REMARKS ON THE FUNCTIONS OF THE SUPRARENAL GLANDS AS REVEALED BY CLINICAL-PATHOLOGICAL STUDIES OF HUMAN BEINGS AND BY EXPERIMENTS ON ANIMALS.*

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The Association for the Study of the Internal Secretions has been organized and its journal, Endocrinology, is being published in the interests both of the advance of science and of better medical practice. Our objects include not only the further development of a pure science of endocrinology, but also the evolution of an applied science of endocrinology and the improvement of the medical art as far as it is exercised in endocrine domains. The membership of our Association includes therefore not only investigators and teachers in the pre-clinical medical sciences of anatomy, histology, embryology, physiology, physiological chemistry, pharmacology and experimental pathology, but also many representatives of the clinical sciences of diagnosis and therapy and of the closely allied sciences of pathological anatomy and pathological physiology. Only through the mutual respect, the thorough reciprocal understanding and the closest co-operation in every way of workers in all these sciences can

*Address of the President of the Association for the Study of Internal Secretions, Atlantic City Meeting, June 9th, 1919.
progress in knowledge of the internal secretions and utilization of it best be made. It is hoped and believed that the Association and its journal may go far toward stimulating research in clinics as well as in laboratories and toward co-ordinating the interests of the workers in all subdivisions of the endocrine field.

No better example of the value of correlation of the activities of endocrine investigators of different sorts could, perhaps, be given than that offered by a consideration of studies in the functions of the suprarenal glands in health and in disease; and at this meeting, at which it is my privilege to preside, it is to this subject that I desire to refer. From the time of the great clinician Addison to the present, practising physicians have been deeply interested in the normal and abnormal functioning of the suprarenals, and with the rise of laboratory research a goodly number of scientists have busied themselves with researches bearing upon the structure and functions of these mysterious organs. You will recall that the president of this association last year took one phase of the subject into careful consideration, and a glance at the several quarterly issues of our journal shows how widespread throughout the world and among different types of investigators is the interest in, and how painstaking is the research at present going on in attempts to elucidate, the influences of these glands upon other parts of the body under normal conditions and in pathological states. That out of the studies already made and those that will be conducted in the near future, when they are properly co-ordinated, much will emerge that will illuminate an area hitherto dark and obscure, no physician with vision can doubt. Though we know but little as yet in comparison with what there is still to be learned about the suprarenal glands, the contributions that have been made and that are now being made give us every reason to hope that ere long the secrets of these organs will, by a band of earnest workers, be wrested from nature.

The advantages for the study of the suprarenals derivable from division of labor in the clinical and preclinical medical sciences lie especially in the variety of the backgrounds of the workers in the several sciences, in the differences in the problems they set out to solve, and in the modes of approaching the solution of these problems by means of practical-technical procedures of different kinds. The anatomical group, the physiological-
pharmacological group, the experimental pathological group, and
the clinical group of workers have different kinds of past experi-
ences to draw upon, different materials to occupy themselves
with, a different body of principles to guide them, a different set
of technical methods to employ, different interests to stimulate
them, and different purposes to achieve. In the end, their activ-
ities and results, when co-ordinated, converge; for all make use
of the general method of science, and each contributes to knowl-
edge that can be used by all. Thus the special desires, the
special ideas, and the special activities of the single workers can
ultimately be fused in the service of the emotions, the ideas and
the purposes of endocrinologists in common.

Certain very stimulating ideas regarding the significance of
the suprarenal glands have come, as everyone will admit, from
observation at the bedside of sick human beings, and in the post-
mortem room. Thus, when Addison observed that certain pa-
tients manifested profound asthenia, marked disturbances of
digestion, and a peculiar bronzing of the skin, and that in their
bodies, after death, there was extensive chronic disease and
destruction of the suprarenal glands, the first great step toward
the recognition of the significance of these structures was made.
Clinicians and pathologists since Addison’s time have done much
to elaborate the syndrome he first observed and to enlarge our
ideas of the pathological changes that may underlie it, and of
its etiology. On the clinical side there are many special observa-
tions upon the motor asthenia (affecting both the voluntary
muscles and the heart muscle), the low blood pressure, the
anorexia, nausea, vomiting and diarrhoea, the tendency to faint-
ing spells, the pigmentation of the skin and mucous membranes,
the white line phenomenon, the anaemia, the oliguria, the slow-
ing of the metabolic processes, the hypothermia, and the lowered
resistance to infections. In some cases there was obesity, in
others emaciation. In addition, clinicians have studied certain
syndromes that more or less closely resemble the symptom-com-
plex of Addison’s disease, but are not identical with it—synd-
romes that may be met with in infancy and childhood, in ado-
lescence, in middle life or in old age, syndromes that sometimes
develop slowly, sometimes acutely. On the pathological side
many special observations have also been made on the bodies of
patients dead of Addison’s disease or of diseases, chronic or
acute, resembling it. The frequency of tuberculous lesions of the suprarenals in such cases was early recognized, and the occasional occurrence of cancerous disease and of diffuse fibrosis of these glands was described. In some instances, no changes could be recognized in the suprarenal glands themselves, but lesions involving the nerves that supplied them were discovered. In still other cases, neither the glands nor their nerves showed any recognizable changes, and a functional disorder of the glands secondary to diseases elsewhere in the body had to be assumed to have existed. After the doctrine of internal secretions developed and it was believed that the suprarenal glands belong among the endocrine organs, it was natural for clinicians to advance the hypothesis that the symptoms of Addison’s disease in which the glands were slowly destroyed were due to insufficiency of the internal secretions of these glands—to a hypo-suprarenalism (or hypoadrenia), and that in conditions resembling but not identical with Addison’s disease there was also a greater or less degree of suprarenal insufficiency or hypofunction. As a result of this conception there has been, on the one hand, much speculation as to the possible causes of the hypofunction in instances in which no organic changes in the suprarenals could be found, and, on the other, an attempt favorably to influence the course of Addison’s disease and of allied conditions by the institution of substitutive organo-therapy of different sorts. Another very important idea that emanated from clinical-pathological observations is that of a connection between the function of the suprarenal glands and the development, and behavior during life, of the secondary sex characters. Thus clinicians and pathologists have observed that in association with certain diseases (especially tumors) of the suprarenal glands, or of aberrant masses of suprarenal tissue in other organs, peculiar disturbances in sex domains may be met with. For example, if the disease be present in the foetus, and the child live, the condition of pseudo-hermaphroditism is prone to develop, the individual presenting to a greater or less extent the external habitus and the external genitalia of one sex though the primary sex organs (testes or ovaries) are those of the opposite sex. Or, if the disease be a little later in its development, the external and internal genitalia may be in accord, but the child matures too soon (pubertas praecox), a little girl of 2, 3 or 4 years of age perhaps, presenting the sexual
appearances of a girl of 14 (pubic and axillary hairs, mammary development, menstrual flow, adolescent psyche), or a boy of 6 or 7 may exhibit the somatic and psychic sexual phenomena of a boy in his teens. Or, again, should the disease develop still later in life, the body may become slowly or quickly covered by an abundant growth of hair (hirsutismus) and in the case of a female, in addition to the hirsutism of the trunk and extremities, and the growth of a beard and moustache upon the face, the patient may present somatic and psychic asthenic features resembling those of the male (large clitoris, great muscular power, masculine voice, love of hard labor, etc.), a condition known in clinical papers as virilismus. Since this sthenic condition contrasts strongly with the asthenia or adynamia that characterizes Addison's disease, in which the suprarenal glands are, as a whole, slowly destroyed, it was natural for clinicians to think of virilismus (and the allied conditions—hirsutism, premature puberty and pseudo-hermaphroditism) as examples of overactivity or hyperfunction of the suprarenal glands, though the terms hyper-suprarenalism and hyperadrenia, when they have been used at all, have been applied in a different way, and perhaps less justifiably, namely, to conditions in which the blood pressure is increased. Clinical observations then, controlled by pathological-anatomical examinations made after death or after operations upon the living, have yielded these two great conceptions: (1) the conception of a loss or diminution of the function of the suprarenal glands characterized by the Addisonian syndrome, and (2) the conception of an overactivity of these glands characterized, according to the time at which the overactivity appears, by pseudo-hermaphroditism, by precocious puberty or by virilism.

Before considering further the bearing of clinical-pathological observations upon the functions of the suprarenals, let us recount some of the more important contributions of pre-clinical scientists, working in experimental laboratories, to our understanding of the nature and activities of these organs. First of all, the anatomists and histologists showed us that each human suprarenal gland is divisible into two parts, cortex and medulla, which differ from one another entirely in their morphological appearances, and which, therefore, presumably, have entirely different functions. The cells themselves, as well as the way
they are arranged, are wholly different in the cortex from those in the medulla. The medullary cells closely resemble certain cells found along the sympathetic trunks, along the aorta, and in the carotid glands; they show an especial affinity for compounds of chromium, and are accordingly known as chromophile cells. Indeed, it is believed that the medulla of the suprarenal gland is only a part of a much larger anatomical-physiological system of cells, now known as the chromaffine system. So firmly accepted is this conception of the identity of the widely distributed chromophile cells that what is proven to be true of one portion of the chromaffine system is now likely to be assumed to be true of all the other portions of this system, though strange to say many investigators, who should be familiar with the total extent of the chromaffine system, seem, when writing of suprarenal function, to forget that there is a considerable body of chromaffine tissue outside of, and even far distant from, the suprarenal glands. A second important laboratory contribution that goes far toward confirming the views just mentioned of a totally different structure and function for cortex and medulla respectively has been made by the embryologists and comparative anatomists who have demonstrated (1) that in human beings and higher animals generally the medulla of the suprarenal is derived from the Anlage of the sympathetic nervous system, whereas the cortex of the suprarenal has an entirely different genesis, being derived from the germ epithelium, and (2) that what correspond to cortex and medulla of the suprarenal of higher forms are in lower vertebrate forms not even spatially associated, but exist as parts of two anatomically separate and independent series of organs—the one a part of the so-called interrenal system of organs, the other as a part of the chromaffine system. Thus, in the eel, what corresponds to cortex or interrenal system includes the corpuscles of Stannius and Giacomini’s mass in the pronephros. Even in man it has been found that small masses of accessory interrenal cells (‘‘suprarenal rests’’) may be met with in the kidneys and at various sites within the abdomen and pelvis, though by far the majority of cells of interrenal origin in man and higher vertebrates are included in the suprarenal cortex. A third important contribution made by laboratory experiment was the bringing of the proof that the functions of the interrenal system are necessary for life and
that the death of a higher animal that is due to total extirpation of the adrenals must be the result of removal of the interrenal portion (cortex) rather than of the removal of the chromaffine portion (medulla) of these organs; it would seem that though there is enough chromaffine tissue outside of the suprarenal glands to maintain life (if, and we are not yet sure of this, the functions of the chromaffine system are essential to life) there is not enough interrenal tissue outside the suprarenals to maintain life after the suprarenal cortex has been extirpated. A fourth discovery of great significance was that of Schafer, who demonstrated that extracts of the suprarenal glands when injected cause a rise in blood pressure. And a fifth fundamental laboratory contribution was the demonstration that this blood-pressure-raising substance is derived from the chromaffine part (medulla), not from the interrenal part (cortex), and that it is a well-defined substance (adrenalin of Takamine; epinephrin of Abel) the chemical constitution of which has been determined, and methods for its artificial manufacture worked out. A sixth laboratory discovery that may prove to be of real importance is the isolation by Voegtlin and Macht of a pressor substance, not epinephrin, from the suprarenal cortex; this substance and the abundance of lipoid substances present in the cortex require study.

Coincident with and following upon these several fundamental findings by laboratory workers began a series of experiments further to determine the functions of the medulla of the suprarenal and the epinephrin it produces. A period of intensive experimental research yielded results that served as materials out of which various hypotheses concerning the significance of the suprarenals were constructed. Among the better known of these attempts at generalization are what are known as (1) the tonus theory, which assumes that epinephrin maintains in one way or another constantly a state of tonus in smooth muscle innervated by the sympathetic nervous system; (2) the emergency theory, which regards the suprarenals as an apparatus for discharging epinephrin in emergencies only; (3) the antitoxic theory, according to which suprarenal products neutralize poisons; or its variation, which assumes that the suprarenal products themselves are detoxicated substances; and (4) the metabolic theory; which postulates that the presence of minute quantities of
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epinephrin are necessary for the metabolic activities of the tissues, including the oxygenation of the blood. Thus the results of experiments led to the formulation of hypotheses, which in turn stimulated further research.

These speculations have really had a heuristic effect, for groups of experimental workers have undertaken investigations in laboratories to corroborate or to refute them, and as results of their studies many important discoveries can be recorded. Thus we now possess valuable information regarding (1) the quantity of epinephrin present in the suprarenals, in other chromaffine tissues, in the various organs, and in the blood, under certain conditions; (2) the circumstances (pain, asphyxia, excitement) in which epinephrin is discharged into the suprarenal veins; (3) the influence of epinephrin (a) on the body as a whole, after subcutaneous injection, (b) on perfused organs like the heart, the spleen and the kidney, (c) on strips of muscle like that of the uterus, the intestine, the iris, the bronchial musculature and the bundle of His; (d) on the calibre of, and the blood-flow through, arteries, veins and capillaries in different regions of the body; (e) on the functions of nerves and of neuronal synapses; (f) on the content of the blood in its different varieties of white corpuscles; (g) on the discharge of red blood corpuscles from the sinuses of the liver; (h) on the secretion of saliva and other digestive juices, and (i) on the mobilization of sugar and the sugar-content of the blood. Discoveries such as these show the great value of hypotheses as the groundwork of action, for the careful testing of a hypothesis, whether it be true or not, advances knowledge. John Hunter's "Don't think; try," really meant, "Think, but do not stop at thinking; test your thought by trial." Clinicians and pathologists, to-day, are making their observations and their classifications of disease of the suprarenal glands in the light of all this new knowledge. They, too, are speculating regarding the significance of their observations at the bedside and are subjecting their hypotheses to tests by means of experimental methods carried on during the life of patients and by means of histological and chemical studies of the dead. I need refer only to (1) the use of epinephrin in the treatment of asthma, of urticaria, and of angio-neurotic oedema, (2) the administration of suprarenal gland in Addison's disease, and in other states of asthenia, hypotension, and
hypothermia, (3) the clinical conceptions of the chromaffinopathies and the interrenopathies and their subdivisions of hyperfunction, hypofunction and dysfunction, and (4) the Loewi test and the Goetsch test in clinical diagnosis, to recall to your minds some of the directions in which physicians are speculating and working in the hope of advancing knowledge in the clinical sciences of diagnosis and therapy. Real progress is here certainly being made. Though many of the hypotheses now held will later be discarded and some of the classifications will doubtless have to be revised, still these hypotheses and classifications will have served their purpose if they have stimulated closer observation and continuous experimentation, and have been regarded merely as stepping-stones in the path of progress. Clinicians and pathologists, as well as physiologists, have the right to speculate, provided their speculations are based upon the facts that have already been accumulated, and provided also that they persist in subjecting their speculations to rigid tests by further observation and experimentation.

Time will not permit me further to elaborate the topic in this brief address. But enough has perhaps been said to justify the optimism that exists among those who, both in the pre-clinical and the clinical sciences, are absorbingly occupied with the study of the suprarenal glands.