

## **Adaptation in pathological processes / by William H. Welch.**

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*Adaptation in Pathological Processes*

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*Welch*



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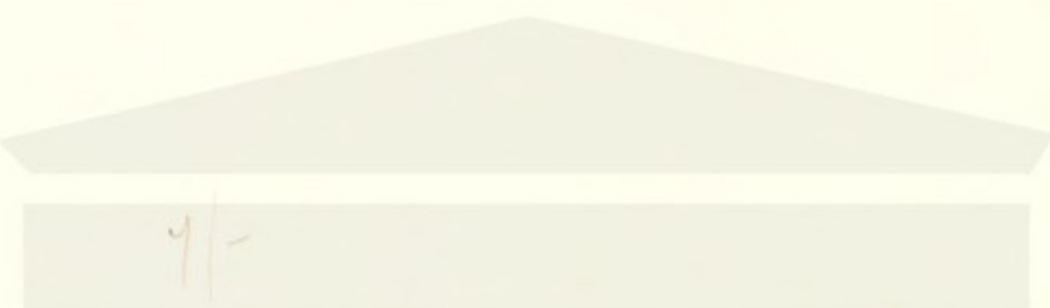
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ADAPTATION IN PATHOLOGICAL  
PROCESSES

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William H. Welch.



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# ADAPTATION IN PATHOLOGICAL PROCESSES

BY  
WILLIAM H. WELCH, M. D., LL. D.

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WITH AN INTRODUCTION BY  
DR. SIMON FLEXNER

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## INTRODUCTION

That a general address of the nature of a presidential oration made forty years ago should be reprinted in a series of modern medical classics is a real distinction. The readers of a new generation will not so much wonder at the unusual occurrence as feel gratitude that the event should have happened at all.

The fundamental problem treated in the address—that of adaptation in pathological processes—has the same profound biological interest today that it had at the end of the nineteenth century. It is apparent that Dr. Welch had pondered it long and deeply before he trusted himself to undertake its definition. It had confronted him from his earlier German period, and he had to meet it squarely in the research which he carried out with Cohnheim as well as afterwards. In the Breslau laboratory he came under the strong influence of the greatest personality who had ever entered the field of general pathology, and incidentally was associated intimately with Weigert, whose broad views on inflammation and regeneration exerted a lasting and forceful influence on Welch's thinking.

The dominant influence of the Cohnheim ideas



is everywhere present in the address. Welch's own development continued, of course, and extended widely in the two decades which separated the year at Breslau and the Congress of Physicians and Surgeons before which the address was delivered. It was the pregnant occasion and Welch grasped it. There assembled at these congresses the elite of the American medical profession—physician, surgeons, laboratory scientists.

The moment was opportune. The now considerable resources of knowledge of evolution, physiology, biochemistry, pathology and bacteriology, and the beginning triumphs in what has since become the illuminating subject of immunology were available and seized upon with a firm hand and applied to the elucidation of the problem of adaptation of living organisms to changing circumstances, among which are those producing pathological conditions to which the epithet "disease" is applied.

The essay, with few amendments and additions, is as applicable to the subject today as it was forty years ago. There is strong temptation to extract and paraphrase many of its informing passages. It is better, I think, for the student to read them in their proper context and to follow the developments

of the fascinating story in the forceful and felicitous language of the author. The first impression produced on the reader is twofold: he is conscious of obtaining deep insight into the subtleties of the subject, and he is filled with wonder at the variety of special knowledge which has been drawn upon in the elucidation of the central theme.

Adaptation is considered in its broad biological connotations and is placed upon a mechanical, as opposed to the teleological, concept of its nature, since it is in the mechanical aspects alone that it is subject to observation and experiment. The approach is strictly along pathological lines and the explanation of physiological adaptation furnished by the doctrine of organic evolution is accepted and applied with confidence to the interpretation of pathological adaptation. How numerous and various the illustrations chosen for the exposition are may be learned from the list given in the table of contents.

I stated that the argument of the address may be followed as confidently today as in 1897, with a few reservations. Bacteriology and especially immunology, were still in a rudimentary state in that year. Five years later, or in 1902, Dr. Welch gave the Huxley memorial address at Charing Cross Hospital



in London. He chose as his subject "Recent Studies in Immunity"; and in that lecture he reverts to the principles enunciated in the earlier address and asks the question as to the physiological mechanism called into action in the processes resulting in the production of antitoxins, cytolytins, and similar bodies, and in reply to the question says that we have no reason to suppose that the animal body is endowed with properties designed to meet pathological emergencies. Indeed, its sole weapons of defense, often lamentably imperfect for morbid states, are adapted primarily to physiological uses. At this time the phenomenon of allergy had not yet been discovered, and its harmful as well as helpful effects had not yet been disclosed,\* so that it argues a certain power of forecasting the future to have perceived that not all the immunological, any more than all the pathological, adaptations are necessarily for the benefit of the individual, for Dr. Welch repeats in the Huxley lecture the maxim "Nature is neither kind nor cruel, but simply obedient to law, and, therefore, consistent," which consideration in the earlier address of other types of pathological adaptation had rendered manifest.

\* Rich, Arnold R., Observations on the relation of allergy to immunity. Johns Hopkins Hosp. Bull., 1930, 47, 189.

The knowledge of the day was especially scant in adaptations among the glandular organs. Illustrations are taken from the kidney and the liver, in which compensatory hypertrophy follows loss of functioning tissues. No field has perhaps been so enlarged by the progress of science in the intervening forty years as this one, and we can only speculate on the uses to which Welch would have put the many subtle and intricate adaptive relationships now known or suspected between the various glands of internal secretion. We can not attempt, of course, to imagine how he would have treated the branch of endocrinology, but that he would have found in the physiological interplay of coordinate activities basis for the pathological manifestations we may be assured.\*

There is a kind of prescience in Dr. Welch's concluding comment on the controversy between Virchow, Weigert, and Ribbert on the causes of pathological cell growth. On the whole he favored Weigert's hypothesis of primary injury to cells inflicted by external agencies rather than the directly exciting

\* For a comprehensive account of the pathology of the glands of internal secretion, consult the textbook on pathology by W. G. MacCallum, sixth edition, 1936.



effects of irritants postulated by Virchow. But Welch also believed that the Weigert formula was too narrow to cover all the observed facts concerning cell proliferation, and he failed "to comprehend the inherent difficulties which some find in admitting the possibility of forms of energy, acting from without, directly increasing the formative energy of the cells; in other words, directly stimulating the cell to growth and multiplication"—a limited restatement of the views advocated by Virchow.

This doctrine is far more defensible today than it was forty years ago. The presence of certain virus entities in cells causes them to proliferate abundantly, to produce new growths of tissue which may present properties of tumors, either malignant or benign, as Rous and Shope and others have shown. Likewise definite chemical compounds such as those contained within coal tar are capable of inducing cell multiplication taking on at times the characters of malignant tumors, and the injection into animals of certain immune cytotoxins leads to hypertrophy of the lymphatic tissues throughout the body. These selected instances may serve to show that examples are not wanting in which external forms of energy, biological or chemical in nature, acting upon cells in-

crease their formative power and lead them to grow and multiply. In this connection it is, therefore, of special interest to note that even in respect to the work hypertrophies, Dr. Welch postulated physical and chemical agencies as the *primum mobile* of the process, the accompanying increase in blood and lymph supply being regarded as merely of secondary importance. And it is fair to assume that he would have found support for the mechanical basis of the adaptive phenomena in the work of Speeman on organizers, for which hormone-like action is now being proposed.†

"We have seen that in the sense in which adaptation was defined we can recognize in the results of morbid processes frequent and manifold evidences of adjustment to changed conditions. These adjustments present all degrees of fitness. Some are admirably complete; more are adequate, but far from perfect; many are associated with such disorder and failures that it becomes difficult to detect the element of adaptation. The teleological conception of a useful purpose in no case affords an explanation of the mechanism of the adaptive process. I have suggested that the adaptability of this mechanism . . .

† Needham, Joseph: Terry Lectures, "Order and Life," Yale University Press, 1936.



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has been in large part determined by the factors of organic evolution, but that in only relatively few cases can we suppose those evolutionary factors to have intervened in behalf of morbid states. For the most part, the agencies employed are such as exist primarily for physiological uses, and while these may be all that are required to secure a good pathological adjustment, often they have no special fitness for the purpose."

With these concluding words of a brilliant address, we commend the essay to the attention of present-day students of medicine, to whom it should not fail to bring the pleasure and enlightenment enjoyed by an earlier generation.

SIMON FLEXNER



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## ADAPTATION IN PATHOLOGICAL PROCESSES

Grateful as I am for the personal good-will manifested by my selection as President of this Congress, I interpret this great and unexpected honor as an expression of your desire to give conspicuous recognition to those branches of medical science not directly concerned with professional practice, and as such I acknowledge it with sincere thanks.

All departments represented in this Congress are working together toward the solution of those great problems—the causes and the nature, the prevention and the cure, of disease—which have always been and must continue to be the ultimate objects of investigation in medicine. It is this unity of purpose which gives to the history of medicine, from its oldest records to the present time, a continuity of interest and of development not possessed in equal degree by any other department of knowledge. It is this same unity of purpose which joins together into a single, effective organism the component parts of this Congress, representing, as they do, that principle of specialization and subdivision of labor which,



notwithstanding its perils, has been the great factor in medical progress in modern times.

Medical science is advanced not only by those who labor at the bedside, but also by those who in the laboratory devote themselves to the study of the structure and functions of the body in health and disease. It is one of the most gratifying results of the rapid advance in medical education in this country during the last few years, that successful workers in the laboratory may now expect some of those substantial rewards which formerly were to be looked for almost exclusively in the fields of practical medicine and surgery. We already have abundant assurance that the steady improvement in opportunities and recompense, and other material conditions essential for the prosecution of scientific work in medicine, will enable this country to contribute to the progress of the medical sciences a share commensurate with its great resources and development in civilization.

The subject of "Adaptation in Pathological Processes," which I have selected for my address on this occasion, is one which possesses the broadest biological, as well as medical, interests. It is this breadth of scientific and practical interest that must justify my choice of a theme which involves many technical

considerations and many problems among the most obscure and unsettled in the whole range of biology and of medicine.

I shall employ the epithet "adaptive" to describe morbid processes which bring about some sort of adjustment to changed conditions due to injury or disease. In view of the more technical and restricted meaning sometimes attached to the term "adaptation" in biology, objection may be made to this broad and general application of the word in pathology; but no more suitable and convenient epithet than "adaptive" has occurred to me to designate the entire group of pathological processes whose results tend to the restoration or compensation of damaged structure or function, or to the direct destruction or neutralization of injurious agents. Processes which may be described variously as compensatory, regenerative, self-regulatory, protective, healing, are thus included under adaptive pathological processes. These processes are, in general, more or less advantageous or useful to the individual; but for reasons which will be stated later the conception of pathological adaptation and that of advantage to the individual are not wholly coextensive.

Within the limits of an address I cannot hope to



do more than direct attention to some of those aspects of the subject which seem to me to be of special significance. Although most striking examples of adaptation are to be sought in comparative and vegetable pathology, what I shall have to say will relate mostly to human pathology. My purpose is not to point out the beauties or the extent of adaptations in pathological processes, but rather to say something concerning the general mechanism of their production and the proper attitude of mind regarding them, and to illustrate the general principles involved by a few representative examples.

It has been contended that the conception of adaptation has no place in scientific inquiry; that we are justified in asking only by what means a natural phenomenon is brought about, and not what is its meaning or purpose; in other words, that the only question open to scientific investigation is *How?* and never *Why?* I hope to make clear by what follows in what light I regard this question, and in this connection I shall simply quote Lotze, who, beginning as a pathologist, became a great philosopher: "Every natural phenomenon may be investigated not only with reference to the mathematical grounds of its possibility and the causes of its occurrence, but



also as regards the meaning or idea which it represents in the world of phenomena."

The most wonderful and characteristic attribute of living organisms is their active adaptation to external and internal conditions in such a way as tends to the welfare of the individual or of the species. Of the countless physiological examples which might be cited to illustrate this principle, I select, almost at random, the preservation of the normal temperature of the body in warm-blooded animals under varying external temperatures and varying internal production of heat, the regulation of respiration according to the need of the tissues for oxygen, the influence of the load upon the work performed by muscles, the accommodation of the heart to the work demanded of it, the response of glands to increased functional stimulation, the adjustment of the iris to varying degrees of illumination, the influence of varying static conditions upon the internal architecture of bone.

The most striking characteristic of these countless adaptations is their apparent purposefulness. Even if it be true, as has been said by Lange, that "the formal purposefulness of the world is nothing else than its adaptation to our understanding," it is none

the less true that the human mind is so constituted as to desire and seek an explanation of the adaptations which it finds everywhere in organic nature. From the days of Empedocles and of Aristotle up to the present time there have been two leading theories to explain the apparent purposefulness of organic nature—the one, the teleological, and the other, the mechanical theory. The teleological theory, in its traditional signification, implies something in the nature of an intelligence working for a predetermined end. So far as the existing order of nature is concerned, the mechanical theory is the only one open to scientific investigation, and it forms the working hypothesis of most biologists. This theory, in its modern form, seeks an explanation of the adaptations of living beings in factors concerned in organic evolution. What these factors are we know only in part. Those which are most generally recognized as operative are variation, natural selection, and heredity. That additional factors, at present little understood, are concerned seems highly probable. The acceptance of the explanation of physiological adaptations furnished by the doctrine of organic evolution helps us, I believe, in the study of pathological adaptations.



As the word "teleology" has come to have, in the minds of many, so bad a repute in the biological sciences, and as I desire, without entering into any elaborate discussion of the subtle questions here involved, to avoid misconceptions in discussing subjects whose ultimate explanation is at present beyond our ken, I shall here briefly state my opinion that all of those vital manifestations to which are applied such epithets as adaptive, regulatory, regenerative, compensatory, protective, are the necessary results of the action of forms of energy upon living matter. The final result, however useful and purposeful it may be, in no way directly influences the chain of events which leads to its production, and, therefore, the character of the result affords no explanation whatever of the mechanism by which the end, whether it appear purposeful or not, has been accomplished. In every case the ultimate aim of inquiry is a mechanical explanation of the process in question. Notwithstanding valuable contributions, especially within recent years, toward such mechanical explanations, we are still far removed from the attainment of this aim.

The knowledge of the fact that the living body is possessed of means calculated to counteract the



effects of injurious agencies which threaten or actually damage its integrity must have existed as long as the knowledge of injury and disease, for the most casual observation teaches that wounds are repaired and diseases are recovered from. It is no part of my present purpose to trace the history of the numerous speculations or even of the development of our exact knowledge concerning the subjects here under consideration. I cannot refrain, however, from merely referring to the important *rôle* which the conception of disease, as in some way conservative or combative in the presence of harmful influences, has played from ancient times to the present in the history of medical doctrines. Whole systems of medicine have been founded upon this conception, clothed in varying garb. There is nothing new even in the image, so popular nowadays, representing certain morbid processes as a struggle on the part of forces within the body against the attacks of harmful agents from the outer world. Indeed, Stahl's whole conception of disease was that it represented such a struggle between the anima and noxious agents. What lends especial interest to these theories is that then, as now, they profoundly influenced medical practice and were the origin of such well-

known expressions as *vis medicatrix naturæ* and *medicus est minister naturæ*.

It is needless to say that there could be no exact knowledge of the extent of operation or of the nature of processes which restore or compensate damaged structures and functions of the body or combat injurious agents, before accurate information was gained of the organization and workings of the body in health and in disease. Although the way was opened by Harvey's discovery of the circulation of the blood, most of our precise knowledge of these subjects has been obtained during the present century, through clinical observations and pathological and biological studies. In the domain of infectious diseases wonderful and hitherto undreamed-of protective agencies have been revealed by modern bacteriological discoveries. Here, as elsewhere in medicine, the experimental method has been an indispensable instrument for discoveries of the highest importance and for the comprehension of otherwise inexplicable facts. Very interesting and suggestive results, shedding light upon many of the deeper problems concerning the nature and power of response of living organisms to changed conditions, have been obtained in those new fields of experimental research called



by Roux the mechanics of development of organisms, and also in part designated physiological or experimental morphology. Although we seem to be as far removed as ever from the solution of the most fundamental problem in biology, the origin of the power of living beings to adjust themselves actively to internal and external relations, we have learned something from these investigations as to the parts played respectively by the inherited organization of cells and by changes of internal and external environment in the processes of development, growth, and regeneration.

In physiological adaptations, such as those which have been mentioned, the cells respond to changed conditions, to meet which they are especially fitted by innate properties, determined, we must believe, in large part by evolutionary factors. In considering pathological adaptations the question at once suggests itself whether the cells possess any similar peculiar fitness to meet the morbid changes concerned; whether, in other words, we may suppose that evolutionary factors have operated in any direct way to secure for the cells of the body properties especially suited to meet pathological emergencies. Can we recognize in adaptive pathological processes any



manifestations of cellular properties which we may not suppose the cells to possess for physiological uses? This question appears to me to be of considerable interest. I believe that it can be shown that most pathological adaptations have their foundation in physiological processes or mechanisms. In the case of some of these adaptations, however, we have not sufficiently clear insight into the real nature of the pathological process nor into all of the physiological properties of the cells concerned to enable us to give a positive answer to the question.

While we must believe that variation and natural selection combined with heredity have been important factors in the development and maintenance of adjustments to normal conditions of environment, it is difficult to see how they could have intervened in any direct way in behalf of most pathological adaptations.

An illustration will make clear the points here involved. Suppose the human race, or any species of animal, to lack the power to compensate the disturbance of the circulation caused by a damaged heart-valve, and that an individual should happen to be born with the exclusive capacity of such compensation. The chances are that there would arise no op-

portunity for the display of this new capacity, and it is inconceivable that the variety would be perpetuated through the operation of the law of survival of the fittest by natural selection, unless leaky or clogged heart-valves became a common character of the species. When, however, we learn that the disturbance of circulation resulting from disease of the heart-valves is compensated by the performance of increased work on the part of the heart, and that it is a general law that such prolonged extra work leads to growth of muscle, we see at once that this compensation is only an individual instance of the operation of a capacity which has abundant opportunities for exercise in normal life, where the influence of natural selection and other factors of evolution can exert their full power.

In a similar light we can regard other compensatory and functional pathological hypertrophies—indeed, I believe, also to a considerable extent the pathological regenerations, inflammation, and immunity, although here the underlying factors are, of course, different.

We may, however, reasonably suppose that natural selection may be operative in securing protective adjustments, such as racial immunity, against mor-



bific influences to which living beings are frequently exposed for long periods of time and through many generations.

These considerations help us to explain the marked imperfections of most pathological adaptations as contrasted with the perfection of physiological adjustments, although I would not be understood to imply that the absence of the direct intervention of natural selection in the former is the sole explanation of this difference. The cells are endowed with innate properties especially fitted to secure physiological adaptations. No other weapons than these same cells does the body possess to meet assaults from without, to compensate lesions, to restore damaged and lost parts. But these weapons were not forged to meet the special emergencies of pathological conditions. Evolutionary factors have not in general intervened with any direct reference to their adaptation to these emergencies. Such fitness as these weapons possess for these purposes comes primarily from properties pertaining to their physiological uses. They may be admirably fitted to meet certain pathological conditions, but often they are inadequate. Especially do we miss in pathological adjustments that co-ordinated fitness so characteristic



of physiological adaptations. So true is this that the propriety of using such terms as compensation and adaptation for any results of pathological processes has been questioned.

A heart hypertrophied in consequence of valvular lesion does not completely restore the normal condition of the circulation. Experience has shown that a kidney hypertrophied in consequence of deficiency of the other kidney is more susceptible to disease than the normal organ. What an incomplete repair of defects is the formation of scar-tissue, and with what inconveniences and even dangers may it be attended in some situations! If we look upon inflammation as an attempt to repair injury, and, therefore, as an adaptive process, with what imperfections and excesses and disorders and failures is it often associated! How often in some complex pathological process, such as Bright's disease or cirrhosis of the liver, can we detect some adaptive features, attempts at repair or compensation, but these overshadowed by disorganizing and harmful changes!

It is often difficult to disentangle, in the complicated processes of disease, those elements which we may appropriately regard as adaptive from those which are wholly disorderly and injurious. There are

usually two sides to the shield, and one observer from his point of view may see only the side of disorder, and another from a different point of view, only that of adaptation.

The conception of adaptation in a pathological process is not wholly covered by that of benefit to the individual. I understand, as has already been said, by an adaptive pathological process one which in its results brings about some sort of adjustment to changed conditions. This adjustment is usually, wholly or in part, advantageous to the individual; but it is not necessarily so, and it may be harmful. The closure of pathological defects by new growths of tissue is a process which must be regarded as adaptive. But one would hardly describe as advantageous the scar in the brain which causes epilepsy. A new growth of bone to fill in defects is often highly beneficial; but what grave consequences may result from thickening of the skull to help fill the space left by partial arrest in development of the brain in embryonic life or infancy! We see here, as everywhere, that "Nature is neither kind nor cruel, but simply obedient to law, and, therefore, consistent."

In turning now to the more special, but necessarily



fragmentary, consideration of a few of the pathological processes in which adaptation, in the sense defined, is more or less apparent, I shall have in view the answers to those two questions, What is the meaning of the process? and How is it caused? which confront us in our investigation of all natural phenomena. At the outset it must be admitted that our insight into the nature of many of these processes is very imperfect, and that here answers to the world-old riddles Why? and How? are correspondingly incomplete and liable to err.

Although almost all of the elementary morbid processes, even the degenerations and death of cells, may, under certain conditions of the body, serve a useful purpose—the pre-eminent examples of pathological adaptation, in the sense of restoration or compensation of damaged structure or function, or the direct destruction or neutralization of injurious agents, are to be found among the compensatory hypertrophies, the regenerations, and the protective processes. To this last ill-defined group I refer parasitidal and antitoxic phenomena, and some of the manifestations of inflammation, and perhaps also of fever. In the last analysis these protective processes, no less than the others mentioned, must depend upon the activities of cells.



As it is manifestly impossible, within the limits of a general address, to attempt a detailed consideration of any large number of these adaptive pathological processes, and as such consideration would necessarily involve the discussion of many technical and doubtful points, I have thought that my purpose would be best served by the selection of a few representative examples.

The compensatory hypertrophies afford admirable illustrations of certain fundamental principles regarding adaptations in pathology which I have already stated. The hypertrophy secures a functional adjustment, often of a highly beneficial character, to certain morbid conditions. This useful purpose is attained by a succession of events determined from beginning to end by the necessary response of cells and tissues, in consequence of their inherent organization, to the changed conditions. Given the changed conditions, on the one hand, and the organization of the cells, on the other, the result must follow as surely as night follows day, and this final result influences the preceding series of events no more in the one case than in the other. That the cells possess the particular organization determining the manner of their response to these changed conditions,

and, therefore, the beneficial character of the result, is dependent upon innate properties whose fitness for the purpose doubtless has been largely fixed by evolutionary factors, operating, however, mainly in behalf of physiological functions and not directly toward pathological adjustments. In correspondence with this view we find that our knowledge of the manner of production of the compensatory hypertrophies of various organs and tissues stands in direct relation to our knowledge of the physiology of the same organs and tissues.

Those compensatory hypertrophies into the mechanism of whose production we have the clearest insight are referable to increased functional activity, and are, therefore, spoken of as work-hypertrophies. This has been proved for the muscular hypertrophies and compensatory hypertrophy of the kidney; but the demonstration is not equally conclusive for the compensatory hypertrophy of other glands. I know, however, of no instance in which this factor in the explanation can be positively excluded.

The relationship between increased functional activity and hypertrophy is so evident in many cases that there is strong presumption in favor of this explanation of those glandular compensatory hyper-



trophies which have not as yet been clearly referred to the class of functional hypertrophies. The very occurrence of compensatory hypertrophy of an organ may direct attention to the fact that it is endowed with definite functions, and the conditions under which the hypertrophy occurs may shed light upon the nature of these functions. I need only remind you of the significance, from this point of view, of the compensatory hypertrophy of the thyroid, adrenal, pituitary, and other glands with internal secretions. I fail to see why Nothnagel should consider *a priori* improbable the occurrence of compensatory hypertrophy of one sexual gland after loss of the other, even before sexual maturity, or why Ribbert, who has apparently demonstrated experimentally such an occurrence, should find it necessary to seek the explanation in reflex nervous influences or mere hyperæmia. The so-called secondary sexual characters and the changes following castration, including the influence upon a hypertrophied prostate, point to important, even if little understood, functions which for the present we can perhaps best attribute to so-called internal secretions of these sexual organs.

The name compensatory hypertrophy is sometimes applied to growths of tissue that merely take the



place of another kind of tissue which has fallen out, as, for example, the growth of adipose tissue around a shrunken kidney or pancreas, or between atrophied muscle-fibres. Here there is only compensation of space, but no compensation of structure or function. Such hypertrophies and growths are described better as complementary than compensatory.

Familiar examples of pathological hypertrophies from increased work are the hypertrophy of the heart from valvular disease and other causes, that of the muscular coats of canals and bladders behind some obstruction, and that of one kidney after loss or atrophy of the other.

In order to understand fully the manner of production of work-hypertrophy of a part resulting from some morbid condition, it is essential to know the nature of the disturbances induced by the underlying morbid condition, how these disturbances excite increased functional activity of the part which becomes hypertrophied, and what the relation is between this greater activity and the increased growth of the part.

It is impossible on this occasion to go through the whole list of compensatory hypertrophies with reference to the application of these principles. In no instance can the requirements stated be completely

met in the present state of our knowledge. It will suffice for an understanding of the principles involved, and it is only with these that I am now concerned, if I take a concrete example. I select the classical and best studied one—compensatory hypertrophy of the heart. I trust that I shall be pardoned for selecting so commonplace an illustration, as the main points involved must be familiar to most of my audience; but it is possible that the application made of them may not be equally familiar. The only matters essential to my present line of argument are the mechanism of production of the hypertrophy and the general character of the adaptation thereby secured.

The heart, like other organs of the body, does not work ordinarily up to its full capacity, but it is capable of doing at least three or four times its usual work. The excess of energy brought into play in doing this extra work is called conveniently, although not without some impropriety, "reserve force." It has been proved experimentally that this storehouse of reserve power is sufficient to enable the healthy heart, at least that of a dog, to accommodate itself at once or after a few beats to high degrees of insufficiency or obstruction at its valvular orifices with-



out alteration in the mean pressure and speed of the blood in the arteries. But even so tireless and accommodating an organ as the heart cannot be driven at such high pressure without sooner or later becoming fatigued, and consequently so dilated as to fail to meet the demands upon it. If it is to continue long the extra work, it must receive new increments of energy.

The cardiac muscle is far less susceptible to fatigue than the skeletal muscles, but that it may become fatigued seems to me clear.

Leaving out of consideration some doubtful causes of cardiac hypertrophy, such as nervous influences, the various morbid conditions which lead to this affection are such as increase either the volume of blood to be expelled with each stroke, or the resistance to blood-flow caused by the pressure in the arteries or by narrowing at one of the valvular orifices, or both. Unless some regulating mechanism steps in, each of these circulatory disturbances must increase the resistance to contraction of the cardiac muscle, and it is evident that the heart must do extra work if it is to pump the blood through the arteries with normal pressure and speed. It is, however, no explanation of this extra work simply to say that it



occurs because there is demand for it. Increased work by the heart in cases of disease of its nutrient arteries would often meet a most urgent demand on the part of the body, but here the heart flags and fails.

The physiologists have given us at least some insight into the mechanism by which the heart responds through increased work to the circulatory disturbances which have been mentioned. These disturbances all increase the strain on the wall of one or more of the cavities of the heart; in other words, increase the tension of the cardiac muscle, in much the same way as a weight augments the tension of a voluntary muscle. Now it is a fundamental physiological law that with a given stimulus greater tension of a muscle, within limits, excites to more powerful contraction, and thus to the performance of greater work. It seems clear that this law applies to the muscles of the heart, as well as to voluntary muscle. We do not know precisely how increased tension facilitates the expenditure of greater muscular energy.

Another well-known fact in the mechanics of muscle is of importance in this connection. With increase of muscular tension under a given stimulus

a point is reached where the extent of contraction is diminished, although the mechanical work done, determined by multiplying the height to which the load is lifted by the weight of the load, is increased. This law applied to the heart, whose contractions are always maximal for the conditions present at any given time, signifies that, with increased resistance to the contraction of the muscular wall of one of its cavities, this cavity will empty itself during systole less completely than before. In other words, dilatation occurs, and, as has been shown by Roy and Adami, to whom we owe important contributions on this as well as on many other points relating to the mechanics of the heart, dilatation regularly antedates hypertrophy. This primary dilatation, however, is not to be looked upon as evidence of beginning heart-failure, for, as these investigators have pointed out, it is within limits only an exaggeration of a physiological condition, and can be subsequently overcome by hypertrophy, which, in consequence of increase in the sectional area of the muscle, lessens the strain upon each fibre, and thereby permits it to shorten more during contraction. If this result is completely secured, we have simple hypertrophy. More often the dilatation remains, and must necessarily remain, and



we have eccentric hypertrophy, which secures, for a time at least, adequate, but I do not think we can say perfect, compensation.

The weight of existing evidence favors the view that the power of the heart to adapt its work to the resistance offered resides primarily in its muscle-cells, and not in intrinsic or extrinsic nervous mechanisms, although doubtless these latter in various ways, which cannot be here considered, influence and support this regulating capacity. Nor can I here pause to discuss the influence of blood-supply to the cardiac muscle upon the force of ventricular contraction, although Porter has demonstrated that this is important.

In tracing the steps from the primary morbid condition to the final hypertrophy, we have thus far had to deal mostly with known mechanical factors. We now come to the question, How does increased functional activity lead to increased growth?

Inasmuch as greater functional activity is regularly associated with a larger supply of blood to the more active part, the view is advocated by many that the increased growth is the direct result of this hyperæmia, and one often encounters, especially in biological literature, this opinion expressed as if it were



an indisputable fact. There is, however, no conclusive proof of this doctrine, and many facts speak against it. The examples from human pathology commonly cited to support the doctrine that local active hyperæmia incites growth of cells are, so far as I am able to judge, complicated with other factors, such as injury, inflammation, or trophic disturbances. Transplantation - experiments, such as John Hunter's grafting the cock's spur upon the cock's comb, sometimes adduced in this connection, are not decisive of this question, for here a new circumstance is introduced which some suppose to be the determining one for all morbid cell-growth, namely, the disturbance of the normal equilibrium between parts. Local active hyperæmia may exist for a long time without evidence of increased growth in the congested part. To say that the hyperæmia must be functional is at once to concede that it is not the sole factor. Experiments from Bizzozero's laboratory, by Morpurgo and by Penzo, indicate that local hyperæmia due to vaso-motor paralysis, or to the application of heat, favors cell-multiplication in parts where proliferation of cells is a normal phenomenon or is present from pathological causes, but that it is incapable of stimulating to growth cells whose pro-

liferating power is suspended under physiological conditions, as in developed connective tissue, muscles, and the kidneys.

It has been usually assumed that the way in which local hyperæmia may stimulate cell-growth is by increasing the supply of nutriment to cells. The trend of physiological investigation, however, indicates that the cell to a large extent regulates its own metabolism. If the cell needs more food, of course it cannot get it unless the supply is at hand, and in this sense we can understand how a larger supply of blood may be essential to increased growth; but this is a very different thing from saying that the augmented blood-supply causes the growth.

It is by no means clear that the question as to the influence of increased blood-supply upon cell-growth is identical with that of increased lymph-supply. The experiments of Paschutin and of Emminghaus, from Ludwig's laboratory, nearly a quarter of a century ago, indicate that local hyperæmia due to vaso-motor paralysis does not, as a rule, increase the production of lymph; and more recent experiments, although not wholly concordant in their results upon this point, tend to the same conclusion. Functional activity, however, has a marked influence in increasing the



quantity and affecting the quality of lymph in the active part. Our knowledge of the physical and chemical changes in working muscles and glands enables us to conceive why this should be so, for all are now agreed that the formation of lymph is due not simply to filtration from the blood-plasma, but also to diffusion, and some believe likewise to active secretion by the capillary endothelium. Doubtless arterial hyperæmia is essential to the maintenance of the increased flow of lymph in working organs.

There are difficulties in the way of supposing that increased supply of lymph in itself furnishes the explanation of cell-growth, and especially of that which characterizes hypertrophy of muscles and glands. Pathologists have frequent opportunities to study the effects of all degrees of increased production and circulation of lymph associated with venous hyperæmia. A kidney or a muscle may from this cause be subjected for months and years to an excess of lymph-flow, but there is no demonstration of any consequent hypertrophy or hyperplasia of renal epithelium or muscle-cell. It is true that the chemical composition of the lymph is not the same as that of lymph resulting from increased function, and it is possible that in this chemical difference lies

the kernel of the whole matter. It may also be urged that in venous hyperæmia there are circumstances which restrain or prevent growth. Nevertheless, if overfeeding, merely in consequence of increased supply of nutriment, were the real explanation of work-hypertrophies, one would expect to find some evidence of this in the class of cases mentioned.

Ribbert has recently given a new shape to the doctrine that local hyperæmia excites growth. While rejecting the usual explanation that it does so by supplying more food, he contends that distention of the blood vessels and lymph-spaces, by mechanically disturbing the mutual relations of parts, removes obstacles to growth. This theory cannot be advantageously discussed until the fact is first established that uncomplicated local hyperæmia does incite growth.

As the matter now stands, it seems to me that any satisfactory explanation of the cell-growth causing work-hypertrophies must start from physical or chemical changes in the muscle- or gland-cell itself directly connected with the increased function. These changes are the *primum mobile*, and, however important increased supply of blood or lymph may be in the subsequent chain of events, it is not the deter-



mining factor. The whole problem is part of the general one of the causes of pathological cell-growth, to which I shall have occasion to refer again.

It is interesting to note that not all kinds of excess of functional activity lead to hypertrophy. A heart may beat for years faster than normal without becoming hypertrophied. Small movements of muscle, often repeated, do not cause hypertrophy. It would appear that the amount of work done in each functional act must attain a certain height in order to stimulate growth. On the other hand, if the muscle be stretched beyond certain limits, it does not hypertrophy; on the contrary, it may atrophy, as may be seen in greatly distended canals and cavities with muscular walls. This behavior is also in accordance with physiological observations.

The compensatory hypertrophy of muscle seems to be due mainly to increase in the size of cells, although there are observations indicating that they may also multiply. That of most glands is referable to increase both in number and size of cells. Within four or five days after extirpation of a kidney karyokinetic figures may be found in increased number in the cells of the remaining kidney.

The general character of the adaptation secured by

compensatory hypertrophy of the heart is sufficiently well-known. I wish to point out certain of its imperfections. I shall not dwell upon the well-known abnormal conditions, with their remote consequences, of the systemic or pulmonary circulation, which are present during the stage of compensation, nor shall I speak of the various circumstances which may interfere with the establishment of compensatory hypertrophy.

The muscle of a hypertrophied heart is sometimes compared to that of the blacksmith's arm, and the statement is made that there is no reason inherent in the muscle itself why the one should fail more than the other. This may be true, but it is not self-evident. Exercise may influence in various ways the nutrition, function, and growth of muscle as well as of other parts. Mere increase in bulk is a coarse effect. Quality may be improved as well as quantity. The biggest muscle is not necessarily the best or the most powerful. As every trainer knows, various conditions under which work is done influence the result. Increase in the reserve energy of the heart, secured by judicious exercise—and this is the main factor in endurance—probably cannot be attributed mainly to hypertrophy; indeed, enlargement of this organ from



exercise is often a serious condition. Much more might be said in this line of thought, but I have indicated why it seems to me unjustifiable to assume, without further evidence, that the condition of the muscle in pathological hypertrophies is necessarily identical in all respects with that in physiological hypertrophies.

There is an important difference in the working-conditions between most hypertrophied hearts and the normal heart. Although the maximal available energy of a hypertrophied heart during compensation is greater than that of the normal heart, clinical experience shows that in the majority of cases the energy available for unusual demands—that is, the so-called reserve force—is less in the former than in the latter. Sometimes, especially when the hypertrophy has developed in early life, the hypertrophied heart is at no disadvantage in this respect. As pointed out with especial clearness by Martius, the significance of this alteration in the ratio normally existing between the energy expended for ordinary needs and that available for unusual demands, is that it furnishes an explanation of the greater liability of the hypertrophied heart to tire upon exertion. Fatigue of the heart is manifested by dilatation of its cavities, and

when this dilatation from fatigue is added to that already existing in most cases, relative insufficiency of the mitral or tricuspid valve is likely to occur, and the compensation is, at least for a time, disturbed. The circulation through the coronary arteries, whose integrity is so important for the welfare of the heart, is impaired, and a vicious circle may be established. Notwithstanding the valuable contributions from the Leipzig clinic as to the frequency of various anatomical lesions in the muscle of hypertrophied hearts, it does not seem to me necessary to have recourse to them as an indispensable factor in the explanation of the breakage of compensation; but I shall not here enter into a discussion of the general subject of the causes of failure of compensation.

I have described with some detail, although very inadequately, the manner of production of compensatory hypertrophy of the heart, in order, by this representative example, to make clear what seem to me to be certain general characteristics of many adaptive pathological processes, and I beg here to call attention especially to the following points. As has been emphasized by Nothnagel and others, no teleological idea or form of language need enter into the explanation of the mechanism of the process. The



final result is the necessary consequence of the underlying morbid conditions. We have satisfactory mechanical explanations for essential steps in the process, and there is no reason to assume that other than mechanical factors are concerned in those vital manifestations which at present we are unable to explain by known physical and chemical forces. The properties of the cells which determine the character of their response to the changed conditions are none other than their well-known physiological properties. The adaptation finally secured, admirable as it is in many respects, and perhaps adequate for long and active life, is generally attended with marked imperfections, and, strictly speaking, is not a complete compensation. It does not present that co-ordinate and special fitness which we are accustomed to find in physiological adaptations, for the explanation of which so much has been gained by the study of the factors concerned in organic evolution.

It may be argued that under the circumstances no better kind or degree of adaptation can be conceived of than that which actually occurs, and that the operation of evolutionary factors, with especial reference to the adjustment of the organism to the conditions causing cardiac hypertrophy, could not secure any

better result. I think that it is not difficult to conceive how improvements might be introduced. It is, however, permissible to suppose that the introduction into the workings of the organism of some better mechanism to compensate the morbid conditions, might be at the sacrifice of more important physiological attributes of the body. More perfect pathological adaptations might in many instances involve a deterioration of the physiological characters of the species. It is often the case that the more highly organized living beings lack some capacity possessed by those lower in the scale of organization to resist or compensate injury and disease. This is notably true of the power to regenerate lost parts. It is, however, along the lines of improvement in the physiological characters of the individual or species that the opportunity often lies for securing increased resistance to disease or better pathological adaptations.

It would be interesting to continue our consideration of the compensatory hypertrophies by an examination of those of glandular organs from points of view similar to those adopted for the heart. For the kidney, at least, the materials are at hand for such a purpose; but, as I desire, in the limited time at my disposal, to touch upon other varieties of pathological



adaptation, I must refer those interested especially to the investigations of Grawitz and Israel, Ribbert, Nothnagel, and Sacerdotti as to the conditions underlying compensatory hypertrophy of the kidney. I can likewise merely call attention to the interesting researches of Ponfick upon the most wonderful of the compensatory hypertrophies in higher animals, that of the liver. Ponfick, as is well known, has demonstrated that after removal of three-fourths of this organ new liver-substance, with normal functions, is recreated from the remainder and to an amount nearly equalling that which was lost.

The chapter of pathological adaptations in bones and joints I shall leave untouched, notwithstanding the admirable illustrations which might be drawn from this domain.

There is no more fascinating field for the study of pathological adaptations with reference to the mechanical factors involved than that furnished by the blood vessels, as has been shown especially by the brilliant researches of Thoma. With wonderful precision can a vessel or system of vessels adjust itself to changes in the pressure, velocity, and quantity of blood, and thereby serve the needs of the tissues for blood. Under pathological, as well as physiological

conditions, this adjustment may be brought about not only through the agency of vaso-motor nerves and the physical properties of the vascular wall, but also, when the necessity arises, by changes in the structure of the wall.

The changes in the circulation introduced by the falling out of the placental system at birth are essentially the same as those resulting from amputation of an extremity, and the consequent alterations in the structure of the umbilical artery are identical with those in the main artery of the stump after amputation. The closure of the ductus Botalli and the ductus venosus soon after birth, and, still better, transformations of vessels in the embryo, furnish physiological paradigms for the development of a collateral circulation. Many other illustrations might be cited, did time permit, to show that in the processes of normal development, growth and regressive metamorphosis of parts, both before and after birth, and in menstruation and pregnancy, changed conditions of the circulation arise analogous to certain ones observed under pathological circumstances, and that the mode of adjustment to these changes by means of anatomical alterations in the vessels may be essentially the same in the physiological as in the



morbid state. I see in these facts an explanation of the relative perfection of certain vascular adaptations to pathological or artificial states, as may be exemplified by changes in a ligated artery and by the development of a collateral circulation. The mechanisms by which the adjustments are secured have, in consequence of their physiological uses, for reasons already explained, a special fitness to meet certain pathological conditions. That this fitness should be greater in youth than in old age is in accordance with laws of life, indicated with especial clearness by Minot in his interesting studies on "Senescence and Rejuvenation."

But these mechanisms are not equally well adapted to meet all morbid changes in the vessels. Although Thoma's interpretation of the fibrous thickening of the inner lining of vessels in arterio-sclerosis and aneurism as compensatory, or, as I should prefer to say, adaptive, is not accepted by all pathologists, it seems to me the best explanation in many cases. But the adaptation, if it be such, is here usually of a very imperfect nature, and it is not surprising that it should be so, when one considers the improbability of any mechanism developing under physiological conditions which should be specially fitted to meet

the particular morbid changes underlying aneurism and arterio-sclerosis.

I shall not be able to enter into a consideration of the mechanical factors concerned in adaptive pathological processes in blood vessels, although perhaps in no other field are to be found more pertinent illustrations of the views here advocated concerning pathological adaptations. The whole subject has been studied from the mechanical side most fully and ably by Thoma, whose four beautifully simple histo-mechanical principles are at any rate very suggestive and helpful working-hypotheses, even if it should prove, as seems to me probable, that they are too exclusive. I shall call attention in this connection only to the inadequacy of the old and still often adopted explanation of the development of a collateral circulation. The rapidity with which a collateral circulation may be established after ligation of a large artery, even when the anastomosing branches are very small, is known to every surgeon. This was formerly attributed to increase of pressure above the ligature; but this rise of pressure has been shown to be too small to furnish a satisfactory explanation, and Nothnagel has demonstrated that there is little or no change in the calibre of arteries



coming off close above the ligature unless they communicate with branches arising below the ligature. Von Recklinghausen several years ago suggested a better explanation. The bed of the capillary stream for the anastomosing arteries is widened by ligation of the main artery, inasmuch as the blood can now flow with little resistance from the capillaries of the anastomosing branches into those of the ligated artery. The result is increased rapidity of blood-flow in the anastomosing vessels. According to one of Thoma's histo-mechanical principles, increased velocity of the blood-current results in increased growth of the vessel-wall in superficies—that is, in widening of the lumen. The tension of the vessel-wall, which is dependent on the diameter of the vessel and the blood-pressure, is, according to Thoma, thus increased; and, according to another of his principles, this greater tension results in growth of the vascular wall in thickness. The changes in the walls of the anastomosing vessels seem to me best interpreted as referable to a genuine work-hypertrophy, a conception which has already been advanced by Ziegler.

The pathological regenerations constitute a large group of adaptive morbid processes of the highest

interest. Their study has become almost a specialized department of biology, and occupies a very prominent place in the extensive literature of recent years relating to experimental or physiological morphology. It has revealed in unexpected ways the influence of external environment upon the activities of cells, as is illustrated in a very striking manner by Loeb's studies of heteromorphosis.

Although the capacity to regenerate lost parts must reside in the inherited organization of the participating cells, there are observations which seem to indicate that in the lower animals this capacity may exist independently of any opportunity for its exercise during any period of the normal life of the individual or species or their ancestors, including the period of embryonic development. This is the inference which has been drawn from Wolff's observation, that after complete extirpation of the ocular lens with the capsular epithelium in the larval salamander, a new lens is reproduced from the posterior epithelium of the iris. There are other observations of similar purport. The acceptance of this inference, however, seems to me to involve such difficulties that we may reasonably expect that further investigations will afford more satisfactory explanations of these



curious and puzzling phenomena of regeneration. Of much interest and significance are the so-called atavistic regenerations, where the regenerated part assumes characters belonging not to the variety or species in which it occurs, but to some ancestral or allied species. For these and other reasons Driesch refers the pathological regenerations to what he calls the secondary self-regulations, by which term he designates those adjustments of artificially induced disturbances which are brought about by factors foreign to the normal development and life of the individual.

The view advocated by Barfurth seems to me more probable, that the pathological regenerations depend upon cellular properties pertaining to the normal life of the organism. This view is supported by the fact that, with a few probably only apparent exceptions, the regenerations conform to the law of specificity of cells. The pathological regenerations occurring after birth can be referred to the retention in greater or less degree of formative powers possessed by the cells pre-eminently in embryonic life. These powers in general tend gradually to diminution or extinction as the individual grows older, although in some cells, such as the covering epithelium of the

skin and mucuous membranes, this loss of regenerative power with advancing years is scarcely manifest. Even after the cessation of growth the regenerative capacity is not wholly in abeyance under physiological conditions. Bizzozero has studied and classified the various tissues of the body according to the activity of their physiological regeneration.

In general, the more highly differentiated and specialized a cell, the less is its capacity for regeneration; but we now know that such differentiation is attended with less sacrifice of its regenerative power than was once supposed. Even such highly specialized cells as those of striped muscle are capable of regeneration. Indeed, the nerve-cells seem to be the only ones incapable of proliferation, and even this is not certain, for there are competent observers who claim that these cells may multiply, although there is no evidence that in the higher animals they can give rise to functionally active new nerve-cells. The ease with which a part of the nerve-cell, namely, its axis-cylinder process, can be regenerated is well known.

The cell-proliferation in regeneration is attributed to the removal of resistance to growth in consequence of the defect resulting from loss of tissue. It has



been pointed out, especially by Ziegler and by Ribbert, that not only cells in the immediate neighborhood of the defect multiply, but likewise those at such a distance that it is difficult to suppose that the latter have been directly influenced by the loss of tension in the tissues caused by the defect. Ziegler refers the proliferation of the distant cells to compensatory hypertrophy, and Ribbert attributes it to hyperæmia resulting from the presence in the defect of foreign materials, such as extravasated blood, exudation, and necrotic tissue.

We are brought here, as we were in the consideration of the compensatory hypertrophies, to one of the most fundamental and important questions in pathology—the causes of pathological cell-growth. The interpretation of many pathological processes as adaptive or not, hinges often upon opinions held concerning the underlying causes of cell-proliferation. The main question at issue is: How far is one willing to go in attributing cell-growth to primary defects in the tissue, and interpreting the growth as for the purpose of regeneration or filling up a defect? Differences of opinion upon this subject are illustrated by the different interpretations of the cell-proliferations in acute and chronic inflammations,

some pathologists considering these to be essentially regenerative and compensatory; others regarding them, at least in large part, as directly incited by inflammatory irritants and not to be ranked wholly with the regenerative processes.

The doctrine of Virchow was long accepted without question, that inflammatory cell-growth is the result of the action of external stimuli, the so-called inflammatory irritants, upon the cells, which are thereby directly incited to grow and multiply. The attack upon this doctrine has been vigorously led by Weigert, who denies absolutely the power of any external agencies to stimulate directly cells to proliferation. He considers that to concede such a bioplastic power to external agents is equivalent to the acceptance of a kind of spontaneous generation of living matter.

Weigert's views upon this subject have undoubtedly had a most fruitful influence upon pathology. It has been such an influence as a good working-hypothesis, whether finally demonstrated to be true or not, has often had in the development of science. In putting to the test of actual observation Weigert's hypothesis, we have been led to recognize the frequency and the importance of primary injuries to cells



inflicted by external agencies. Not only various degenerations and necroses of entire cells, but more subtle and partial damage of cytoplasm and nucleus have been made the subject of special study. It has been recognized that our older methods of hardening tissues reveal often only very imperfectly the finer structure of cells, and new and better methods have been introduced which enable us to detect more delicate lesions of cell-substance which formerly escaped attention, as is well illustrated in recent studies in neuropathology. Weigert's postulate of some primary injury to the tissues as the immediate effect of mechanical, chemical, and other external agencies, which were formerly regarded as the direct stimuli of cell-growth and multiplication, has been fulfilled in many instances where such damage had previously been overlooked or unsuspected. It is his belief that in cases where we cannot now detect such primary injury more thorough search and better methods will enable us to do so. One may, of course, reasonably cherish such an expectation; but at the same time we must recognize the fact that morbid cell-proliferations occur under circumstances where we cannot at present associate them with any demonstrable injury to the tissues—indeed, in some

cases where our insight into the structure of the part seems to be so clear and satisfactory that one is very reluctant to admit the existence of an undetected damage to the cells.

Perhaps the most important modification of former pathological conceptions, resulting from the belief that cell-growth is caused by primary defects and injuries of tissue, relates to the chronic interstitial inflammations or fibroid processes. The older view that in these processes the active and essential feature of the disease is the new growth of connective tissue, which strangled the more highly organized cells of the part, has been replaced to a large extent by the opinion that the primary and most important lesion is the degeneration, atrophy, or necrosis of the more specialized cells, whose place is taken by the new growth of interstitial tissue. In many instances, as in fibroid patches in the myocardium, and in many scleroses of the central nervous system, this latter conception forms the best and most natural interpretation of the facts. There are, however, great difficulties in explaining all chronic interstitial inflammations by this doctrine, and I must take side with those who admit the occurrence, for example, in the kidney and in the liver, of primary interstitial in-



inflammations characterized by proliferation of the connective tissue and endothelial cells.

Indeed, it seems to me that Weigert's formula is too narrow to cover all of the observed facts concerning cell-proliferation. Essential features of the theory that cells cannot be directly stimulated to growth by external agents were present in Boll's doctrine of border warfare between neighboring cells. Weigert's presentation of this theory is in a far more acceptable shape than that of Boll. A still more comprehensive statement of the general theory is that cells are incited to growth through removal of obstacles to growth in consequence of some disturbance in the normal relations or equilibrium of the cells with surrounding parts. The capacity to proliferate must be present in the cells, but with the cessation of growth this capacity is rendered latent or potential by the establishment of definite relations or an equilibrium between cells and neighboring parts, including under the latter not only adjacent cells, but also basement-substance, lymphatics, blood vessels, tissue-juices, chemical substances, etc. It is evident that under these circumstances in only two ways can the cells be incited to growth, either by removal of resistance or obstacles to growth,

or by an increase in the formative energy resident within the cell, and that in either way energy must be used, whether it be employed to remove obstacles to growth, or to increase the proliferative forces within the cell.

It appears to me by no means an easy matter to decide in all cases in which of the two ways mentioned cell-proliferation is brought about. Removal of obstacles to growth, not only in the way indicated by Weigert, but also by other disturbances in the neighborhood-relations of the part, and very probably by the presence of definite chemical substances, may be the explanation of all pathological cell-growths. Certainly it would not be easy conclusively to disprove this view. Nevertheless, I fail to comprehend the inherent difficulties which some find in admitting the possibility of forms of energy, acting from without, directly increasing the formative energy of the cell; in other words, directly stimulating the cell to growth and multiplication. If such a possibility be admitted, the natural interpretation of some examples of cell-proliferation is that they are directly caused by the action of external forces, in the sense advocated by Virchow.

Students of the problems of pathological cell-



growth must take into consideration not only the facts of human and allied pathology, but also those which are so rapidly accumulating in the domain of experimental embryology and morphology, to the importance of which I have repeatedly referred in this address. I would call attention especially to the observations from this source as to the influence of various changes of environment, particularly of definite chemical, thermic, and mechanical changes in surrounding parts, upon the direction of movement and of growth of cells. The use at present made of chemotactic phenomena in explaining the direction of movement of cells in human pathological processes is only a very limited and inadequate application of these important observations concerning tactic and tropic stimuli. We shall probably come to realize more and more the operation of these factors in determining cell-movements and cell-growth in human pathology. We already have evidence that different kinds of leucocytes not only possess different specific functions, but also respond in different ways to definite tactic stimuli. The long-standing problem of the lymphoid cell in inflammation approaches solution along these lines of investigation.

A burning question, and one of perennial interest,

relating to our subject is: How far are we justified in regarding acute inflammation as an adaptive or protective morbid process? There is fair agreement as to the essential facts of observation, but regarding their interpretation there are wide differences of opinion, and when one considers the complexity of the process and its still unsolved riddles, it is not hard to see why this should be so. Much depends upon the point of view, and in this respect there can be recognized a certain antagonism between the purely clinical and the purely pathological and experimental views, an antagonism, however, which must be reconciled by a fuller knowledge of the subject.

It is not likely that the purely clinical study of inflammation would ever lead to the idea that the general tendency of this process is advantageous to the patient. The more severe and extensive the inflammatory affection, the more serious, as a rule, is the condition of the patient. The surgeon sees his wounds do well or ill according to the character and extent of inflammatory complication. Measures directed to the removal of inflammatory exudation, such as the evacuation of pus from an abscess or an empyema, are the most successful methods of treatment, and the rules are embodied in ancient surgical



maxims. How can one conceive of any purpose useful to the patient served by filling the air-cells of his lung with pus-cells, fibrin, and red corpuscles in pneumonia, or bathing the brain and spinal cord in serum and pus in meningitis? If nature has no better weapons than these to fight the pneumococcus or meningococcus, it may be asked, "What is their use but to drive the devil out with Beelzebub?"

But the pathologist and bacteriologist sees another aspect of the picture. An infectious micro-organism has invaded the tissues, where it multiplies and where its toxic products begin to work havoc with the surrounding cells, and by their absorption to cause constitutional symptoms and perhaps damage to remote parts. Is the destructive process to go on without any defence on the part of the body? There are attracted to the injured part an army of leucocytes from the blood vessels, and perhaps other cells, from the neighboring tissues, and it has been conclusively shown that these cells can pick up foreign particles and remove them, and that they contain substances capable of destroying many micro-organisms. At the same time serum accumulates in and around the injured area, and this may aid by its chemical properties in destroying bacteria, in diluting poisons, in

flushing out the part. Fibrin may appear, and some think that this may serve in some situations as a protective covering. If these agencies, hostile to the invading micro-organism, gain the upper hand, the débris is cleared away by phagocytes and other means, and the surrounding intact cells, which had already begun to multiply, produce new tissue which takes the place of that which had been destroyed. The victory, however, is not always with the cells and other defensive weapons of the body. The struggle may be prolonged, may be most unequal, may cover a large territory, and the characters and extent of the inflammation furnish an index of these different phases of the battle.

Such in bald outlines are two divergent views of inflammation.

I do not see how we can fail to recognize in that response to injury which we call inflammation, features of adaptation. Inflammation may be in some cases the best response to secure the removal or destruction of injurious agents, but we cannot look upon it as the most perfect mode of protection of the body against invading micro-organisms. One may inoculate into three animals, even of the same species, but possessed of different individual resist-



ance, the same quantity of the same culture of a pathogenic micro-organism and obtain sometimes the following results: The first one will present no appreciable inflammatory reaction whatever, and no evidences of any other disturbance, and examination will show that the micro-organisms have quickly disappeared. The second one will develop an extensive local inflammation and survive, but after a long illness. The third one will offer little resistance to the micro-organism, which rapidly multiplies without causing marked inflammation, invades the blood or produces toxæmia, and quickly destroys the life of the animal. Now, it is evident that the best protective mechanism is that brought into action by the first animal, but that the inflammatory reaction set up in the second one is better than the absence of reaction and of other defences in the third animal.

I can scarcely do more on this occasion than to indicate some of the points of view from which it seems to me that we can best approach the study of inflammation as an adaptive process. With inflammation, as with other adaptive processes, any useful purpose subserved affords no explanation of the mechanism of the process. We should guard against all ideas which introduce, even unconsciously, the

conception of something in the nature of an intelligent foresight on the part of the participating cells. The response of these cells in inflammation is a necessary and inevitable one, determined by their innate properties. Our efforts should be directed, in the first place, toward as near an approach as possible to a mechanical explanation of inflammatory processes by a study, on the one hand, of the properties and mode of action of the causes of inflammation, and, on the other hand, of the nature and source of the cellular properties concerned. We may properly inquire whether these properties fit the cells to counteract the effects of injury, and if so, whence comes this fitness. Has the fitness those attributes of relative perfection which we find in most physiological adaptations? Is the character of the response to injury in inflammation such as to indicate that the agencies concerned have acquired through evolutionary factors a special fitness to meet the pathological emergencies? Are all or only a part of the manifestations of the inflammatory processes adaptive?

It cannot be doubted that there are innate properties of certain cells called into action in inflammation, such as those manifested in the attraction of leucocytes and other cells by definite chemical substances,



the capacity of cell-proliferation from causes connected with injury, the power of phagocytosis and other bactericidal properties, which may be adapted to counteract the effects of injurious agents. When these forces bring about the prompt destruction or removal of the injurious substances and the defect is quickly repaired, the adaptation is complete and unmistakable. When, however, the inflammatory irritants and their destructive effects persist, and the proliferation of cells and accumulation of inflammatory products become excessive and occupy large areas, the features of adaptation are not so easily recognized. The mere occupation of territory by inflammatory products is often a serious injury and it can be regarded as an adaptive feature only when they fill some artificial defect. Such occupation may be in itself enough to counteract any useful work in which these products may be engaged.

We can reasonably seek in the relations of the body to the outer world an explanation of the development of certain properties of cells which serve a useful purpose in mechanical and other injuries. These properties find application also in the normal life of the organism. Their exercise in response to injury imparts to inflammation important adaptive or

protective characteristics, but I fail to see in this process any such special fitness as would justify extravagant statements which have been made, to the effect that inflammation ranks among the adaptations of living beings by the side of digestion and respiration.

I have endeavored in this address to present certain general considerations concerning pathological adaptations. It has been possible to bring under consideration only a small part of an immense field, and this very inadequately. We have seen that in the sense in which adaptation was defined we can recognize in the results of morbid processes frequent and manifold evidences of adjustment to changed conditions. These adjustments present all degrees of fitness. Some are admirably complete; more are adequate, but far from perfect; many are associated with such disorder and failures that it becomes difficult to detect the element of adaptation. The teleological conception of a useful purpose in no case affords an explanation of the mechanism of an adaptive process. I have suggested that the adaptability of this mechanism to bring about useful adjustments has been in large part determined by the factors of organic evolution, but that in only relatively few cases can we suppose these evolutionary factors to



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have intervened in behalf of morbid states. For the most part, the agencies employed are such as exist primarily for physiological uses, and while these may be all that are required to secure a good pathological adjustment, often they have no special fitness for this purpose.

The healing power of nature is, under the circumstances present in disease, frequently incomplete and imperfect, and systems of treatment based exclusively upon the idea that nature is doing the best thing possible to bring about recovery or some suitable adjustment, and should not be interfered with, rest often upon an insecure foundation. The agencies employed by nature may be all that can be desired; they may, however, be inadequate, even helpless, and their operation may add to existing disorder. There is ample scope for the beneficent work of the physician and surgeon.













