried out have fallen into one or the other of these general categories. The successes in prosecuting them have constituted one of the most brilliant chapters in the history of biological and medical advancement. Nevertheless many things remain to be done not only within the bounds mentioned but also in the filling of gaps that a systematic consideration of the whole field discloses as needing attention.

Glandular Deficiencies

Broadly speaking, the complete gamut of effects of the destruction of any given endocrine gland has never been adequately determined. It is to be anticipated that many increments of our knowledge could be derived by extending this type of studies to all measurable functions of the body. For example, it is totally unknown what effect parathyroid deficiency has upon the amount and composition of the bile. Many similar gaps could easily be mentioned. The knowledge is especially needed by clinicians to aid them in reaching accurate diagnoses of endocrine defects in their patients.

Physiological Effects of Glandular Derivatives

Similarly defective is our knowledge of the detailed influences of the administration of any given glandular deriva-

tive. What effect has testosterone upon the secretory or motor functions of the digestive system? What is the influence of parathormone upon the development of the brain? Again many such questions could be asked and each constitutes a legitimate problem for research. Not only are the answers needed for the systematic rounding out of physiology and pathology, but likewise to furnish a guide to clinicians in their use of such substances therapeutically. It is highly important to know not only what are the immediate and intended effects but also of the by-effects, either good or bad. Until this knowledge is available the clinician must proceed blindly and may either do unwitting harm or fail to realize potential gain. Let it be said, then, that we need accurate determinations of the effects of each of the active principles—natural or synthetic—on the functions of each of the organ systems—including such processes as *weight, growth, development, irritability, motor and secretory activities, absorption, assimilation* and *tissue* metabolism. Many items of this category are still lacking.

Factors Determining Reactions to Hormones

The discussion up to this point has assumed that the only necessity is to isolate and determine the properties of the various hormones—the tacit assumption being that the experimental animal is a constant. As a matter of fact he is a composite of "x's" quite as complex as the endocrine "y's." Hitherto too little attention has been paid to the factors which determine the reaction to a given hormone. Riddle has recently reported that even so fundamental a reaction as the basal metabolic response to thyroid may be completely overthrown by changing the *temperature* at which the test is made. In the case of adrenine it is known that the blood pressure may be made to rise or to fall, depending upon the amount that is given. Similarly, thyroid hormone may cause a marked gain or a marked loss of weight, again depending upon dos-

age. A sizeable problem confronts us to determine whether this principle of *diphasic response* to varying dosage is a common characteristic of hormones. Just now a study of insulin from this point of view seems to offer promise of results that are of special interest to the clinician. If such diphasic response should prove to be a general characteristic of hormones, many a puzzling contradiction of data might thus be explained.

But there are other factors than dosage that determine reactions. Fragmentary evidence indicates that some of these are the degree of *acidity* or *alkalinity* of the reacting tissues, the temperature of the tissues or of the environment, *diet, vitamine and salt balance,* and the amount of the various *other hormones* to which the tissue at the given time is being subjected. The effects of these and perhaps other variables should be systematically explored. No doubt each of the hormones would need to be dealt with separately. Such an investigation would break up into many sub-problems.

A special phase of the problem of body reactivity is that of *acquired tolerance.* With some of the hormones the more given, the more must be given to produce the desired effect. Lisser, for instance, has reported the case of a child suffering from chronic tetany who at first responded gratifyingly to parathyroid extract but who became increasingly resistant and finally died in spite of the use of heroic doses. By the use of thyrotropic hormone the guinea pig can readily be thrown into an attack of a disorder closely simulating human exophthalmic goiter, but the effect soon wears off even though the dosage is continued. In the use of adrenine in the treatment of asthma the dosage often has to be gradually increased. More knowledge is needed as to the way tolerance is acquired.

Another important variable in the operation of endocrine factors that has received only desultory attention is the *genetic.* We know that the guinea pig is more suitable for some tests than is the rat and that the monkey reacts differently than

the mouse, but there is nowhere in the literature a systematic list of such *species differences* as are known. Even were this available, however, the gaps would be much more prominent than the items that have been determined. For example, what effect has progestin on the secretion of gastric juice in species A as compared with species B or indeed in any species at all? There are many permutations of the known active principles and the available experimental animals that have received no attention whatever. Before endocrinology shall have reached the full status of a systematic science, these permutations will have to be worked out. Many individual problems are suggested here. There is practical need for a considerable extension of studies of the type mentioned to permit the differentiation between general biological principles and species peculiarities.

But even within a given species, considerable variability may exist. Riddle, for example, has learned that twenty times as much prolactin is required to elicit a given crop response in one strain of doves as is needed in another strain to bring out the same reaction. Some strains of rats appear to be more susceptible to adrenal deficiency than are others. This topic becomes of special interest when we think of the human species. It seems obvious that if one kind of people were ten times as reactive to a given hormone as some other kind, considerable differences in their liability to endocrine disorders might thus arise.

One is then led to wonder whether there are as great differences in the *ability to produce hormones* as there are in the ability to react to them. The theory that evolution may have been guided through the agency of the endocrine glands is well known. The recent astonishing results reported by Rowntree, Hanson and their collaborators on thymic and pineal extracts when given through successive generations have brought this possibility into sharp focus. As Stockard has emphasized in the case of dogs, "endocrine types" are heredi-

tary. Thus the Great Dane is a giant and the Pekingese a dwarf in the technical as well as the common sense of those terms. The problem is twofold: is the Great Dane a giant because of an hereditary *high level of efficiency* of his pituitary gland or because of *high susceptibility* to the growth hormone? Stockard has come to lean toward the latter possibility as the probable explanation.

From the standpoint of the practical clinician perhaps the most important phase of heredity concerns endocrine diseases, as such. From this point of view it is more or less immaterial whether the thing that is inherited is on the one hand a special susceptibility to a given hormone or on the other a special level of glandular efficiency. Suppose that one's grandmother died of exophthalmic goiter. Does that establish any special probability that he will develop the same disease? Another practical phase of the problem is whether specific endocrine disorders are inherited as such or whether there is such a thing as tendency to endocrinopathy in general. In other words, would the grandmother's exophthalmic goiter have any tendency to make the grandchildren liable to Addison's disease? Other obvious questions in genetics are whether a hereditary endocrine peculiarity is sex-linked as is the tendency to hemophilia, whether it is dominant or recessive, and whether singly or multiply determined. These ramifications of the general problem are sufficient to give scope for many investigators working for many a year. The whole problem is in need of systematic study.

Another variable in the hormone equation is the *age factor*. By and large we know that kittens react somewhat differently to endocrine manipulation than do adult cats. But only fragments of knowledge on this general problem are yet available. The pediatrician has special need for the solution of two phases of this problem, namely, the endocrinology of the fetal and that of the prepuberal ages. How is the *development of the fetus* influenced by the endocrine functions

of the mother? How is the transition from maternal *hormonal support* to *postnatal autonomy* achieved? Conversely, what part do the hormones of the fetus play in determining the phenomenology of pregnancy in the mother? These hints may serve to suggest several lines of systematic exploration that are needed.

Parenthetically, we are somewhat better informed about endocrine factors that play a part in determining whether the infant can begin existence at all. But many things yet remain to be learned regarding the *endocrine factors* in *sterility* or *fecundity*. Many a family has to remain childless, there is reason to believe, because of our ignorance here.

We need, also, much more knowledge of the endocrinology of old age. To what extent is *senescence* determined by hormone factors? What could be done by control of these either to delay its approach or to mitigate its effects? Werner's recent results in the treatment of involutional melancholia by esterone suggest that endocrinology may have important contributions to make. It would be unfortunate to see in the problem nothing but the possibility of sexual rejuvenation. From the broadly biological point of view the individual who has made his contribution to the perpetuation of the species is a superfluity, but from the more narrowly human point of view, the mere passing of years is not in itself an adequate reason for euthanasia. The old man, if with age he has attained wisdom, still has great social value. The mere prolongation of existence might be a dubious boon, but anything that would add to the productivity and enjoyableness of the last years would be worth while. In any case, as a matter of rounding out knowledge, the endocrinology of senescence and senility ought to receive further systematic attention. As in various other instances, this general problem breaks down particularly into two sub-problems, namely, the reactivity of senile tissues to the given hormone and the relative efficiency of hormone production by the individual's own glands.

Control of Hormone Production

A problem that is ever with us and toward the solution of which progress is but slow is that of the *control* of the endocrine glands. The hormones largely regulate the body but what regulates the regulators? We know that excitation of the sympathetic nervous system by emotions or otherwise causes a discharge of adrenine. The thyroid gland seems to share in the excitation. Erotic excitement seems to stimulate the pituitary. Some glands are set into activity by the hormones of other glands and some perhaps are depressed by similar agencies. More significantly, we know that the glands of most people most of the time are by one agency or another kept in a suitable state of activity or of quiescence. By and large, however, our knowledge of the control of hormone secretion is in a fragmentary state. As a particular phase of this problem, the question of *secretory centers* in the brain needs investigation. There is some reason to suspect that from this point of view it would be profitable to explore the hypothalamic region. Especially do we need to know the effects of prolonged *emotional strain* and of *environmental vicissitudes* on the various glands. As soon as the psychologists come seriously to grips with the aspects of endocrinology in which they are especially concerned, they will insist upon much more adequate knowledge than is as yet available regarding the repercussions of life experiences in the endocrine apparatus. Many individual problems—and they promise mostly to be difficult problems—will have to be solved before we can walk with assurance in this part of our field.

Hormones and the Nervous System

In an earlier paragraph stress was laid on the desirability of determining the influence of the various hormones in each of the organ systems. Special importance attaches, however, to the nervous system. It is known that thyroid deficiency in

tadpoles results in marked lagging of brain development and the offspring of human mothers suffering from serious thyroid deficiency apparently show a comparable condition. During infancy and afterward, thyroid deficiency can likewise bring about all degrees of mental retardation. But when these facts have been recited, we are about at the end of the story as it is known today. The mere statement of this fact implies the need for many studies of hormone factors in brain development and function. It is probable that different parts of the brain should be investigated separately. Perhaps it will be found that the ancient thalamic region where the vegetative processes are controlled may show special relationships to the hormones. It is here, perhaps, that the internal secretions chiefly impinge in exerting their important influences upon the instinctual life.

Pottenger has often called attention to the fact that, from the standpoint of the clinician, with his special interest in symptomatology, the relationship of the hormones to the functioning of the autonomic nervous system is a matter of special importance. That the relationship is close in some instances is well known. In effect, the sympathetic system and the adrenal medulla function largely as a unit. The imagination of clinical theorizers has been especially intrigued by such relationships, which offer suggestions for the explanation of much obscure symptomatology. The problems, however, in their physiological aspects have received relatively little systematic investigation. Some twenty years ago, Hoskins and collaborators studied the influence of a variety of gland extirpations on sympathetic reactivity, but the parasympathetic system which is in equal need of systematic exploration has not received even this modest attention. The effect of administering the various hormones upon either sympathetic or parasympathetic reactivity has been little studied. These are topics of signal importance both to physiology and to clinical medicine.

That hormones may greatly modify behavior is well

known, and it is highly probable that the influence is largely mediated through the central nervous system. For example, Bard has been able to induce in a spayed cat a state of prolonged estrus in which the complex reaction pattern with its curiously ecstatic episodes was maintained for weeks on end. Of similar import is Riddle's observations on the influence of prolactin in bringing out the maternal behavior pattern in rats. A given young rodent miss one week is completely oblivious to babies that may be offered to her for adoption. The next week, after a few injections of prolactin, she will eagerly adopt and mother as many as may be placed in the cage with her. Her maternal yearning seems to have become universal. Not only will she cherish infants of her own species but also baby mice, baby rabbits, or indeed, even squabs. For a healthy adult rat to do other than make a prompt meal of a proffered squab betokens a fundamental change in her disposition. What is the explanation of the change? The reacting organs are the same, the energy of the system is the same, yet the reaction is strikingly different. We seem to be introduced here to what may well prove to be a far-reaching biological principle that may be designated as "chemical conditioning." That we "learn" by experience has long been known. It now appears that we can also "learn," and that with remarkable promptitude, by the injection of a hormone. The question may well be raised, to what extent conditioning in the ordinary sense may depend upon hormone factors, and to what extent experiential conditioning and hormonal conditioning may fundamentally amount to the same thing. That a genuine relationship exists is indicated by the recent work of Liddell and Hartman. These investigators, by a process of experiential conditioning, first set up in sheep a state that could fairly be described as experimental psychoneurosis, and then by injections of cortin succeeded in ameliorating the condition. To what extent the psychoneuroses of man may be dependent upon, or amenable to treatment by, hormones presents a problem of no little importance.

Endocrine Diagnosis

One of the major problems in clinical endocrinology is that of diagnosis. The current practice is to learn as accurately as possible the life story of the given patient and from the vicissitudes disclosed attempt to make an educated guess as to the operation of hormone factors past and present. The next procedure is to make a careful physical examination and from the amount and distribution of fat, bodily proportions, hirsute peculiarities and skeletal structure deduce, as well as may be, the endocrine status of the patient. In an occasional instance the sign-boards thus discovered permit an adequate diagnosis of at least the major endocrine disorders. But there are many cases in which only a suspicion of explicit endocrine malfunction can be achieved. The laboratory is then called upon for further enlightenment. Routinely a basal metabolism test is scheduled, and almost as routinely a false high reading is obtained. Blood counts, sugar tolerance tests and chemical and urine analyses are added to the ritual and with an occasional informative positive result, but often with dubious or equivocal findings. Various special tests such as fat or protein tolerance have been proposed, but the status of these is by no means sure. Since both depend upon basal rate determinations, they partake of the uncertainties of the latter. The late Allan Winter Rowe spent twenty years studying the metabolic pictures presented by thousands of patients who showed various evidences of endocrine disorders. So great, however, is the complexity of the general problem that many more studies such as those initiated by Rowe are needed. There are said to be over two thousand tests of physiological functions that are clinically feasible. From these it is likely that a considerable number could be selected that would be specially informative as to endocrine conditions. Each of the selected tests should be systematically made on an adequate number of patients who present clean-cut glandular disturbances. From the results it might be possible to build up com-

binations of findings — metabolic patterns — that would be characteristic of each glandular disorder. This procedure, indeed, was the basis of Rowe's work. The chief difficulty in such a project is to obtain enough subjects with sufficiently uncomplicated uniglandular disorders. It can be taken for granted that most patients available for such tests will have been suffering for a considerable period of time, and a variety of secondary changes will have taken place. It is not improbable that in the end a large part of the exploratory work will have to be done on monkeys in which the glandular disorders are created especially for the occasion and the tests made while the primary effects are still clearly operative. This project would demand rather extensive financial resources and the full time of a considerable body of investigators over a period of years. It goes without saying that both glandular deficiencies and glandular excesses should be studied.

So much for acute conditions. It would also be profitable to study the chronic effects of glandular disorders by the same general plan. In this latter project, not only should vital function tests be used, but also gross and microscopic studies of growth and development. True it is that many individual researches on a variety of animals have been made to this general end but the work should be re-done systematically on a primate and with control of such important variables as sex, diet and nutrition, hygiene, age, climate and season.

Experimental Glandular Disorders in Primates

Allusion has been made to secondary complications of glandular disturbances. These include organ hypertrophies (splanchnomegaly) such as are seen in experimental acromegaly, organ atrophies, defects in growth and particularly effects in related endocrine organs. Much has been written and considerable has actually been determined regarding the influence of one gland upon another, but here again our

knowledge has not been adequately systematized and various important variables have not been adequately controlled. Likewise, most of the work has been done on the lower animals with corresponding uncertainty as to the extent to which they are applicable to our own species. This undertaking, too, should be systematized with adequate control of the environmental variables. Each of the glands should be eliminated from the biological equation and the acute, as well as the chronic effects in other glands, determined. Similarly, the acute and chronic effects of administering the various hormones should be further worked out. Such a project would necessitate the use of a large number of monkeys—particularly since the experiments would have to be carried out separately in the different age groups and the two sexes. A great deal could be saved in the way of overhead expense if this project were combined with the diagnostic project previously mentioned.

Hormone Factors in Disease

Another much needed line of development is elaborate study of the influence of hormone factors in disease generally. Well known is the fact that diabetics are prone to boils and to cataract. The suggestion has been offered that susceptibility to poliomyelitis may be determined in substantial measure by hormonal influences. Anti-body formation and other immunity mechanisms may be significantly determined by these same factors. Claims are not lacking that arthritis may be influenced either in its incidence or in its course by the same agents. Evidence has been offered that adrenal deficiency renders the subject more vulnerable to the toxins of bacteria. Other hints of this sort could be cited, but they would serve rather more to emphasize our ignorance than our knowledge. Time was in the memory of living men when pathology—the "grave-yard pathology" of that day—was a matter of little significance to the practical physician.

It was not until the pathology of the old days was wedded to the physiology of that time that it became the meaningful foundation of practical medicine. But the physiology of those days was not the physiology of today. Modern physiology is shot through with endocrinology. The pathology of today has scarcely even begun to incorporate modern endocrinology. One of the major needs, then, is an adequate determination of the influence of hormones on the incidence and progress of diseases in general. Endocrinology will not have reached its full fruition in practical medicine until its relationships to general pathology shall have been clearly worked out.

Endocrine Factors in Personality

In an earlier paragraph attention was called to the relative increase in the number of patients presenting "functional" as contrasted with organic disorders. It is a substantial sign of progress that physicians are becoming increasingly alert to this situation and are giving more and more attention to what might be called psychological medicine. But endocrinologists have as yet shared but little in the growing enlightenment. Their thought is still of thyroids, of estrus, of growth or what not, but little do we hear from them of the person in whom the interesting happenings are taking place. Equally unfortunate is the fact that trained psychologists are giving little attention to endocrinology. Thus one of the major problems in this field, that of the relationship of the hormones to personality, is largely going by default.

We know of the subdued truculence of the hypothyroid and of the stridulent captiousness of the hypogonad subject. We are being assured with increasing frequency that problem children are often victims of glandular perturbations. We hear of irascibility corrected by parathyroid extract. Hyperinsulinism has, as a matter of record, led to diagnoses of hysteria and of dementia praecox. Thyroid deficiency occasionally leads to a psychosis that cannot be differentiated clinically

from schizophrenia and hyperthyroidism can lead to acute mania. We hear of women taking estrone and becoming so uncomfortably erotized as to refuse to go on with the medication. Werner reports upon the marked amelioration, if not the cure, of involutional melancholia by the use of estrone. Many psychiatrists suspect that endocrine factors may be of importance in the psychoneuroses and the psychoses, but crucial facts are needed. Perhaps no other aspect of endocrinology than that of its relationship to personality and its disorders is so meaningful in terms of ultimate human welfare. Researches in this field are especially worthy of encouragement.

A few of the most needed lines of development may be suggested. One of the most poignant of human tragedies is that of the man who fails to reach a normal heterosexual adjustment, but whose sex drives forcibly impel him to intimate relationships with other males. This state of affairs probably represents in most cases a failure of the normal emotional evolution that should take place during the puberal years. Some of the results of homosexuality in man are lack of a sense of security and social status and, in extreme cases, perhaps, a psychotic adjustment to life. A moot point at present is the extent to which homosexuality is due to the operation of social forces or to endocrine abnormalities. Experimentally, it is quite easy to produce homosexuality in lower animals and although the actual experiment has not been made it would probably be possible to bring about a secondary transformation to conditions appropriate to the original sex of the subject. The problem in a human setting is, on the one hand, to determine the sorts of sex hormones secreted by the homosexual individual and the relative amounts of each and, on the other, to determine the possibilities of normalizing the sex impulses by hormonal agents.

To the extent that homosexuality is due to the operation of social forces it is apparently determined largely by early

experiences—i.e., by "conditioning." This, however, is only one special phase of the general problem of the interplay between phases of conditioned behavior and the endocrine functions. The problem should also be studied in the larger frame of reference.

Another maladjustment which leads in the gross to a vast amount of human unhappiness is impotence in men and frigidity in women. Either of these conditions can be set up by social conditioning or by endocrine abnormalities. The extent to which the two factors are operative in the individual case and the extent to which they can be ameliorated by hormone therapy demand intensive study.

In an analysis of the nature of the sex drive, both in its primary and in sublimated aspects, several points need investigation and for such investigation technics are now available. It is known that both men and women have in their blood stream the hormones of their own specific sex but also, to some extent, those of the opposite sex. We need to know more concerning the amounts of each present at various ages and under various conditions, also the degree to which these hormones affect the "libido"—a matter of great concern to the psychiatrists—and likewise the extent to which personality traits, such as dominance and aggressiveness, are the result of early conditioning or of the influence of hormones.

These suggestions by no means exhaust the topic; they are cited merely to illustrate potentially valuable lines of research. In such studies most rapid progress can be anticipated from cooperative efforts of internists, psychiatrists, sociologists and endocrinologists. The most fundamental issues of human happiness are involved in these problems.

V. SUMMARY

Disorders of the human body, like those of a motor car, are mostly due to two factors operating jointly or independently. One is the breaking down of the machinery and the

other is derangement of control. Control is mostly of two sorts, nervous and chemical. This report is largely concerned with matters of chemical control and the results of disorders in the control mechanisms.

The principle of chemical control of the bodily functions was dimly foreshadowed in the folk lore of the ancients. The outstanding effects of castration have long been known. A century ago the importance of the thyroid gland in the production of exophthalmic goiter and myxedema began to be apparent. Through the years the primary clinical aspects of endocrinology have gradually developed to the point at which we recognize that a considerable number of diseases are of primary endocrine origin and that endocrine abnormalities are important in many others. For an understanding of the methods of operation of the endocrine factors we have become increasingly indebted to the experimental scientists.

The Thyroid and Thyroxine

Deficiency of the thyroid hormone results in a marked slowing of all the vital processes, with consequent inefficiency in the physiological functions and impoverishment of the personality. Over-activity of the thyroid results in an uncontrollable drive which causes the individual to live at an unwholesomely rapid pace, with tenseness, nervousness and insomnia as outstanding symptoms. If the over-activity of the thyroid is not curbed the subject is likely literally to burn himself to death.

The thyroid hormone, *thyroxine,* apparently stimulates all of the body cells, including those of the nervous system, hence all the physiological processes are modified by its action. Among the consequences of defective thyroid function are sterility, inability to bear normal offspring, inability to grow normally, disturbances in the processes of ripening into adulthood, inability to live an efficient adult life and dis-

turbances in the personality. The thyroid may also play an important role in the onset of senility.

The Adrenals

The adrenal glands consist of two parts, the *medulla* and the *cortex*. From the medulla is derived the hormone, *adrenine,* which selectively stimulates the sympathetic nervous system at its terminals throughout the body. Its chief function seems to be to help the organism to integrate its forces in meeting emergencies. The *cortex* of the gland is essential to life. When it is destroyed by infection or otherwise, as in Addison's disease, the subject goes through a period of weakness to prostration and death. The gland is obviously essential for preservation of bodily vigor. It is concerned in the maintenance of muscular efficiency, normal blood pressure, the stability of the body fluids, and carbohydrate metabolism. It is related fundamentally to the sexual functions.

The Sex Glands

The *testes* of the male have been known from time immemorial to be the basis of the attributes connoted by the term *virility*. Deprivation of the testicular hormone results in failure of normal growth and development and of emotional maturing. Male sex principles, or *androgens*, one or more of which probably represents the true testis hormone, have recently been secured in chemically pure form and are now being synthesized artificially.

The *ovaries* contribute at least two different hormones. One, derived from the follicles in which the egg cells are produced has a stimulating influence upon various structures and functions having to do with the reproductive process. Because this type of hormone is effective in bringing an animal into heat or estrus it is called *estrogenic*. There are now several estrogens available in pure form. The estrogens have a variety of influences connoted by the term, *feminine*. Following

the discharge of the egg cell from the ovary a secondary endocrine structure, the *corpus luteum* is formed. The secretion of this structure, namely *progestin,* has as its chief function the preparation of the uterus for the reception of the fertilized egg cell and then the regulation of processes involved in normal pregnancy. Deficiency of progestin seems to be an important cause of sterility.

The Pituitary

The pituitary consists principally of two apparently independent organs, the *anterior lobe* derived from the primitive digestive system, and the *posterior lobe* derived from the nervous system. From the posterior lobe are obtained two hormones which influence blood pressure, water metabolism, probably fat metabolism, and the functions of the involuntary muscle structures throughout the body. The posterior-lobe hormones are of practical therapeutic use chiefly in the treatment of *diabetes insipidus* and in stimulation of the processes of *child-birth.*

The *anterior lobe* has significant regulatory influences upon numerous bodily processes and hence is a fundamental factor in determining health or disease. It is primarily concerned in the control of growth and in associated protein metabolism. It fundamentally affects carbohydrate and fat metabolism and thereby is involved in the disease *diabetes mellitus.* It is essential for proper action of the thyroid, the adrenals, the sex glands, probably the parathyroid glands, and for milk secretion. Through its relations with the other endocrine glands, and especially the sex glands, the anterior pituitary seems to play an important role in determining personality and behavior.

Other Glands

The discovery of *insulin,* a pancreatic derivative, marked one of the major steps of modern endocrinology. It has

proved to be an invaluable agent in the treatment of diabetes mellitus. Recent work shows that other hormones participate in this disorder and suggests that the future may bring forth additional aids to its treatment.

The *parathyroid glands* have been shown to be of primary importance in the regulation of *calcium* (lime) metabolism. Calcium is a physiological sedative. When, through parathyroid deficiency a lowering of the calcium level in the blood takes place, numerous evidences of exaggerated *irritability* occur and these may progress to the point of fatal cramps. Calcium is the chief structural material in the skeleton. In defective parathyroid function the integrity of the bone suffers. When calcium wastage occurs the excretory organs may be overwhelmed in dealing with it and hence the parathyroids are also involved in certain *kidney* disorders. The glands, too, may determine variations in placidity of *temperament.*

The *thymus* has long been regarded as a regulator of growth but the evidence was insecure. Recent studies are more convincing. A thymus extract has been prepared which is reported to cause a remarkable foreshortening of the development span in young animals. The astonishing claim is made that it operates cumulatively when administered through successive generations. The extract may prove useful in the treatment of *retardation* in children.

The *pineal gland* has likewise had a dubious status among the endocrine organs. Cases have been described in which pineal tumors were associated with precocity of sexual development. Pineal extracts, however, aside from certain interesting effects on tadpoles, have until recently proved essentially inert. At present substantial claims are being made that a special pineal extract, made from the glands of well-fed calves, causes early *sexual development* and halting of body growth with the production of *dwarfism.* The effect of this extract, too, is reported to be cumulative through successive

generations. It has not yet been applied clinically but offers promise of affording a valuable remedy for a human disorder which is characterized by delayed maturity and pathological tallness of stature.

Current Researches

Many laboratories and clinics in this country and abroad are engaged in extensions of our knowledge in the directions suggested in the foregoing paragraphs. The various endocrine organs are being studied intensively as sources of active hormonal substances. The chemical nature of each known active principle is being rigorously studied and, as this becomes known, the problems of making the hormones synthetically are being vigorously attacked. The latter studies are imperative as a means of bringing the cost of the hormones within the economic resources of patients who need them. Preparatory to their therapeutic use much knowledge is needed of the effects of the various hormones throughout the body; accordingly, many investigators are studying the physiological properties of the different endocrine products. The findings of the laboratory investigators are being tested in the clinics to determine the actual medicinal value of the various products and their practical limitations for human use. Such studies are also meaningful in the elucidation of the nature of disease processes. Alert clinicians are constantly on the look-out for new endocrine diseases and in various centers are studying the detailed manifestations of the better known as well as the more recently discovered disorders. Numerous and important additional discoveries in these ranges of interest are to be anticipated.

Endocrinology of the Future

Few of the problems mentioned in the foregoing paragraphs have yet come to full solution. Productive extensions of the current researches are highly desirable. Especially do

we need to know much more about the effects of individual glandular deficiencies and about the physiological properties of the different hormones.

It is becoming increasingly evident that several sorts of study which have as yet received relatively little attention should be vigorously prosecuted. Among these are the determination of the *conditions* which influence bodily reactions to the different hormones. Factors which demand consideration are dosage, the nutritional state of the subject, species, age, sex and the influence of other hormones acting conjointly with the particular one under investigation. The mechanism of acquired tolerance to hormones presents a problem directly bearing on clinical practice. The genetic aspects of endocrinology have been largely neglected.

A better knowledge of the hormones, and particularly of hormone deficits, as factors in the onset and manifestations of *senescence* is needed. Such knowledge might afford means of postponing the decline of bodily and mental functions incident to aging and of mitigating the attendant disabilities. Sexual rejuvenation is a minor aspect of this problem.

A special problem calling for intensive research is the *interrelationship* of the *endocrine* and the *nervous systems.* These jointly constitute the chief governing mechanisms of the body and the two systems interact constantly in health and in disease. Each carries out its functions to a considerable extent through the agency of the other. Many symptoms of disease are set up jointly by the two agencies, and the unravelling of complicated symptoms of disease is dependent upon a deeper insight into the relations between nervous functions and the endocrine organs.

Closely united with the foregoing problem is that of the influence of hormones on *behavior* and *personality.* The instincts and the emotions as well as the mentality are demonstrably affected by the hormones, but as yet the endocrine aspects of psychology and psychiatry have received relatively

little competent attention. A better understanding, and possibly the cure, of various *neuroses* and *psychoses* might result from an adequate determination of the influences of hormones on mental states. Just now investigators in psychiatry are studying with interest and enthusiasm the possibilities of the insulin treatment of schizophrenia (dementia praecox).

One of the outstanding difficulties in clinical endocrinology is that of recognizing clearly the presence of glandular abnormalities in patients. The results obtained in experiments on the lower forms can often be translated into human terms only with great difficulty. It would be advantageous if the results of all the producible glandular anomalies were worked out in monkeys or apes with special regard to features which would lend themselves to more exact diagnoses in man.

Finally, mention may be made of a major topic to which adequate attention has not been given. This is the operation of *hormone factors in disease processes generally,* in contradistinction to endocrine disorders proper. In the past, the incorporation of physiological concepts and data into pathology has proved to be highly significant in establishing a basis for sound clinical medicine. The newer physiology, which includes much of endocrinology, remains yet to be similarly incorporated.

It would appear, then, that while endocrine research is in a healthy state and while progress has been gratifying, there are certain topics which have received less attention than their importance warrants. There is need of additional agencies to offer support and encouragement to investigators who are carrying out valuable researches in all parts of the field, but especially is there need of stimulating a higher degree of systematization of researches. Probably such agencies would be well advised in certain instances to formulate specific directions of research and seek competent investigators to follow them.

Conclusion

Medical and biological investigation has, as its ultimate goal, the improvement of human health and happiness. Of the various aspects of biology, the endocrine is particularly attractive because of the immediate applicability of its advances. The endocrine field is broad; hormone influences permeate the life processes in all their known aspects. The science of endocrinology is one of the most recent to develop, and, despite its rapid advances, it is still in its beginnings. There are now apparent many problems, the solution of which is imperative. As the science continues its expansion, many more will inevitably emerge. In comparison with the magnitude of the field, the laborers are few and the available resources inadequate. Abundant opportunity exists for the devotion of further funds to endocrine research and there are bright prospects for returns which will redound immediately to human well-being.

VI. HOW A RESEARCH FUND MIGHT BE USED

In this section we propose to consider briefly the value of financial support for research, the most efficient and economical mode of administering a research fund, and the possible development of a program of research with the aid of monetary subventions.

1. *The value of financial support for research.* In general terms what financial support does for an investigator is to increase and accelerate his output. The investigator who has money to aid him is not compelled to spend time in a shop making necessary apparatus; he can order it made by skillful machinists. He is not required to undertake the labor of rearing and attending to animals for his studies; he can buy the animals from reliable dealers or can hire a servant to breed them and give them proper care. He need not make charts, graphs and tables, or prepare tracings and records for publi-

cation; he can employ a technician to attend to these incidental matters. Just in so far as the investigator is freed from distracting attention to a variety of tasks which, though essential, are better performed by expert technicians in the several fields, he is enabled to devote himself to his own special functions—those of keeping in touch with the moving frontier of knowledge (the newest literature, the latest discoveries), considering the significance of fresh achievements in relation to his studies already in progress, and, by conferences with his fellow workers and personal participation in experiments, leading the advance into unexplored territory.

A seasoned investigator has many more pregnant ideas than he alone can work upon. His service to society, therefore, can be enhanced by increasing the number of his collaborators. For that reason the establishment of fellowships and research assistantships is justified. When such positions are occupied by intelligent and well-trained young devotees of science, they augment the productivity of a leader in research, not only by adding to his "hands," but also by helping to evolve novel ideas, methods and theories in the natural give-and-take of collaboration.

Sometimes special, expensive apparatus is needed for the conduct of an investigation. Sometimes travel must be undertaken to reach a region which is unique for the study of animals in their natural habitat, or to consult collections of unpublished data, or to learn new methods, or to compare uses of the same method by different investigators. Sometimes investigators working on similar problems in different regions may receive a great stimulation by being brought together in conference. Sometimes proper publication of results demands costly plates or tables which journals cannot afford. Indeed, not uncommonly facilities for publication of any acceptable sort are inadequate because of lack of financial assistance. Experience has shown that for all these purposes the spending of money is justified—justified in the only way recognized

by men of science—by the advancement and spread of knowledge.

2. *The most economical and efficient mode of administering a research fund.* There is a common wish to see tangible results of the expenditure of money; for example, a building which can be pointed to and which will serve as a memorial. Not infrequently in this way funds are permanently fixed in bricks and mortar, when the very service for which the building was erected languishes in poverty. Insight and appreciation of real values are required in choosing the support of scholarly endeavor rather than the construction of a monument. Ultimately the best investment is in brains. That choice does not involve a surrender of the idea of a memorial, however, for it is a well-established custom for investigators to express, in publications which result in whole or in part from grants, their gratitude to the foundation from which the grants came. Thus the beneficence of a donor may be made more widely known and his name may be more lastingly preserved than might be true by any material structure.

Money devoted to accelerating valid research activities already started is likely to be especially productive. It finds a "going concern" and facilitates its progress. Expenses for preliminary exploration, for buildings, for water, for heat, light and power can be wholly avoided. The investment is made in the central enterprise for which all the appurtenances have been gathered, built and maintained, i.e., in promoting the efforts of scientific investigators.

As a rule, research is being conducted most vigorously and most competently in the laboratories of large universities and special institutes. In such organizations are likely to be gathered not only the leaders of investigation, but also associates and the novitiates of science who, by mental attrition, learn from one another and stimulate one another to new ideas. It was such a society of scholars which Josiah Royce

had in mind when he remarked that one could always depend on "the fecundity of aggregation."

Experience has shown, however, that not all the valuable research of the world comes forth from university centers. Occasionally an isolated investigator in a small college or a private laboratory proves to be an important contributor to knowledge. Or even a genius may first come to light in that setting. The labors of such a man are quite as worthy of practical encouragement as are those of more favored men of science in large institutions.

In the experience of the Committee on Problems of Sex, appointed by the National Research Council, various university departments have used grants ranging from $2,000 to $15,000 per year. On the other hand, isolated investigators have received grants ranging from $200 to $1,000 per year. The larger sums were not given in the early years of the Committee's service; they were gradually increased as leaders of research proved their ability to use the sums with prudence and skill. But it goes without saying that for a project of major scope and promise, a greater expenditure of funds than any mentioned above might be wise.

Probably a research fund can be employed more economically, certainly it can be employed more efficiently, when the recipient knows that he can count on continuing support. Such support may not be promised for more than three or four years, and the promise may be limited by any reasonable conditions, but when a well-tested and reliable investigator knows he may fairly definitely expect uninterrupted financial aid for his researches through a series of years, he can plan ahead, undertake long-lasting experiments, which are often the most important, and be freed from worries and anxieties about the future of his efforts that may interfere seriously with single-minded devotion to scientific interests.

3. *The development of a research program in endocrinology with financial support.* The effective distribution of

grants in aid of investigative projects requires the attention and judgment of experts. If money should be made available for the promotion of research in endocrinology, a Committee should be appointed representing different aspects of the field and having a wide acquaintance with the men who are engaged in cultivating it. It should be large enough to provide expert opinions on the varieties of problems which would be submitted and not too large for concerted action. A committee of seven would perhaps be ideal. We doubt whether a field secretary would be necessary, for the activities of various centers would be well known. But at times a visit to a laboratory or to an isolated investigator by a member of the Committee might be necessary in order to learn about special circumstances affecting a judgment. Otherwise not much travel would be required.

From knowledge of research achievements and acquaintance with responsible investigators, and also from experience gained in the administration of other research funds, a well-chosen Committee could judge not only the relative merits of proposals and where financial support would be most likely to yield good returns, but also the size of grants which would be reasonable in the various circumstances. The details as to application forms, specified uses of money requested, recognition of the Foundation in printed papers, reprints, etc., could be arranged on the basis of the extensive administrative service of the National Research Council. Indeed, a Committee, confronted with a problem, would do well to consider the wisdom gained in that Council through many years of employing funds for research purposes.

Specific Plans

There are three possible plans for establishing a committee which the Trustees of the Markle Foundation might follow: A, they might ask the National Research Council to administer such funds as the Trustees might wish to devote

to the promotion of research in endocrinology; B, they might ask the National Research Council to nominate a committee which could be self-perpetuating or could be continued by nominations from the Council; or C, the Trustees themselves might select a committee. In the last two plans the Trustees would have direct control of the administration of their fund. These three courses may be further considered.

Plan A. The National Research Council has had extensive administrative experience in the employment of funds for research purposes. If the Trustees of the Markle Foundation should wish to make use of that experience the proper procedure would be as follows. They would express to the Chairman of the Council an intent to provide a considerable sum of money annually for research in endocrinology, and would ask the Council to establish a special Committee on Endocrinology to learn the needs of reliable investigators in that field, to assign grants to applicants for aid in their researches, and to assure, so far as possible, that the grants be effectively used. The Chairman of the Council would refer the matter to the Chairman of the appropriate Division—presumably, in this instance, to the Division of Medical Sciences. This Chairman, after consultation with informed persons in the medical sciences, would suggest to the Council the personnel of the proposed Committee and, if the Council approved, it would appoint the Committee with the Chairman of the Division as a member *ex officio*. Soon after the appointment, the Committee would have a meeting to discuss policy and procedure, and it would then take steps to let its existence and its functions be known. Applications for grants would be requested with the provision that they must be submitted by a certain date.

The Committee would then have another meeting at which the applications would be reviewed and carefully considered. On the basis of such consideration, the Committee would recommend to the National Research Council the assignment

of the grants. After these grants were voted the officials of the Research Council would attend to the placing of the grants in responsible hands—e.g., the Treasurer of a university or research institute—, and would demand quarterly reports of the use of the grants and a return of any unused portion. In the annual application for a grant each investigator would be required to report to the Committee his use of the grant of the previous year and his intentions as to the year ahead. Any publication resulting from a grant would be expected to give credit to the Markle Foundation for aid in the research thus recorded, and to the Committee of the Council.

Each year the Committee would report its actions to the National Research Council, and would estimate the sum desirable for continuation of its work for the next year. It might ask for an increase in the sum desired from the Markle Foundation, or it might suggest that a certain sum be provided for a series of years in order that grants for a longer period than one year could be arranged. The Committee itself would have no direct relations with the Trustees of the Markle Foundation. It would make its suggestions to the Chairman of the National Research Council, and he would have the duty of presenting the case to the Trustees.

Plan B. Should the Trustees of the Markle Foundation not care to abrogate their responsibilities to the extent suggested in Plan A, most or all of the values therein suggested could be secured through the choice of Plan B—namely, the appointment, on advice of the National Research Council, of an Advisory Committee which would derive its authority from the Trustees of the Foundation and perform its functions in a manner directly answerable to them. The Foundation would, of course, be compelled to provide the machinery for distributing grants and checking reports on the use of grants.

Plan C. Under this Plan the Trustees of the Markle Foundation would preserve complete autonomy. An inde-

pendent Advisory Committee, selected by the Trustees, would be charged with devising methods of procedure and making recommendations either in detail or in general terms, as desired, to the Trustees of the Foundation. If the Committee should include a member who is in touch with procedures of the National Research Council, the experiences of the Council could be readily available. The Trustees would administer their funds directly, as in Plan B.

A committee made up of responsible and well-informed endocrinologists would be able to function with approximately the same efficiency under any of the three plans. The plans differ essentially and practically only in the degree to which they leave primary administrative responsibility with the Trustees of the Markle Foundation.