From the
Workshop of Discoveries

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by

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I

Reflections on the Study of Medicine

WE MAY divide the different studies roughly into two main groups. One group comprises "humanities," the other "science." "Humanities" have as their object achievements of the human brain. Think, for instance, of philosophy. "Science" has as its object knowledge of the achievements of nature and the laws which seem to be at their basis and control them. Science we may subdivide into the science of the inanimate and of the animate world, and the latter again may be subdivided into the science of man and that of the other living beings. The study of medicine consists of the study of man, more exactly of the study of his structure and function in health and disease. As I see it, there is no study more satisfactory to the average man than that of medicine. In the first place, it seems obvious that no interest is closer to man than the study of man; secondly, in contrast to most other studies, here not only our mind but also our spirit is involved, at least in that part of medicine which strives for supporting the healing power of nature itself. I should first like to dwell on this point. For this reason I have to deal with its background.

Medicine has to deal with living beings. What is life? St. Augustine, when asked about the meaning of time, answered: "Si nemo ex me quaerat, scio, si quaerenti explicare velim, nescio." If nobody asks me I know it; but if I wish to explain it I do not know. We are faced with the same situation if we are asked for a comprehensive definition of life. We can feel what life is, but we do not know how to express the feeling plainly; so we must content ourselves with examining the marks which appear to characterize for us the living in contrast to the not living.

Life, first of all, is motion. The motion need not be obvious. Beneath external calm there proceed in the living being continual changes, chemical motions, commonly grouped under the name of metabolism. This uninterrupted changing goes on in the living being also in absence of any influence from without; it is an autonomous process. The ancients spoke of "Motus sui ipsius," that is, of the spontaneous motion and spontaneous change of living beings. Chemical movements go on in non-animate systems too. Take, for instance, the course of enzymatic reactions *in vitro*. In contrast to these, spontaneous change of living, consisting in a continuous breaking down and building up, runs according to a plan. These processes are confined and limited by the momentary requirements of the organism. For instance, in the growing organism, building up predominates. Later on building up is balanced by breaking down. So must it be, if there is to be life at all; for disintegration without corresponding building up leads to death. And that this is so is the expression of the existence of a self-preserving drive, to which we shall have to come back later. To this drive is joined—and here we become acquainted with another characteristic of the living being —its ability to reproduce itself by dividing. This is the expression of the striving to preserve the species too.

The tendency and potency of the organism to maintain its chemical equilibrium and to remain in it represents only one side of its tendency and potency to maintain its characteristic state. It extends in fact to its whole structure and function and holds true also in cases where the organism is facing interference from within and from without. This means that the organism is able to react in an autonomous manner to changes exerted on it. The reactions are also characterized by the tendency to maintain the form or by compensation for changes exerted on it or by adaptation to them. These regulations occur if the organism has to deal with changes lying within the limits of normal life and its appropriate environments.

It is almost needless to illustrate this fact. You know, for instance, as well as I do that the muscle after having lost energy during work regains it a short while afterwards.

Moreover, even in those cases where the organism has to face influences not lying within the limits of normal life and its appropriate environment, it tries at least to maintain itself. I should like to illustrate this point by a few examples arbitrarily chosen, since the presentation of mere principles in most cases is colorless and therefore fatiguing.

The first example deals with a particular occurrence in the bee-hive. The bee-hive, in my opinion, does not represent a state but a proper organism, as achievements needed for its existence are distributed to various kinds of individuals, corresponding to various organs. In the bee-hive there exists a definite rhythm of labor. The bees which recently have slipped out, feed older larvae with honey and pollen; during this time their salivary glands grow. In a later state the salivary glands atrophy and are transformed to wax-forming glands used for the construction of honeycombs. Finally, the wax glands also atrophy and the architect bees become collector bees. We distinguish, therefore, nursing bees, architect bees, and collector bees.

Some years ago, it could be shown that as a consequence of withdrawal from a bee-hive of the collector bees, the salivary glands of the nursing bees degenerate and nursing bees become collector bees. On the other hand, as a consequence of withdrawal from a bee-hive of the nursing bees, old collector bees rebuild their salivary glands, previously atrophied, and again become nursing bees. In my opinion, a more striking example demonstrating a purposeful transformation needed for the maintenance of a whole is hardly to be found.

Another example is one I have chosen because it represents a transition from artificially created changes as happen in diseases. The heart beat, as you know, starts from a special part of the heart, the sinus node, and the excitation is conducted from there to the various compartments of the heart. The conduction can be interrupted by experimental means or in a special disease. Even under such most extraordinary conditions the heart is able to compensate for the disturbance, created by the interruption of the conduction from its normal leader, by establishing a secondary or even tertiary automatism elsewhere.

You know, furthermore, that the organism reacts to the introduction of all kinds of foreign proteins, especially also toxic ones, by forming so-called antibodies which are extremely helpful in the treatment of many infectious diseases. In time, more and more antibodies are formed in a measure far exceeding the amount of proteins and toxins introduced, apparently even long after these substances have ceased to circulate.

Two further illustrations: you know that we use insulin in treatment of diabetes in order to reduce the hyperglycemia. You also know that if this reduction goes too far, most disagreeable symptoms appear, like secretion of cold sweat, disturbance of equilibrium, drowsiness, even unconsciousness and, incidentally, shock. The symptoms can be quickly reduced by application of glucose or of adrenalin which releases glucose from the liver into the blood. Therefore, people treated with insulin usually carry sugar with them. Such a person one day, sometime after having left his home, felt symptoms of hypoglycemia, which rapidly increased. He had forgotten to take some sugar along and when he came to a druggist to buy some, he already showed disturbances of equilibrium. The druggist, assuming that the man was drunk, yelled at him and refused to give him sugar. This behavior provoked such an excitation in the diabetic that his adrenals started to secrete adrenalin, enough to elicit production of glucose from the liver, and by this means the man got rid of his hypoglycemic symptoms.

Finally, consider cases of serious bleeding. As a consequence of the disproportion of the tonus of the blood vessels and the diminution of the blood volume, the blood pressure drops and as a consequence of the loss of erythrocytes there exists an anoxemia. What happens now without our interference? The anoxia stimulates the vasomotor center in order to constrict the vessels; the spleen, which stores blood to be used in cases of emergency, releases this blood into the general circulation; and there is in addition an inflow of salt solution from the tissues into the blood vessels to refill them. Consequently the blood pressure rises. Finally, the anoxia provokes in time a new formation of erythrocytes in the bone marrow.

These cases are sufficient to demonstrate the creative healing power of the organism in disease. Very often—for instance, in all the cases cited—the physician has to do nothing else but support this autocreative striving of the organism.

The curative power of the organism illustrates just one side of its general tendency to maintain its structure and function and if needed to re-establish them. As a matter of fact, all that happens in the organism undeniably tends to a useful end. This end concerns the self-preservation of the organism. The whole specific organization of living beings serves this end.

To get an insight into the organismic order we have to look for the relation of the single factors of the whole to the end. In dealing with this relation we obviously take a viewpoint of teleology or finality. In fact, this view represents the starting point if we study the chemical and physical factors involved in the single functions and their coordination, in order to relate them to their purpose. This seems to me so self-evident that I have never understood why so many scientists have always been reluctant to express or even touch on this view. It is, of course, only a view, not an explanation. For them teleology is just tabu. I myself fully agree with an old friend of mine, the late physiologist E. von Bruecke, who once said in a lecture, "Teleology is a lady without whom no biologist can live. Yet he is ashamed to show himself with her in public." I furthermore fully agree with the view of Edwin Conklin, "The fact is that organisms are fundamentally teleological and although it may be impossible to explain this in a mechanistic or causal manner, this failure is no excuse for denying the reality of the phenomenon itself. It has been argued that ends exist only in the minds of the observers, but the same could be said with equal cogency, for instance, of causality. Who, however, would deny causality?" The teleology of the organism is both undeniable and incomprehensible. It may be helpful to give just one illustration of what is meant. It is definitely established that the respiratory center possesses a specific sensitivity to CO_2 which is most useful. It may be that one day we shall find out the physical or physico-chemical basis for this specific sensitivity. This knowledge, however, will not explain the fact that this sensitivity is useful. I personally am not a bit astonished or disappointed that we do not, and, in my opinion, never in the future will understand the teleology of living beings. How could we expect this understanding? We know that our perceptions are dependent on our sense organs. They therefore must be limited and imperfect. In addition, how could it happen that our brain should be the object of understanding and at the same time the only tool for this understanding? Should we be disappointed about this limitation of human capacity? I do not feel this way. I am deeply thankful that there remains something great to be admired and to be revered, namely, that inconceivable creative power of nature which really gives rise to a deep religious feeling.

We started this whole discussion from the fact that we recognized a realization of teleology in the reaction of the organism under normal and abnormal conditions. The illustrations which I gave you and which could infinitely be multiplied reveal still another most important factor. They demonstrate that the reaction to events happening in one place of the organism is not restricted to this place but provokes purposeful reactions also somewhere else. As a matter of fact, the organism represents a unity, a whole. This is made possible by such an arrangement that the single parts of the organism are closely dependent on each other and work harmoniously on behalf of the whole. From this originates and is maintained the proper melody characteristic for each species of organism. The factors producing the mutual relations indispensable for the maintenance of the unit among the organs are in the main of the same nature as those calling forth or modifying the functions of the organs, namely, of chemical and nervous character. As a rule, both sets of factors are working together. These factors are, of course, accessible to analysis.

The fact that the single parts of the organism are working on behalf of the whole makes it understandable that in many cases we get an insight into the separate functions only by relating them to the whole. I should like to illustrate this point by a striking example. It deals with the function of the so-called autonomic nerves. They run from the central nervous system to the vegetative organs, in contrast to the so-called somatic or spinal nerves which run to the striated muscles. The autonomic nerves are, according to their origin, classified as sympathetic and parasympathetic nerves. As a rule, each vegetative organ receives a sympathetic as well as a parasympathetic nerve. The effect of these nerves on the organs is on the whole a mutually antagonistic one. In some organs the sympathetic nerve stimulates and the parasympathetic inhibits the function, whereas in others the sympathetic inhibits and the parasympathetic stimulates. The meaning of the fact that nerves of the same group influence the various organs in an opposite sense cannot be understood if we consider the effects of the nerves separately. The meaning, however, will be disclosed if, according to the view of Walter B. Cannon, we relate the action of the individual nerves to the whole organism. In this case we not only understand why the nerves belonging to the two groups influence the various organs exactly as they do, but we also find that the different actions of the various nerves closely join to a functional unit. Looking on the nerve action in this synthetic manner, we come to the following statement: the so-called somatic nervous system regulates the relation of the whole organism to its environment; that means it is responsible for orientation, for motion, for provision of food, for defense, etc. The autonomic nervous system, however, controls the conditions of the inside of the organism. As there exist functional correlations between the somatic and the autonomic organs, obviously the two related nervous systems share in them. Since we started from the question as to how we could understand the isolated actions of the sympathetic and parasympathetic nerves, respectively, we now have to examine whether perhaps we could conceive them by starting from the statement of the existence of the correlation between the somatic and vegetative spheres. From this functional viewpoint, the sympathetic system is regarded as a system innervating all the functions which enable the organism to make an immediate display of energy. The sympathetic, therefore, augments all the functions needed for bodily achievements: The circulation is increased, since the sympathetic augments the activity of the heart by direct action on it and by dilating its vessels. At the same time, the spleen is contracted, whereby the blood volume is increased; by contraction of the other vessels in the splanchnic area the blood is shifted from there to the working striated muscles. The respiration is increased, at least by the dilation of the bronchial muscles. The amount of available fuel is increased by glycogenolysis. Finally, the fatigue of the striated muscle is diminished. These hints may suffice to show that the augmentory and inhibitory, apparently arbitrary, single activities of the sympathetic system are subordinated to a special goal. This makes them appear understandable. In contrast to the sympathetic, the parasympathetic is responsible for the restitution of the energies given out by the support of the sympathetic. From this it is evident that the sympathetic and the parasympathetic nerves, being antagonists with respect to their isolated partial functions, appear as real synergists if we look upon them from the point of view of the maintenance of the whole.

I did not deal with the topics touched on so far merely in order to deliver a lecture about principles of life and organisms, but because of the unique importance of the knowledge of these principles for the medical student as well as for the physician. As a matter of fact, I would be most satisfied if in the future you would keep in mind the words of Claude Bernard, "Nature is a unity; the frontiers in nature are erected by mankind." The same holds true for the single organism.

In regard to this it is obvious that structure and function are intrinsically connected. The knowledge, therefore, of the macroscopic and microscopic structure should be acquired in relation to the respective functions. I don't think it is mere chance that in this dynamic country the study of pure morphology, a kind of static science, has never had many adherents.

The relations of the single parts to each other and of the single parts to the whole make it self-evident that a change, at first strictly localized in a particular place within the organism, regularly provokes changes somewhere else. I already have given examples to illustrate this fact. At this place I want only to stress the importance of this knowledge for the physician, especially with regard to the diagnosis of the primary seat of disease. It is almost trivial to point out that in many cases the seat of complaints in a particular organ is not identical with the seat of the primary disturbance, which in its turn may not even show any symptoms. It may therefore happen that the treatment of the organ which is the seat of the complaints may not cure the patient. Do think always of the whole and of the close connections of its parts.

I should like now to touch on another point of high importance for students of medicine. Are they to study everything that is known in the field of medicine? I am convinced that not even the best-educated medical man would be able to become familiar with everything. Consequently, the student of medicine has to make a selection. He has to select the most important things. You will obviously ask me: "How can we know what is important and what is not?" The question is justified and embarrassing. What could I answer? I always have accepted the following definition of intelligence: "An intelligent man is he who knows how to distinguish between essential and not essential." I therefore cannot do anything else but appeal to your self-confidence. Incidentally, I may give you still another bit of advice. It may happen that you repeatedly study certain things and forget them time and again. Hence it becomes evident that you are not interested in them. This is the reason why they make no impression—in the literal meaning of this word—on your brain. Memory is just a function of interest with consecutive impression. In many cases things which do not interest you may prove not to be important; for instance, because they may be isolated facts, in little or no connection with other facts. Just drop them; it is useless to memorize them, since at any rate after the examination they will escape your memory again. Remember: "Non scholae sed vitae discimus." Bear also in mind the following: you should feel like workmen collecting all kinds of material needed for a building. At the same time, however, you should feel like architects having before their mental eye the building to be erected and making the selection of the material accordingly. You may feel that it is easy for me to give such advice, since I myself no longer have to pass examinations. The horror of them seems to be the same all over the world. One always is afraid of too much curiosity on the part of the examiner. Though I have no great personal experience as to the fashion of examination in this country, I'm pretty sure that, according to the general way of thinking, one is not examined on details which only could be learned by heart. In spite of this, the students most carefully study textbooks or even learn them—this may be a little exaggerated—by heart. On the one hand, it may be true that this fashion of studying guarantees a kind of security. But, it involves, in my opinion, great dangers. Textbooks often contain apparent facts or interpretations of facts which, after a short while, may prove to be wrong. At any rate, in my opinion, you should not consider textbooks a Bible; or else a dogmatism may be created, even for a lifetime, as dangerous as all dogmatisms are, since it may prevent you from independent thinking. This danger is still increased if you use most of your time for the study of textbooks. How could you then spare time for thinking? Don't misunderstand me.

You obviously should use textbooks. But let me caution you, "Try all things, yet hold fast to that which is good."

Since I have broached the question concerning the bad terms existing between the study of textbooks and the spare time, I want to discuss the question from another angle. Whenever one speaks with students, they claim that they have so much to study that they can't spare time for anything else. I do think that quite often a self-deception is involved there. In my experience, even the busiest people can spare time if they have the strong will to do it. This will, however, is only present if another achievement seems to be more important than the routine work. I am sure that if people fall in love, they will always find the time to meet, however busy they may be. Or, whenever the question of career comes into play, suddenly time will be available for writing many long letters or for paying visits to influential people. Very often, however, the same people may postpone even indefinitely the writing of letters on behalf of other people. This obviously seems to be not so important and therefore they do not find the time. In addition, most of us, especially those who are accustomed to one-sided work, are suffering from a genuine inertia of mind, and a strong expenditure of mental energy is needed to overcome it. It is this inertia of mind which creates our unwillingness to change our habits, to interrupt or abbreviate our routine occupation in order to spare time for other things. It is this inertia of mind which is at the basis of the excuse for not having time. As a matter of fact, in most cases, this proves to be an unconscious sham excuse.

I am sure that you are curious to learn why I am dwelling on this topic. Here is the answer. It is at least highly desirable that we get training, not only of one ability, but of as many as possible. There exists a physiological background for this. We know that abilities and qualities, if not utilized, become atrophied. By utilization, they are developed. This development at the same time is connected with satisfaction. As a matter of fact, there exists no greater satisfaction than that which results from achievements accomplished by the utmost display of our abilities. Why miss it?

Furthermore, I am sure that occupation with other things than our routine work favorably reflects on it. We almost never know where our ideas come from. It may be that deep impressions which we get in other lines than in the line of our routine work are unconsciously stimulating.

I obviously cannot give you any guarantee that by occupation with things apart from medicine you would get new ideas. At any rate, however, I am convinced that conditions for creative work would be improved, since deep impressions of any kind would raise the level of the brain. In addition, they enrich life and enlarge our horizon. All this, at the same time, serves to benefit our professional work. I wish to dwell for a moment on this very point. By far the most of you in future will have to deal with sick people. Out of the close mutual relations, discussed before, existing among all parts of the organism there have been stressed since olden times, and are stressed nowadays to an ever increasing extent, the influences exerted by the state of the psyche on the somatic functions. You are familiar with this relationship. You know, for instance, as well as I do, that if we are in low spirits we are lacking appetite—this means that, owing to psychical influences, the secretion of our gastric glands is diminished; you also know that sudden sad impressions by whatever door they enter our consciousness, may provoke fainting, which means a transitory paralysis of the respiratory and vasomotor center. You know, furthermore, that the state of the psyche to quite a large extent is responsible for the outbreak and the course of diseases. On the other hand, influences exerted on the psychical state play a big part in therapy. Here the personality of the physician comes into play. A good deal of his personality obviously is inborn. There is, however, no doubt that it can be strongly developed by the assimilation of experiences collected from all fields of human aspiration and achievement. By this means the physician's understanding of the patient, and in return the confidence of the patient, will be increased; a necessary condition for favorable influence.

I hope that I have succeeded in convincing you of the importance of broadening your horizon. If so, I am sure that you will find the time to do it. Where there is a will, there is a way. You may object that giving way to my suggestion would interfere with your much-needed relaxation. Do not believe that one relaxes only by keeping the brain passive, as happens for instance, at least to me, in most cases in movies. This passivity is the reason why we rarely get a lasting impression of them. I can, of course, not exclude the possibility that this is one of my own shortcomings. Be that as it may, this much is certain; that you get out of things only as much as you have put in. By engaging in activities which exercise other faculties, we really relax much better from a job which keeps busy only one side of our mental abilities. It is in the main the change as such, which produces relaxation. Why not choose a change which at the same time supports the growth of spirit and mind, thereby contributing to the perfection of the personality and preventing one from becoming the worst thing I could imagine—a narrow-minded, complacent bourgeois? You are in the very age where one is most susceptible to impressions. Do utilize these years and do strive to give the lie to the sad words: "Life is a chain of missed opportunities."

There exist many opportunities for our perfection. But how to select them? We need an inborn instinct or, in most cases, a challenge from without. Whether or not this challenge is offered to us is partly dependent on chance. When I was fifteen years old, a cousin of mine who studied history of art returned from a trip to Italy. He was enthusiastic about it and showed me photos of the paintings of the great masters. Never before had I cared for art. From that very day I started to read about art and to visit museums whenever I had the opportunity. Eventually my interest had grown so strong that I began to study history of art when I first came to the university. Furthermore, there were very famous symphony concerts in my home town. I was taken to three of them with the result that every time I fell asleep. Later at the university, I made the acquaintance of a fellow student who was an oustanding musician. He encouraged me to go to concerts with him. Eventually he succeeded in persuading me to do so. He helped me to understand the essence of musical creations, with the final result that ever since I have been a great lover of music. In fact, I simply cannot imagine how I could have enjoyed life as I have, without my enthusiasm for fine arts and music, once aroused just by chance. By the way, art, undoubtedly the highest human achievement, means much more than a mere contribution to the enjoyment of life, which can be created by other means as well. Most people feel this instinctively. What is it? I could not express it better than by quoting some of the philosophers. They suggest that the exposure to beautiful sights and sounds must inevitably raise the spirit and refine the temper of those who see and hear, and make them communicants of the same divine order. The love of music, according to Plato, is a hopeful symptom, an aspiration toward harmony in an inharmonious world. This really means something more than mere enjoyment.

I have presented my personal experiences in connection with art not only because they demonstrate the important role played by chance in our life, but also because they show at the same time that we may possess hidden inclinations and qualifications of which we are not aware and which, once they are discovered by chance, we are able to develop even to a high degree. We always will come across such chances provided we own that curiosity which creates the will to learn, to search, to perfect ourselves.

I was eager to outline some of the principles which seem to me most important to yourselves and your fellow men, for your profession as well as for your life. The epoch in which we live may be not too favorable for the full realization of these principles. Taking this into account I have to be satisfied and, indeed, I would be satisfied, if at least I had succeeded in convincing you of the value of these principles. I could not summarize them better than by quoting the words: "A man's reach should exceed his grasp, or what's a heaven for?"

II

From the Workshop of Discoveries

THE MAIN purpose of a single lecture, in my opinion, is not so much to mediate the knowledge of facts collected from a special field, as to give the audience an opportunity of becoming a little acquainted with the personality of the speaker, regardless of whether or not this would turn out to his advantage. Considering the huge amount of time wasted during everybody's lifetime, I have always felt that there may not be too much of a risk involved in sacrificing just one hour for any speaker, in order to find out what kind of man he is. This acquaintance can best be mediated by the presentation of ideas and experiences out of the sphere of the speaker's particular interests. For decades I have been interested in the psychological background of discoveries. I am well aware that this interest is widely shared. That is why I have chosen this topic.

What does discovery mean? Evidently an act by which something that was hidden or covered, is no longer covered; that means "discovered." The word "disclosed" has nearly the same meaning; closed before and then not closed, "disclosed." From this definition we learn that all discoveries, especially those dealing with the puzzles of life, only reveal something that has been present before.

How are discoveries made? In regard to this point a famous scientist in medicine a few years ago expressed the following opinion: "Most important advances in scientific research are made by methodical investigation under favorable conditions. The popular conception of the scientist as an intellectual superman, achieving amazing results through sheer mental brilliance, is quite unfounded. I mention these facts," he continued, "in order to emphasize that the opening of new fields in science is generally not due to the activities of some particularly smart person. Progress of this kind much more frequently arises simply because somebody is in a position where it is possible to utilize existing facilities and build up new ones where necessary."

This view, held by a great many people, seems to me to be at least too limited. Anyway, it is diametrically opposed to the more general view expressed in the well-known saying:

> The cage is by no means the thing
> Determining whether the bird can sing.

In fact, there exist several modes of discovery. We may distinguish roughly at least three of them: discoveries made by chance, discoveries made by intention, discoveries made by intuition or imagination. I want to emphasize, however, that the borderlines are not always sharp. There exist transitions and combinations.

The first category of discoveries, made by chance, originates from an unintentionally made, hitherto unknown observation. The mere observation is not yet a discovery. It becomes one only if one makes a proper use of one's good fortune. This is possible only if one recognizes its importance. For this, one has to be prepared. This view is expressed in a fine way in a well-known saying of the great Louis Pasteur: "Dans les champs de l'observation le hazard ne favorise que les esprits préparés." "In the field of observation chance favors only the prepared mind." I was quite impressed when I saw these words carved in golden letters at the entrance of Vanderbilt Hall at Harvard.

In order to prove that an observation without full recognition of its importance is not highly appreciated, I feel that I have to bring some examples. In 1860, Woehler, a pioneer in chemistry, isolated cocaine, a so-called alkaloid. I am sure that you are familiar at least with the name of this important drug. Woehler took a trace of it in his mouth and noticed that it made the tongue numb and almost devoid of sensation. Since he was a chemist, one could not expect him to recognize the importance for medicine of this observation. About twenty years later, in 1879, someone else found that after subcutaneous injection of cocaine the skin overlying the injected area became insensitive to the prick of a pin. He recommended this agent as of possible use clinically as a local anaesthetic, or analgesic—as a tool for preventing pain. His suggestion was not acted upon. Why not? There must have been something wrong about it. Either the man did not fully recognize the importance of his observation or he was not persistent enough to attempt to convince other people by a more glamorous experiment. At any rate, his name is sometimes mentioned by experts, but he has had little credit for his work. The credit for a discovery is in general awarded to the man who puts the dot on the *i*. In the case under discussion the credit has been unanimously awarded to Karl Koller, an assistant to Sigmund Freud, later a famous ophthalmologist in New York City. I cannot refrain from quoting a letter of Sigmund Freud's wherein he describes the circumstances:

> In the autumn of 1886 I settled down in Vienna as a physician and married the girl who had been waiting for

> me in a distant city for more than four years. I may here go back a little and explain how it was the fault of my fiancée that I was not yet famous at that early age. A side interest, though it was a deep one, had led me in 1884 to obtain from a chemical firm some of what was then the little-known alkaloid cocaine and to study its physiological action. While I was in the midst of this work, an opportunity arose for me to make a trip to visit my fiancée, from whom I had been parted for two years. I hastily wound up my investigations on cocaine and contented myself in my book on the subject with prophesying that further uses for it would soon be found. I suggested, however, to my friend Koenigstein, an ophthalmologist, that he should investigate the question of how far the anaesthetizing properties of cocaine were applicable in diseases of the eye. When I returned from my holiday, I found that not he but another of my friends, Karl Koller, to whom I had also spoken about cocaine, had made the decisive experiments on animals' eyes and had demonstrated them at a congress in Heidelberg. Koller is therefore rightly regarded as the discoverer of local anaesthesia by cocaine, which has become so important in surgery; but I bore my fiancée no grudge for her interruption of my work.

Koller demonstrated before the congress that after previous instillation of a little bit of cocaine in the eye of a rabbit, the lid could be cut out without any reaction by the animal indicating pain. Cocaine as a local anaesthetic was immediately accepted and has been in extended use up to our day.

Now I would like to cite a classical, most important and far-reaching discovery originating from the purely accidental observation that frog legs, hanging by a copper wire suspended from an iron balustrade in Galvani's home in Bologna, twitched when they swung in the wind and happened to touch the iron. This accidental occurrence was the beginning of long series of researches on the electrical manifestation of living tissues. Later on it led to experiments of Volta on the production of electrical currents by contact of two dissimilar metals and thus to the invention of the electrical battery, with all its later consequences of the telegraph and, indirectly, of the telephone and radio broadcast—not to mention television. And such was also the origin of our knowledge of animal electricity, for which now, for instance, we find use in the electrocardiogram or the encephalogram for information about the condition of the heart or of the brain.

Another example of a purely accidental observation whose importance was immediately recognized by the observer is the following: Pasteur, as far back as 1878, observed by chance that contamination of cultures of bacteria by air-borne organisms prevented the further growth of the bacteria. Pasteur immediately recognized the importance of this observation and prophesied that one day this observation might become the starting point for the cure of infectious diseases. A sick man, he was not able to follow this lead. In 1929, Alexander Fleming in London rediscovered the matter. He noticed that a mold, *Penicillium notatum,* similar to the one that grows on shoes, at the seashore, and on bread and cheese, had contaminated some of his culture media on which he was growing a particular species of bacteria (called staphylococci). This is quite a common occurrence in any bacteriological laboratory, usually resulting in discarding of the cultures. But Fleming observed that around a large colony of mold there was a clear area, the staphylococcic colonies having become transparent. This made him stop to think. Perhaps the mold produced some substance that killed the surrounding bacteria and thus accounted for the clear zone. He was right. It was no guess, but a logical deduction based on a piece of shrewd and careful observation.

Attempts made by himself, and a few years later by another English scientist, to isolate the active principle from the mold in a durable form, were unsuccessful. It was not until 1940-42 that other scientists in England, Florey and Chain, succeeded in purifying the product obtained from the culture, wisely preserved by Fleming through all these years, analyzing it chemically, studying its properties, standardizing it, and putting it to therapeutic use in a few selected cases of grave bacterial infection. Since then their observations have been amply confirmed and, as you know, this new drug, penicillin, has become the most priceless therapeutic agent ever offered to mankind.

These examples may suffice to illustrate discoveries based on ingeniously used observations made by pure chance.

The second way in which discoveries can be made — I called them discoveries by intention — consists in carefully investigating a subject, which is of interest for one reason or the other, without knowing at the very start how to attain decisive results and of what kind they eventually may be. As an example, I should like to cite the following: The outstanding American physiologist, the late Walter B. Cannon, as a young student, more than fifty years ago, shortly after the X-rays had been discovered, was using them to look into animals in order to watch the little-known process of digestion. Occasionally he observed that the motions of the intestinal tract came to a dead stop. Soon Cannon noticed that the cessation of the digestive activity was associated with signs of emotional disturbance in the animal. These observations were the beginning of extended research by Cannon on the influence of fear and rage on bodily functions, research which ultimately led to insight into the agencies of our organisms which maintain its stability and to a suggestive concept of the nature of emotional excitement. In fact, they form a good deal of the experimental background of our knowledge in modern psychology and psychiatry.

The third mode in which a discovery can come about is by way of intuition. Nowadays one likes to call the phenomenon a hunch, a word introduced by Platt and Baker in 1931 in a paper on "The Relation of Scientific 'Hunch' to Research." "Hunch" originally meant a push or sudden thrust. Platt and Baker characterized the scientific hunch as "a unifying or classifying idea which springs into consciousness as a solution to a problem in which we are intensely interested." Intuition or hunch has played an enormous part in a great many discoveries. An inquiry made by Platt and Baker among chemists showed that by far the majority did have hunches. The similarity of their reports on their personal experiences is striking. Here are just a few examples:

"At three o'clock in the morning I awakened with an entirely new process before my mind's eye." "Sunday in church the correct principles came like a flash, as the preacher was announcing the text." Or "Freeing my mind of all thoughts of the problem, I walked briskly down the street, when suddenly at a definite spot which I could locate today, as out of the clear sky above me, an idea popped into my head as emphatically as if a voice had shouted it."

Among the discoveries due to hunch are most — not to say *the* most — important ones. Let me mention just two most famous cases:

For years Charles Darwin was accumulating great numbers of facts without being aware of their general meaning.

Then one day, all of a sudden, like a flash, a hypothesis as to the origin of species occurred to him which allowed him to interpret the meaning of most of the collected facts from a single point of view. After having had this hunch Darwin elaborated and finally framed his statement of the theory of biological evolution.

The second famous case is the following: The great German chemist Von Kekulé solved the problem of the structure of a most important organic molecule. He hit on the conception that benzene had the structure of a ring, an idea that revolutionized organic chemistry. He reported that he came to this idea when, in a fatigue-engendered daydream, he saw a snake catch its tail, thus forming a ring.

The description of this event reminds me of a statement ascribed to Leonardo da Vinci, wherein he contends that the repeated sight of the shape of a ruined wall suddenly led him to the creation of the "Madonna of the Cave," one of his finest paintings.

Am I entitled in speaking of discoveries in science to bring in an analogy taken from the realm of art?

I would not venture to decide the question whether or not creations of art can be called discoveries in a special sense. One thing, however, is clear: though the essence of art and science is different insofar as art appeals to our emotions, science to our reasoning, there exists a huge body of evidence that intuition is at the basis of creation in art, as well as in science. Furthermore we have to recognize that the analogy between artistic and scientific creation extends beyond the basic act of imagination. In art as well as in science, the final achievement depends on the shaping of the original idea into the finished work. This effort has to be continued until the result conforms to the original concept. One may sometimes succeed in doing this in a short span of time. More often it may require months or even years of sustained effort, demanding all the skill and patience one can muster. In art one can find legions of examples for this in sketches, notebooks, and manuscripts of the great masters.

In the field of science, the sudden idea enlightening relations which were before obscure, is combined with the conviction that the idea is correct. This conviction is so strong that even if one meets with the greatest difficulties in attempting to prove the correctness of the idea, one is not discouraged but continues to work. Several times in my life, I have had the good fortune to make discoveries. I should like to discuss two of them, as they show at the same time similarities and divergences. I trust that you do not consider that the discussion of some of my own work originates from a lack of modesty. Only the author himself is in a position to report correctly on his inner experiences.

The first discovery relates to a problem concerned with the metabolism of proteins which are, as you know, indispensable for the structure and function of the organism. The discovery was made by me in 1901. Up to that time no one had succeeded in maintaining animals by feeding them, in place of native protein, with the products of its degradation, even if the degradation had not gone very far. It looked, therefore, as if animals were not able to synthesize their own proteins from the degradation products. I knew of course about this state of knowledge; I was, however, not especially interested in the question. This state of mind, all of a sudden, was remarkably changed.

One evening it happened that I read a paper just published by one of my colleagues who was the biochemist at my university. In that paper he showed that, by a simple procedure, one can decompose the proteins of an organ to such a degree that there is no longer present any reaction characteristic of proteins. At once I got the idea and the firm conviction that I would succeed, by feeding such degradation products of a whole organ, in reaching a protein synthesis in animals. If anybody would have asked me why I was so firmly convinced of the eventual success of such an experiment after all the negative experiences of the past, I could not have given him any answer. By now I have at least a guess. I was so excited that, when I went to bed that night, I was unable to find any sleep. At one o'clock, therefore, I got up again, in order to make immediately sure whether my colleague, the biochemist, did not himself want to perform these experiments. He was, of course, already asleep. I remember very well how he, not very congenial even in daytime, berated me for my brainstorm. Without opening the door, he yelled at me: "No, and now let me alone." My project seemed so important to me that early the next morning I sent one of my friends to him, to verify that he really did not intend to work it out. His answer was: "I don't care whatever this fool does, who wakes up decent people after midnight."

So I immediately started with my experiment. For a very long time I encountered the greatest difficulties, mainly for the reason that the animals did not relish the unusual food, which in fact was not a very appetizing one. I am pretty sure that many another would have been discouraged and would have stopped the experiments. I, however, had such strong faith in final success that I persisted. This was rewarded, as eventually I overcame all the difficulties and was able to prove the correctness of my hunch that animals are able to rebuild their proteins from their final degradation products. In fact, total degradation within the intestine has since been shown to be the normal fate of fed protein. From that time to the present day this discovery has proved to be of utmost importance for the science and practice of nutrition. At the time I made the discovery, I did not at all foresee this consequence. That often happens and it reminds me of a well-known saying of Benjamin Franklin. He was witnessing the first demonstration of a purely scientific discovery and people around him asked, "But what is the use of it?" Franklin answered: "What is the use of a new-born child?"

My second discovery due to mere intuition relates to the mechanism of the transmission of the nervous impulse to the effector organs. I feel that I have to explain what this means. Suppose that you intend to raise your arm and you achieve this movement. This comes about in the following way: The intention is located in the cortex of the brain and provokes here an impulse. This travels to the co-ordinating centers of the intended movement, from there to the nerves, controlling the muscles to be involved in the movement, and is finally transmitted to the muscles. You can obtain the same movements by stimulating directly by electrical means the respective parts of the brain cortex. Let us take another example: you know that joy very often accelerates the beats of the heart and that sudden fright may slow or even stop it. How does this happen? Both emotions start also in the cortex of the brain, as this is the first recipient of impressions leading to emotions. In the case of joy the impulse raised by it travels in the way of the so-called sympathetic nerves; in the case of fright it travels in the way of the so-called vagus nerves to the heart. This is proved by the fact that, exactly as by joy or fright, you can produce acceleration or slowing of the heart beats by directly stimulating the respective nerves. The problem was to find out by what kind of mechanism an impulse, raised in a nerve by stimulation of its center or of the nerve itself, is transmitted to the effector organ. All that was known about it was that if a nerve is stimulated, a so-called excitation is produced, which is propagated within the nerve, and that this propagated impulse initiates or modifies the function of its effector organ. It was also known that the propagated impulse is accompanied by an electrical wave. It was generally believed that this electric wave would spread from the nerve to the effector organ and there elicit the specific reaction. This hypothesis, however, for several reasons could not be the correct answer. Therefore, another mode of transmission had to be taken into consideration, and was in fact seriously considered, namely a chemical mechanism. What this means you will immediately learn. As a matter of fact, in 1921, I was fortunate enough to be able to prove beyond any doubt the correctness of this chemical view by a very simple experiment. The hearts of two frogs were isolated, one with the vagus and sympathetic nerves connected to it, one without connecting nerves. The first heart may be designated as the donor heart, the second as the recipient. In each heart a small glass cannula was inserted, containing a bit of a salt solution which is able to maintain normal heart activity for many hours. Now for a short period the vagus nerve connected with the donor heart was stimulated with the usual effect: decrease of the heart beats. Then the solution that had been in the donor heart during vagus excitation was transferred to the recipient heart; the result was that it behaved exactly as the donor heart did during the vagus stimulation. When, instead of the vagus, the sympathetic nerve of the donor heart was stimulated, and the content later transferred to the recipient heart, the effect was again identical with that of the nerve stimulation: increase of the heart beat. By this means it was proved that the stimulation of nerves liberates from their endings chemical substances and that these very substances cause the characteristic modification of the heart action. In other words, a nervous impulse is transmitted to the tissue of the heart by chemical substances which may be called, and are called, chemical transmitters.

This discovery was the starting point for a host of investigations all over the world, eventually resulting in the proof that the transmission of impulses of all the efferent nerves to the effector organs in the organism is of chemical nature.

As I told you before, the possibility of a chemical transmission of nervous impulses had been considered before the time of my experiment. Accordingly, one may perhaps be inclined to say that the idea of such a mechanism was in the air at the time. I, personally, am of the opinion that what may be in the air at any time is not ideas, but rather desires or general views of possibilities or probabilities. An idea apparently means much more, something much more concrete. An idea, in my opinion, must already include the way to be followed in order to solve a problem. If in an age of piety a painter feels the desire to paint a madonna, I don't think one can call this an idea. He has got an idea only in the moment when he has formed a definite mental image of the type of madonna he wants to paint.

Consciously I never before had dealt with the problem of the transmission of the nervous impulse. It therefore will always remain a mystery to me that I was predestined and enabled to find the mode of solving this problem, considered for decades to be one of the most urgent ones in physiology. And like me you will find it still more mysterious when now I tell you the story of how the discovery happened.

In the night of Easter Saturday, 1921, I awoke, turned on the light, and jotted down a few notes on a tiny slip of paper. Then I fell asleep again. It occurred to me at six o'clock in the morning that during the night I had written down something most important, but I was unable to decipher the scrawl. That Sunday was the most desperate day in my whole scientific life. During the next night, however, I awoke again, at three o'clock, and I remembered what it was. This time I did not take any risk; I got up immediately, went to the laboratory, made the experiment on the frog's heart, described above, and at five o'clock the chemical transmission of nervous impulse was conclusively proved.

When I was asked at the International Physiological Congress in Boston in 1929 how I happened to make the discovery, I gave the same account. A former student of mine, the late Sir Walter M. Fletcher, on this occasion, however, reminded me that in 1903 I had already expressed the view that, as certain chemicals act exactly like stimulation of certain nerves, it may be that these nerves, in their turn, act by liberating chemical substances. This I had entirely forgotten.

This story shows that an idea may sleep for decades in our subconscious mind and afterwards can suddenly return and become active. Furthermore, this story indicates that we should sometimes trust a sudden intuition without too much skepticism. Careful consideration in daytime would undoubtedly have rejected the kind of experiment I performed, because it would have seemed most unlikely that if a nervous impulse released a transmitting agent, it would do so not just in sufficient quantity to influence the effector organ, in my case the heart, but indeed in such an excess that it could partly escape into the fluid which filled the heart, and could there be detected.

Yet the whole nocturnal concept of the experiment was based on this eventuality, and the result proved to be positive, contrary to expectation. I needed still some other co-operation from the side of the heart in my effort to detect the dreamed-of substances to be released by nervous stimulation. To go into details in regard to this point would require too many technical explanations and lead us too far afield. It may suffice to tell you that also in this case the heart, unexpectedly, was kind enough to lend me the support I needed. All this tends to prove the correctness of the view pointed out before, that one sometimes should trust a sudden "hunch."

It was my good fortune that at the moment I had the hunch, I did not think, but acted immediately; otherwise the discovery would not have been made, at least not by me. Conforming with this view, Ralph Gerard wrote: "Ideas are mostly bad by the criteria of judgment, and experience or expertness suppresses them." For many years I have liked to contend: "In order to become a discoverer one has to be a naïve ignoramus." I am of course conscious of the fact that this word involves some exaggeration and that the qualities just implied are not quite sufficient prerequisites.

A comparison of the background of the discovery of the synthesis of protein with that of the chemical transmission of nervous impulses reveals at the same time similarities and divergences. I want to deal with this matter a little more closely.

It is evident that in the case of the protein synthesis, chance played a part. There can be no doubt that if on that evening I had not read the paper of my colleague, the idea of the crucial experiment would not have occurred to me. I emphasize "on that evening," as I am not sure whether the idea would have occurred to me at any other moment.

In the case of the chemical transmission of nervous impulses, on the other hand, chance apparently was not involved. Otherwise I could not have forgotten the idea which occurred to me during the first night. This fact, by the way, at the same time makes it most likely that the idea was born during sleep. This assumption is supported by the fact that the idea was already present in the very moment when I awoke. How may one explain this phenomenon? It presents in my opinion just a special manifestation of the general experience that during sleep our mental and emotional life is not entirely stopped but continues in certain lines. Think of the fact that a deeply sleeping mother may not be awakened by thunderstorm, but may be by a soft moaning of her infant, or that many people wake up exactly at the time at which on the preceding evening they had intended to wake up in the morning. Think, above all, of dreams. Most of them seem to be illogical; why should it not happen that once in a while they are logical, sound, and even useful?

At any rate, authors like Nicolle, Cannon, Gerard, and Coleridge, the poet, who dealt with the part played by intuition in the mechanism of discoveries, stress the frequent occurrence of ideas in subconscious states of mind. Let us first listen to Coleridge: "Ideas and images exist in the twilight realms of our consciousness, that shadowy half-being, that stage of nascent existence in the twilight of imagination and on the vestibule of consciousness." Gerard expresses the same idea in this way: "Simple imagination is observable in a pure and untrammeled state in dreams, in the hallucinations of drugs and other agents, in those hypnagogic states which interpose between wake and sleep, or in the slightly fettered day-dreamings while awake." Cannon, finally, writes: "According to my experience, a period of wakefulness at night has often been the most profitable time in the twenty-four hours. This is the only credit I know that can be awarded to insomnia." The most probable explanation, then, as mentioned before, is: release of ideas suppressed during daytime by criticism.

We started from the statement of a divergence between the two discoveries in so far as the part played by chance is concerned. Now let me deal with similarities of the processes which are at the bottom of the two discoveries.

The first similarity is the fact that in both cases the conception of the problem and of the way to solve it occurred to me at a time when I had no particular interest in it. I did not look for this conception; it just came to me. In fact, in both cases I had the feeling that I myself was passive, just a kind of receptive vessel. This is the reason why I never felt a special merit in making these discoveries. All that one could perhaps appreciate is the immediate comprehension of the importance of the ideas and the persistency in carrying them through. The second similarity between the two cases consists in the fact already mentioned before, that from the outset I was firmly convinced, and had the faith, that my intuition met with the truth.

I have no doubt that the characteristic mental process which is the basis for any discovery, is dependent on an instantaneous particular disposition of our spirit. How sad that we don't know anything about the mode of this necessary ceremonial! Otherwise we would often prepare it and our discoveries would not be so rare. We can't do anything about it. It told you that the ideas which led to the two discoveries came to me spontaneously. I did not look for them. On the other hand, I have racked my brain for decades in order to find a way to solve a particular problem most urgent to me. In vain, for this night did not return. Will it come at all? And if so, when? I am almost seventy-nine; there is not too much time left for me. After all, I do not share the optimistic view of Cannon that the advantage of receiving sudden and unexpected insight could perhaps be cultivated and thus possessed by all.

It seems to me almost superfluous to emphasize that the instantaneous particular disposition, just mentioned, becomes manifest only on the basis of particular inborn qualities. Important among them are an unlimited enthusiastic curiosity, striving for causal understanding, and strong perseverance.

Could we not take advantage of such truths as these and thereby obtain the means to support the advancement of science?

About twenty years ago I was asked how to decide whether or not a certain man would be fit to be promoted in his scientific career. I answered: "Do not use as yardstick for his abilities the number or the weight of the publications, as you usually do, but the number of the sleepless nights when he was struggling with problems."

III

Problems in the Field of Adrenal Function

MANY AGING scientists have an ever growing drive to integrate single facts into a whole, which frequently leads to oversimplification. This, however, does not seem to be momentous if one considers the highly stimulating value of general conceptions. I experienced this stimulation when some time ago I had to review the vast bulk of recent studies on adrenal functions, a topic almost as stylish as the isotopes. I hope that the thrill created within me by these studies will prove to be contagious to you.

We owe the initiative, as well as the development, in the field of the adrenals in a great part to scientists and clinicians of this country. It started here, as far as I know, with the work of Walter B. Cannon. It was in 1897 that Cannon, at twenty-six, used X-rays, which were discovered two years before, for the first time as a tool in physiology, especially for exploring the gastric movements.[1] I cannot refrain from quoting part of the report on his first observations made on a female cat, because of the pioneer character of the paper and the beauty of the formulation:

> While the peristaltic undulations were coursing regularly over the cat's stomach, she suddenly changed from her peaceful sleepiness, began to breathe quickly and struggled to get loose. As soon as the change took place, the movements in the stomach entirely disappeared. I continued observing and stroked the cat reassuringly. In a moment she became quiet and began to purr. As soon as this happened the movements commenced again in the stomach. This

> experiment was repeated a great many times on different cats and invariably the evidence of distress was accompanied by a total suspension of the motor activities of the stomach. Since expression of strong feeling on the part of the animal always accompanied cessation of the constriction-waves, the inhibition was probably due to nervous influence. It has long been common knowledge that violent emotions interfere with the digestive process, but that the gastric motor activities should manifest such extreme sensitiveness to nervous conditions is surprising.

This was the beginning of a long series of most successful studies on the effect of emotions on the body.[2] They resulted in the statement that the sympathetic nervous system is especially involved. As the adrenal medulla is innervated by this system, the investigations were extended by Cannon to the question as to the physiological function of this gland; and it was found that any stronger emotion leads to the release of epinephrine, known to influence the single organs exactly as does the stimulation of their sympathetic nerves. Cannon furthermore found that epinephrine is liberated not only in case of emotion but in any case of what he called emergency. Nowadays it is generally called stress. This can be produced by a great variety of factors as, for example, exposure to cold, excessive muscular exercise, asphyxia, strong stimulation of sensory nerves, trauma, drop of blood pressure, hypoglycemia, hemorrhage. As the secretion of epinephrine is mediated exclusively by nervous means, all the factors mentioned before obviously stimulate directly or reflexly the center controlling epinephrine secretion. The ability to respond to such a multitude of stimuli distinguishes the sympathetic center from all the other centers, which as a rule are sensitive only to specific stimuli. This ability is, however, the prerequisite for its essential function, consisting in the adjustment to special needs. Such a need, for example, exists when the organism has to make an immediate display of energy. As has been pointed out by Cannon, the sympathico-adrenal system in such a situation augments all the functions needed for bodily achievements. The second function of the sympathico-adrenal system consists in the readjustment of many disturbed functions, that is, in the maintenance of constancy, called homeostasis.

We have seen that stimulation of the sympathetic center acts qualitatively exactly as does epinephrine released from the adrenal gland or administered from without. This is obvious, as the stimulation of the sympathetic nerves acts by releasing epinephrine from the nerve endings.

By and large our knowledge of the physiological functions of the adrenal medulla in time has become fairly complete, except for its metabolic effects, to be discussed later. Hence research has increasingly turned to the exploration of the physiological functions of the next-door neighbor of the adrenal medulla, the adrenal cortex. This gland shares with the adrenal medulla the function of maintaining homeostasis and of supporting the organism in cases of stress. There exists a kind of division of labor: the control exerted by the sympathico-adrenal system extends in the main to the specific functions of the organs; the adrenal cortex regulates in the main general functions of the tissues — namely, those connected with metabolism in the widest sense. In many cases the two glands co-operate, their activities being complementary. As to the exact character and number of the hormones through which the cortex meets with the organismic requirements, not too much is definitely known. No less than twenty-eight steroids so far have been isolated from the cortex. There is no doubt that most of them are intermediary products used for the formation of true hormones and/or, maybe, represent physiologically active degradation products. Until the present time it has generally been assumed that two major types of steroids are secreted: an 11,17 oxysteroid as cortisone, and a steroid acting like the synthetic desoxycorticosterone, the first responsible mainly for the regulation of the organic metabolism, the second mainly for the control of the water and salt metabolism. The final answer to the question as to the chemical character and number of the true hormones will be found only by their isolation from adrenal venous blood.

The function of the individual hormones has obviously to be disclosed by analysis of their effects; this has been attempted in various ways: Experimenters have studied the effects by applying various doses to normal animals and men under normal conditions. Since their adrenal cortex supplies them with an amount of hormones sufficient to maintain their normal state, the effects produced by additional hormones obviously are not of physiological but of more or less pharmacological or even toxicological character. The procedure needed to get information about the physiological action of the hormones and thereby about the physiological part played by the adrenal cortex, consists in the study of the symptoms produced by adrenal insufficiency and of the influence exerted upon them by adequate doses of hormones. The study of two kinds of adrenal insufficiency has served and will in future serve this purpose: absolute insufficiency as brought about by adrenalectomy, and relative insufficiency as produced, e.g., in stress, where the normally available amount of cortical hormones is not sufficient to cope with the increased needs. A huge bulk of experiments has been conducted also in this connection. From those studies resulted what we know of the main functions of the cortical hormones, especially of cortisone and of a hypothetical desoxycorticosterone-like compound. Yet it has to be stressed that incidentally the effects of these two compounds are overlapping. According to an increasing number of reports, depending on conditions, both may display the same final effect, desoxycorticosterone, for example, influencing also the organic, and cortisone influencing also the salt and water metabolism. Hence, some scientists are inclined to believe that only one hormone may be secreted.

Now I would like to discuss the rather thrilling question of the mechanism responsible for the release of cortical hormones according to the needs of the organism under physiological conditions, as well as under those of stress. Most different kinds of stress have been shown to cause increased secretion not only of epinephrine but also of cortical hormones. To the kinds of stress enumerated before has to be added stress provoked by a colorful series of chemical agents, such as benzene, ether, chloroform, insulin, diphtheria- and tetanus-toxin, histamine, Dibenamine, nicotine, estrogens. How do they produce the increased secretion? It has been definitely proved that the only substance which is able to stimulate the cortex directly and to provoke and maintain its secretion is ACTH, the adrenocorticotrophic hormone of the hypophysis. After hypophysectomy the secretion of the cortex — apparently with one exception — in time almost ceases and the cortex undergoes atrophy. The exception relates to the cortical factor, responsible for the control of the salt metabolism. In some species its secretion apparently is independent of the anterior lobe. Dogs, for example, surviving hypophysectomy for many months, maintain the salt balance until their death,[3] though the zona glomerulosa of the cortex, so far believed to be the source of the salt-water factor, participates in the atrophy of the layers of the adrenal cortex.[4] Hypophysectomized dogs show, however, the same failure as do adrenalectomized dogs in responding to administration of a water load. This failure is partly cured by growth hormone.[5] The elucidation of the whole problem calls for much more work to be done.

From the foregoing it results that all the various factors which finally lead to release of cortical hormone must do so by liberating from the anterior lobe of the hypophysis ACTH, which, as mentioned before, is the only known direct stimulus of the cortex. The question now arises as to the mechanism involved.

It had been known for some years that there exists a mutual relation between and control of the secretion of the trophic hormones of the anterior lobe and the secretion of the hormones of their target glands. A high blood level, for example, of thyroid hormone or estrogen inhibits the release from the hypophysis of gonadotrophic hormone, respectively. A low blood level, on the other hand, of those target hormones is an adequate stimulus for the secretion from the hypophysis of the respective trophic hormones. The same statement is valid for the mutual relations between the secretion of ACTH and cortical hormones. This mechanism regulates the output of cortical hormones under physiological conditions. What happens in case of stress? It has been shown that continued injection of cortical hormone finally leads to atrophy of the cortex: there is no doubt that this is an atrophy by disuse due to the maintained lack of cortical stimulation by ACTH, because of the high cortical hormone titer of the blood, produced by the continued injection. It has been suggested by Sayers[6] that the same mechanism is involved in the stimulation of the cortical secretion by stress, in which he includes the effect of epinephrine. This claim has been based upon the assumption that any kind of stress primarily influences the tissues, which utilize the cortical hormones, in such a way that their utilization is increased, consequently lowering their blood level and thereby increasing the release of ACTH and finally of cortical hormones. It seems difficult to imagine that so many different kinds of stress, like those mentioned before, should have the same primary effect on the tissues, consisting in increased utilization, which means inactivation, of cortical hormones. It is more probable that there exists a common denominator in all cases of stress, responsible for the increased cortical secretion. As we have seen, each kind of stress starts with stimulation of the sympathico-adrenal system; at the same time it has been shown that epinephrine causes secretion of ACTH. C. N. H. Long has therefore suggested that epinephrine might be the common denominator looked for.[7] In fact, he definitely proved that epinephrine, even in very small physiological doses, almost immediately provokes secretion of ACTH. The question was still left open as to where epinephrine should act. Should it act directly upon the anterior lobe or indirectly? It has been reported by Hume[8] and Harris[9] that electrolytic lesions of definite parts of the tuber cinereum blocked completely or partly the release of ACTH following emotional stress, whereas stimulation of definite areas of the hypothalamus provoked it. Since severing of the neural connections between the hypothalamus and the adenohypophysis did not prevent the release of ACTH during stress, it was suggested that the hypothalamus would secrete a humoral agent which would be transmitted through the portal vascular system to the hypophysis and here provoke the discharge of ACTH. From that it was concluded that ACTH secretion is under hypothalamic control. Long,[10] on the other hand, showed that in hypophysectomized rats, in which he had implanted anterior lobe tissue into the anterior chamber of one eye, injection of epinephrine in this eye provoked secretion of ACTH. Injection in the control eye was ineffective. By this means it was definitely proved that epinephrine has not necessarily to act indirectly on the anterior lobe through the hypothalamus or by decreasing the cortisone level of the blood, but that it can act directly upon the hypophysis. The ineffectiveness of stress produced by hypothalamic lesions could be explained, according to Long, by the interruption through these lesions of tracts to or from the hypothalamus, needed for the stimulation in stress, of centers controlling epinephrine secretion. At present the possibility that ACTH secretion may be provoked not only by a direct action of epinephrine on the hypophysis, but also indirectly from the hypothalamus, cannot be excluded. On the other hand, until further notice, I don't see any objection to the view that epinephrine may serve as the trigger mechanism, by which in case of stress cortical hormone would be quickly made available. The maintenance of the secretion of cortical hormones in lasting stress depends, as under physiological conditions, on the rate of their utilization, determining their blood level and thereby the secretion of ACTH.

The disclosure that even the hypophysis, the master-gland, is, as far as the secretion of ACTH is concerned, at least partly under the command of the sympathico-adrenal system, makes it evident that the part played by this system in the adjustment of bodily functions is much greater than Walter B. Cannon, the father of the concept, could possibly have foreseen. The finding, on the other hand, that epinephrine is able to stimulate the secretion of the anterior lobe, fits perfectly into the known functions of epinephrine, consisting in the control of specific organ functions. It seems worth mentioning that the anterior lobe happens to be the only organ which, to my knowledge, is void of sympathetic innervation and whose function can still be provoked by epinephrine.

Apart from stimulating hypophysial secretions controlling metabolic processes, epinephrine regulates some of them also directly, as proved by its influence on metabolic activities also of isolated organs. It frequently happens that the recognition of a physiological function starts from the observation of a pathological event or a pharmacological effect. In the case under consideration it originated from the discovery made fifty years ago that epinephrine injection produces hyperglycemia. This observation finally led to the knowledge that, among others, epinephrine is an important factor in maintaining homeostasis by regulating the conversion of glycogen in the liver into glucose, in the muscle into lactic acid. Epinephrine furthermore regulates the uptake of glucose by the organs according to need. The glycogenolytic action of epinephrine in the liver and muscle is supported by hypophysial or cortical hormone, as it is considerably decreased in hypophysectomized animals.

There is no doubt that the increased glycogenolysis produced by epinephrine at least contributes to its hyperglycemic effect. The question has been discussed whether this hyperglycemia is due exclusively to increased formation or also to decreased utilization of glucose. One has been inclined to assume the participation of the latter factor, especially for the reason that in contrast to normal physiological states which show a significant arterial venous difference of the glucose level, this difference is practically missing during epinephrine hyperglycemia, and, by the way, also in other forms of diabetes. This was, for example, shown by Cori[11] many years ago and quite recently again by Somogyi.[12] To my knowledge it was first tried as far back as 1913 in my laboratory[13] to decide in a more direct way the question whether epinephrine would interfere with glucose utilization, using as test object the perfused heart of rabbits, in which epinephrine previously had been injected subcutaneously. It was found that in contrast to normal hearts, which take up considerable amounts of glucose from the perfusion fluid, the epinephrine-diabetic hearts took up extremely little or even none. We could show that this was not secondary to increased glycogenolysis in the heart. Only quite recently experiments in the same direction were performed in Cori's laboratory with another organ, namely, the rat diaphragm, which led to the same results as our old ones on the heart; epinephrine added to the medium markedly depressed the glucose uptake.[14] Since they are connected with the question of glucose uptake in general, I may mention experiments published by Geiger and me[15] thirty years ago which showed that frog's liver perfused with glucose containing Ringer or normal human serum takes up glucose from these media but not from serum of diabetics; and quite recently—

1950—Weil-Malherbe[16] claimed to have found that diabetic plasma inhibits hexokinase activity in rat-brain slices. Insulin brought the uptake back to normal. This result would fit well into Cori's well-known concept of insulin mechanism,[17] especially if we would accept the view that in diabetic blood a hypophysial factor would be prevailing.

Considering all these findings, it looks as if impairment of glucose utilization would be just a natural consequence of decreased glucose uptake. In this connection I have to mention that insulin, which, in contrast to epinephrine, not only decreases glycogenolysis but also strongly increases the arteriovenous difference of the glucose level of the blood, has until this moment frequently been claimed to do this by increasing the uptake of glucose from the blood, thereby increasing glucose utilization. It seems certain that the influence of each of the two hormones, insulin and epinephrine, on glycogenolysis on the one hand, on glucose uptake on the other, is opposite. This raises the question as to whether these two effects are due to opposite influences on the same underlying mechanism. Provided Cori's interpretation of the mechanism of insulin action should be accepted, increase of hexokinase activity could lead to greater glucose uptake and thereby to glycogen storage. The decrease of glucose uptake produced by epinephrine, according to a recent paper from Cori's laboratory,[18] would, however, not be due to inhibition by this agent of hexokinase activity but to the following mechanism of action. "Phosphorylase in the liver is increased by epinephrine. Liver contains an enzyme system which keeps a balance between an active and an inactive form of phosphorylase, permitting a rapid change in either direction. This enzyme system is apparently influenced by epinephrine." Again one of those cases where a unitarian explanation regrettably does not meet with the facts.

I dwelt perhaps unduly long on these problems. I could not refrain from doing so, as my interest has been focused on diabetes and especially on the influence of epinephrine on carbohydrate metabolism for more than four decades. In fact, it started in 1909 when L. Pollak, one of my students, made the discovery, inexplicable at that time, that epinephrine injection into rabbits, completely depleted by starvation of their liver glycogen, in spite of continued starvation brought the glycogen back to almost normal values.[19] Later it was shown by Cori[20] that this was due to the glycogenolytic action of epinephrine in the muscles, resulting in release from there of lactic acid and its resynthesis in the liver to glycogen.

Following the natural sequence of events, we have now to turn to the discussion of the effects of the cortical secretions and their meaning. Within the scope of a single presentation it would be impossible just to enumerate all of the effects. I therefore had to make a selection. So far the theoretical and clinical interest raised by the pioneer work of Hench, Kendall, and Reichstein has been focused on cortisone. For this reason we know a little more of it and consequently also of the still unsolved problems it offers than we know of other cortical factors; so I decided to deal mainly with the physiological effects of cortisone. Even this report will be incomplete, since for the sake of brevity I have to disregard, for example, most of the innumerable modifications of its effects originating from dosage, from interaction with other hormones and especially from differences in the status of the organism.[21] This restriction does not do any harm. A textbook or a full series of lectures devoted to a special topic should perhaps present a fairly complete report. The task of a single lecture is quite different; it should give a general picture and report on facts only as far as they are needed for this purpose. Apart from the time factor it is this point of view which justifies making an appropriate selection of the known facts.

Among the most striking effects of cortisone are apparently those exerted on the interrelated metabolism of protein, carbohydrate, and fat. Their qualitative metabolism apparently is not influenced by cortisone. This becomes evident from the fact that metabolic processes of normal character go on in the absence of cortisone — for example, after extirpation of the adrenals. One is therefore entitled to draw the conclusion that cortisone, like other, maybe all metabolic hormones, is not an essential part of the enzymes involved in the metabolism of the foodstuffs. Furthermore it could not be demonstrated that cortisone has any direct influence on enzymes, As it does not change the qualitative character of the various metabolic processes, the effects on them can only be, and are in fact, due to regulation by cortisone of the rate of metabolic processes. This regulation is achieved by an influence of cortisone on conditions essential for quantitative co-ordination of metabolic processes. To these conditions belongs among others, the mobilization of endogenous foodstuffs from tissues according to need.

Since the knowledge of this function of cortisone greatly adds to the understanding of the part played by it in metabolism, I want to discuss it. It is well known that during starvation the blood sugar level remains normal until death occurs. This is due to an increase of cortical secretion which, following the early depletion of glycogen stores, provokes and maintains gluconeogenesis, the formation of glucose. In adrenalectomized animals starvation almost from the very beginning leads to hypoglycemia. Cortisone brings the blood sugar back to its normal level.[22] The main cause of the hypoglycemia is the inhibition, in the absence of the adrenals or cortisone, of gluconeogenesis from protein. This inhibition is caused not from an inability of the liver to synthesize glucose from protein, but to inhibition of mobilization of endogenous protein from the stores to the liver, where gluconeogenesis takes place. In fact, making available protein to starving adrenalectomized animals supplied with NaCl, by feeding protein, restores gluconeogenesis and thereby brings the blood sugar back to normal. Not only in starvation, but also in other cases where more glucose is required, as in diabetes[23] or in phlorizin poisoning,[24] gluconeogenesis from protein is increased, as becomes evident by increased nitrogen excretion in the urine. Adrenalectomy also here decreases the protein breakdown and consequently the hyperglycemia by inhibition of the mobilization of endogenous protein, as also here cortisone or protein feeding brings back the former status.

What about the mobilization of fat? It has been well established that in case of lack or of diminished utilization of carbohydrate, as produced by starvation, diabetes, phosphorus — or phlorizin-poisoning, fat is mobilized from the body stores, migrates into the liver, and accumulates there. Adrenalectomy prevents also this mobilization, and cortical hormone restores it.[25]

Finally, as reported before, the mobilization also of glycogen in liver and muscle is strongly decreased in hypophysectomized or adrenalectomized as compared with normal animals and is restored by cortisone.

From these data, it appears that a basic part of the control of metabolism by cortisone consists in its capacity to promote the ability of tissues to mobilize endogenous foodstuffs.

We don't know anything of the chemical process involved in, and responsible for, mobilization. It has of course to be a different one for each individual foodstuff. It is, therefore, as was mentioned before, most unlikely that cortical hormone is involved in the process itself. Mobilization does not, or does only to a very small extent, occur in absence of cortical hormone. Consequently it seems as if cortical hormone would be necessary for the maintenance and control of the overall responsiveness of the tissues to the stimuli, informing them of the needs of the different endogenous foodstuffs. I feel that now I should insert another effect of cortisone though it is produced in the main only by excessive doses. It consists, dependent on conditions, in inhibition of growth processes.[26]

It has been established that ACTH antagonizes the effect of growth hormone in normally growing rats. ACTH acts here, no doubt, through increased secretion of cortisone, since a growth-inhibitory effect of this hormone has frequently been reported. Even if applied locally it can inhibit growth, for example, of hair[27] and granulation of wounds.[28] Like mobilization of protein, inhibition of growth processes is characterized by increased nitrogen excretion, at all events indicative of increased protein breakdown. This in its turn could be due to a primary influence of cortisone upon the protein-catabolizing process. According to Albright[29] it could also be secondary to a primary antianabolic action — namely, inhibition of protein synthesis; thereby, too, more protein would be available for catabolism. The question whether cortisone primarily favors antianabolic or catabolic processes has not yet been definitely decided. From the point of view of mental economy, which often is as erroneous as it is satisfactory, one could feel tempted to surmise that the effect of large doses of cortisone and ACTH, as just discussed, might play a part in the prevention or cure by those agents of the symptoms of acute inflammatory anaphylactic-like reactions and the symptoms of mesenchymal diseases, often regarded also as manifestations of hypersensitivity. In fact, increase of protein catabolism, regardless of whether it be a primary or secondary effect, would obviously interfere with growth and multiplication of cells and with increased turnover of material during inflammation and thereby abolish symptoms originating from that condition. It would also be understandable that a highly reactive tissue would need more cortisone to become depressed than a normal resting one. Needless to say, the extent to which the protein-catabolizing effect of cortisone might be responsible for the symptomatic cure of the disturbances just mentioned, has still to be disclosed.

I have dealt only with the influence of cortical hormone on metabolic functions and such others as are apparently connected with them. I refrained, for example, from discussing the essential role of cortical hormone for the maintenance of vigor and resistance; we don't know whether or not they are related just to their metabolic functions. In any future effort to increase our knowledge of adrenal function, we obviously have to take into account also this important function.

There is little doubt that laboratory and clinic in the years to come will extend our knowledge of normal and pathological events influenced by cortisone. More satisfactory than incidental broadening of our information would perhaps be some insight into the factors responsible for the various effects of cortical hormone. In attempting to approach this problem we have to bear in mind that, as mentioned before, the effects of any single cortical hormone show great variations whose character depends on dosage, on interaction with other hormones, and especially on the state and the needs of the tissues involved. In fact, an individual cortical hormone according to conditions can lead even to opposite final effects; it can increase or decrease growth[30] and glucose utilization,[31] it can produce anabolism or catabolism,[32] retention or excretion of sodium,[33] and so on. The capacity to produce, dependent on conditions, reverse effects is not restricted to cortical hormones: Thyroid hormone, for example, indispensable for normal growth, in adults often leads to degradation of tissues.

It was mentioned before that cortical hormone acts neither directly on enzymes nor on the process of mobilization of foodstuffs. The fact just illustrated by a few examples that cortical hormone can have different, even opposite, effects on the same metabolic process, allows the generalization that not in any single case does it take part in the intrinsic functions which it induces or modifies; or, as Ingle phrases it, that "the cortical hormones have no obligatory actions upon them." They rather have a regulating function resulting in normalization of the functions. Before discussing the means by which they may accomplish this, I would like to refer to the results of experiments which may help in promoting some idea, or more correctly some guess, as to their mode of action.

It was pointed out that after adrenalectomy the normal reaction to stimuli, informing the tissues of the foodstuffs which are needed, is missing and can be restored by cortical hormone. To this I would like to add the results of experiments illustrating the same principle: following fracture of limbs, normal rats develop a negative nitrogen balance; adrenalectomized rats do not, unless they are simultaneously treated with small doses of cortical hormone, inefficient in themselves to raise nitrogen excretion.[34] Adrenalectomized animals do not respond with hyperglycemia to traumatic shock[35] or to anoxia[36] unless they receive cortical hormone. Anterior pituitary hormone causes the development of fatty livers in normal, but not in adrenalectomized animals. After treatment with cortisone, however, which by itself does not produce fatty livers, addition of growth hormone would do it.[37] When an adrenally insufficient animal is given a high sodium or water load, its kidneys are almost incapable of ridding the body of sodium or water excess, but become able to do so when treated with appropriate doses of cortical hormone.[38]

In all these experiments the doses of cortical hormone, supplied in order to replace the adrenal cortex and thereby to restore the normal reaction to the noxious stimuli, were small physiological ones which alone did not produce the effects as produced by the stimuli. This has to be stressed because large doses of cortical hormones often produce these effects and also others of not physiological but toxicological character. They, therefore, obviously do not inform us about the physiological function of cortical hormones. The fact that under the special conditions of the experiments just quoted, physiological doses of cortical hormone were effective, does not permit generalization. The size of the doses needed depends in general on the strength of the requirements. I may remind you that in order to combat the effects of stress, the adrenal cortex does, in fact, augment its secretion.

I referred to these experiments because all of them show that, in contrast to normal tissues, tissues in absence of cortical hormone react to noxious stimuli and changes as little as they react to lack of foodstuffs. They are therefore not able to cope with the requirements to be fulfilled in order to sustain homeostasis; they regain this capability, however, when provided with physiological doses of cortical hormone. This demonstrates that cortical hormone is not just a supporting ("permissive") factor, as is almost generally claimed, but that it is indispensable for enabling tissues to respond to needs. The question naturally now arises why cortical hormone is indispensable for the adequate metabolic reactions of tissues to changes. Cortical hormone, as we repeatedly stressed, does not participate in these metabolic reactions themselves. How, then, could we explain its function?

A prerequisite for the ability of tissues to react properly to changes is their adequate susceptibility or reactivity to changes. Taking into account all the available data, I think it most likely that the presence of cortical hormone is indispensable for the functioning and the proper regulation of this reactivity. This interpretation would provide us with a unitarian concept for the understanding of the part played by cortical hormone in the function we are dealing with.

Reactivity of a very special character is a fundamental property of living matter which is dependent in an unknown way on its also obscure physical, chemical and — pardon the expression — biological structure and function. It therefore is improbable that in a measurable space of time we will find out the underlying mechanism of the part played, according to our concept, by cortical hormone in the functioning and regulation of cell reactivity. It is likely that cortical hormone is needed for all tissues. If this assumption is correct we have to surmise that there exist great quantitative differences of the various tissues in regard to their susceptibility to the hormone action and its insufficiency. This in fact is the case. I may just remind you that lymphoid elements are much more susceptible than others to a disintegrating action of cortical hormone and that also the vital function of the renal tubul to control the reabsorption of sodium and potassium particularly suffers from adrenal insufficiency. Predilection of agents for special tissues would be nothing unusual to the pharmacologist. He constantly come across different reactions to the same agent of functionally different cells, as well as of one kind of cells in different status. In very rare cases only has the cause of these differences been disclosed. These rare cases, by the way, so far do not include any hormone.

Complying with the title, "Problems in the Field of Adrenal Function," I offered more questions than answers and among these several of still hypothetical character. Is such a procedure not the rule if one has to deal with biological problems? I often hear people say: "How wonderful that there is so much left for us to explore." Maybe I am impatient and immodest; anyway I feel that too much is left.

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