

THE INFLUENCE OF THE AMERICAN MEDICAL ASSOCIATION.

The American Medical Association should maintain its interest in the elevation of the standard of medical education, one of the chief reasons of its organization. Its influence in former years was principally moral. This was of considerable value, for the reason chiefly of the high ideals of the founders and first members of the association, who advocated and fought for a high standard of medical education. In the future its influence should be many fold that of the past, for with the reorganization of the profession the better methods of conducting its affairs, the increased and probably very large membership, and its great medical journal, should wield a great influence for good.

As the direct agent by which the American Medical Association may exert its influence in the elevation and control of medical education, the Committee on Medical Colleges and Medical Education should be made permanent and should be given adequate power and sufficient annual appropriation to make its work effective.

This association should, therefore, stand for, and should use its whole power to improve, medical education in this country. It is said that we never exceed our ideals in practice, and that if we lower our ideals our conduct sinks to a lower level.

The American Medical Association should take as its ideal and standard of medical education the university medical college, with all the name implies in regard to the fundamental medical sciences, and to the clinical branches. It should use its influence to drive out of existence those proprietary medical schools, which are conducted solely as money-making institutions. These measures cannot be accomplished at once; but medical science demands it, the profession demand it, the people demand it, and look to the American Medical Association as the chief influence which shall accomplish this end.

CANCER AND IMMUNITY.¹

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On such occasions as this we take great pleasure in recalling the past and dwell with great delight on the achievements along the lines that have most engaged our attention. We, as surgeons, especially those whose professional activity began in the pre-antiseptic period, review the successive changes from that period of expectancy to the present period of aseptic accuracy with the greatest satisfaction. No one can fully appreciate the present status of surgery who is not personally familiar with the period when wound complications were the rule and when faith was pinned on the belief in "laudable pus." . . .

Surgical advance in the future will not consist so much in the radical changes in operative technique as in improvement in diagnosis and diagnostic aids. Many of our diagnostic formulæ are even now undergoing complete changes, and the future will lead us to a precision in the recognition of disease

that we little dream of now. The early recognition of malignant disease is a problem of future development, especially malignancy affecting the internal organs. With our present aids it is impossible to recognize internal cancers sufficiently early to do a radical operation. Our only course at the present is an exploratory incision as soon as reasonable grounds for malignancy exist.

The field that seems full of promise and gives us hopes for great expectations in the future is that of immunity and immunization. It now seems that many tissue changes will be solved along these lines. From our present viewpoint the question of immunity seems to tower above and overshadow all others. . . . The two greatest problems of the future, cancer and immunity, shall engage our attention today. Malignant disease seems to be on the increase. We stand so helpless in its presence when fully developed that we exert our feeble energies and grasp eagerly for any fact that seems to offer new light for its better understanding. It will be our effort at this time to as briefly as possible review the more important facts known regarding the etiology of cancer and then, after making clear to ourselves the revelations thus far made in the recent studies of immunity, determine if possible what relations, if any, exist between the two.

These considerations were prompted by personal observations made in a number of cases of undoubted malignancy that indicated the probable infectiousness of cancer. It is well known to us all that the infectiousness of most infectious diseases was first determined clinically and that the clinical observations were later determined and confirmed microscopically and experimentally. . . .

The term cancer, so commonly employed, refers to growths made up chiefly of epithelial cells. There is really no good reason why the term cancer should be limited to epithelial growths. Cancer signifies "crab." It was originally used to signify malignancy and meant connective tissue growths as well as those of epithelial origin. For our purpose at this time we will limit the term cancer to epithelial neoplasms and we will confine these considerations to its etiologic factors.

The mystery of its origin seems as deep almost as in the days when cellular pathology was unknown. No problem in pathology has received more thought and speculation, no subject has had bestowed on it more earnest effort and unremitting toil. Regarding etiologic evidence we must confess that we have only a mass of negative proof. When observers believed that they had found the specific organisms, scores of workers in the same field soon demonstrated their error. So, today, we can only say that the evidence which shows what we do *not* know of the cause of cancer is voluminous, and we must admit that we know little of its etiology.

We know something of its cell characteristics. We know that malignant disease is essentially a cell proliferation that has, biologically, many features that are opposed to the physiological tissues in which they take their origin. We find an atypical life history in the cancer cells. The nucleus divides in an asymmetrical way. We note that unusual karyokinetic figures in the nucleus are usual in new growths, pointing to changes in the cellular life his-

¹ Oration in surgery, delivered at the fifty-fourth annual meeting of the American Medical Association, held at New Orleans, May 6-8, 1903.

tory. Regarding carcinoma, certain bodies have been demonstrated, believed by some to be parasites, having some causal relation to the cell changes.

It is a well-established fact that the nucleus perpetuates the nature and function of the cell, and any change in the nucleus changes the cell in its function and process of division. According to W. V. Shaw, "The growth of cancer cells is then to be looked on as an effort of reproduction in damaged tissue, the incidence of the damage falling on the nuclear structures."²

This statement is based on observations made by him in connection with experiments on free swimming larvæ which developed from the stimulation of ova of certain lowly organized animals, causing a proliferation of cells. The ova had not been fertilized by spermatozoa. Adult organisms were not developed, but larvæ capable of independent life. These results were obtained by stimulating the ova with strychnia and by mechanical movements of the ova. This cell growth was compared to growth of tissue in partially damaged structures. Shaw believes that such damage alters the nature of these cell structures so that the vegetative functions of the cell run riot and the cells become parasitic toward the organism in which the growth is taking place. This view seems to find support in those connective tissue growths that develop in tissues that have sustained a trauma and in which the sarcoma develops; or in epithelial growths that form on surfaces that have been subject to prolonged irritation, as exemplified by the chimney-sweep's and paraffin-worker's cancer forming on an old chronic dermatitis; or a cancer forming on the site of a prolonged irritation by the smoker's pipe-stem on the lower lip. We have seen many times that cancer develops in epithelial tissue that has been subjected to irritation for a long time, usually extending over a period of years. We have long recognized irritation to be at least one of the causative factors. Just what metabolic disturbances take place, and what the underlying causes are, is not yet clear. That cancer is infectious has been proven by many clinical observations. This has been shown by Eberth, who collected twenty-two cases where cancer was transmitted from lip to lip, tongue and palate. Behla reported eight instances of death from malignant growths in physicians and surgeons who were inoculated from tumors, and four instances of apparent human infection from cancerous animals, dog and hen. He also alludes to a cancer epidemic among the white mice in the Pathological Institute at Freiburg as evidence of the contagiousness of cancer (Hektoen). Roswell Park believes that, for New York State at least, cancer is increasing at an alarming rate.

Attempts have been made to show that cancer is endemic, peculiar to certain localities. Behla cites cases of Behrens, who found in a village ten deaths out of thirty-eight to be due to cancer. Pfeiffer, Powers and Friesinger maintain that in certain houses (cancer houses) and marshy districts in the vicinity of ditches and streams containing sluggish water, especially if the stagnant and polluted water were used for watering garden vegetables and for drinking purposes, cancer is relatively frequent

(Hektoen). This would point rather to a microphyte than to a microzoon as the etiologic factor.

Since infection of living tissue is believed in every instance to be due to bacterial invasion, naturally bacteriologists directed their attention toward the discovery of a specific germ. Very soon we had a long list to enumerate. Plimmer of London examined in six years 1,298 carcinomata, and in 1,130 he believed that he found parasitic bodies. Sjöbring laid much stress on cell inclusions. Russell described his fuchsin bodies which were spherical or oval. L. Pfeiffer of Weimar published several monographs on the protozoa as a cause of cancer. Eisen brought out his *Canceri Amœbae*. Korotneff believed that he had found an organism which he termed *Rhopaloccephalus carcinomatosus*. Bosr found and described an organism that he called *Myxosporidium coccidia*. Gaylord of Buffalo described at great length bodies that he believed bore an etiologic relation to cancer. Sanfelice of the University of Cagliari emphasized the etiologic importance of bodies that he named *Saccharomyces neoformans*. A very large number of other publications on this subject made their appearance, none of which differed in any essential point from those bodies just mentioned.

While the presence of the aforesaid bodies described by the different observers can be demonstrated and are present in a large proportion of the cases of cancer, all the requirements necessary to prove them to be the organisms solely responsible for cancer have not been fulfilled. The requirements necessary are: (1) the organism must be isolated; (2) a cancer must be produced when the organism is introduced into another body; (3) the organism must be recovered from the cancer produced. It has been shown that, while the first requirement has only apparently been fulfilled, the second has been, in a number of cases, seemingly produced. More careful investigations have proven that the experimental growths were not cancer. The third requirement has not been fulfilled.

All of the work mentioned above was carefully reviewed in all its details by the cancer committee, who, in their second annual report to the surgical department of the Harvard Medical School, showed conclusively that the bodies described by the various investigators under different names were not cancer nor the cause of cancer. I can do no better than to quote in full the results of their labors. They bear the marks of painstaking and conscientious work. The conclusions of the Harvard Cancer Committee were written by Edward H. Nichols and were as follows:

It has been claimed by the adherents of the theory of the parasitic origin of cancer that

(1) A proliferation of epithelial cells analogous to the lesions seen in cancerous tumors can be produced by certain well-known protozoa (nodules caused by the *Coccidium oviforme*).

(2) Certain skin lesions characterized by epithelial cell proliferation are due to the action of a so-called protozoon (*Molluscum contagiosum*).

(3) Blastomycetes are constantly present in human cancers and are the cause of the lesion.

(4) By experimental inoculation of animals with blastomycetes, true epithelial or cancerous nodules can be produced.

(5) Finally, the well-known endocellular bodies seen

²The Lancet, Sept. 20, 1902.

in the protoplasm of cancer cells have a definite morphology, are parasites and the cause of cancer.

It has been the object of the investigators, the results of whose work appear in the preceding pages, to study each of these questions. As a result of the lines of work pursued by them under the direction of the Cancer Commission during the past year, it is concluded that:

(1) The lesion produced by the *Coccidium oviforme* is essentially a process of chronic inflammation and is not analogous to the lesion seen in cancer.

(2) The lesion of *Molluscum contagiosum* is characterized by certain changes in the epidermis, is not due to the action of a protozoon and is not analogous to cancer.

(3) The so-called "blastomycetes" (saccharomycetes) of Sanfelice and Pummer are torulæ.

(4) The lesions produced by these "blastomycetes" (torulæ) are, essentially, nodules of peculiar granulation tissue, are not cancerous, nor, in any sense, true tumors.

(5) Blastomycetes are not constantly present in human cancers.

(6) The peculiar bodies seen in the protoplasm of a cancer cell are not parasites, nor the cause of the lesion, but probably are, in part, at least, atypical stages of the process of secretion by glandular epithelium.

It is clear that in the present status of the etiology of cancer, bacteriologically considered, the case has not been proven. But it does not follow that it will not be shown that cancer is due to a specific and well-defined organism. It may be an organism so minute as not to have been brought within the range of the microscope. It is possible that no stains have yet been found that possess the requisite affinity for its complex molecular constitution. The necessary artificial medium for its cultivation remains for some future investigator to solve. Be it what it may, since the clinical features give strong evidence of the infectiousness of cancer, the search must and will be continued along the same lines.

In this search for a specific contagium, cellular metabolism must not be forgotten. Its consideration and study is perhaps more important than the isolation of a specific germ. It cannot be denied that the more exact our knowledge of cytomorphosis becomes the clearer will be our understanding of cell proliferation. It has long been understood that there must be certain stimuli that cause cell growth and certain inhibitors that limit cell development and exercise control in accordance with the requirements of the tissues. Certain other influences bring about a disturbance of the normal equilibrium between the stimuli and the inhibitors. It is evident that the exact nature of the stimuli, the inhibitors and the disturbers must be ascertained. This involves a study of the cell constituents and the fluids that surround it. As we see, it is a question of chemistry. . . .

What has malignant disease to do with immunity? The entire subject of immunity has to do with infection. It has to do with its nature, mode of action and control. Has cancer any characteristics that pertain to infection? Bacteriologically we have found none. Clinically we have a mass of evidence that would seem to place cancer among the infectious diseases.

In order to have a clear understanding of the modern conception of immunity, it is necessary to review, as briefly as possible and in barest outlines, without comment, the most important features of

our present knowledge of the subject. Much material that may seem essential to a complete elucidation of this great and important subject had to be eliminated on account of the limited scope of this dissertation.

More than a century ago we find that John Hunter was familiar with some antiseptic properties of the blood. He found that a small amount of putrefying material could be added to a given quantity of fresh blood without producing putrefaction. Consequently he advanced his doctrine of "the living principle of the blood." This, as an observation, was almost forgotten and its import was not fully realized until Nuttall, in 1888, began his systematic work, in Flügge's laboratory, studying the antibacterial properties of the body fluids, especially the blood serum.

The greatest impetus to the study of immunity was given by Metschnikoff in calling attention to the participation of the leucocytes and other cells in the process of infection, establishing his well-known theory of phagocytosis. His views are so well understood that we need only to call attention to them at this time.

Following Nuttall, Pfeiffer discovered, in 1894, "The extracellular disintegration and solution of cholera spirilla in the peritoneal cavity of immunized guinea pigs."

The greatest attention and interest was aroused by Behring's great discovery of antitoxic immunity. Bacteriologists at once endeavored to elucidate by elaborate researches the exact way in which immunity was established. Chief among these was Ehrlich. It was soon shown, however, that immunity in most bacterial infections did not depend, in the main, on the antitoxic principle.

Pfeiffer's phenomenon afforded a starting point from which Metschnikoff, Bordet, Ehrlich and Morgenroth began their labors and brought forth a series of discoveries that have been epoch-making.

A series of antibodies were differentiated and classified as antitoxins, antienzymes, cytotoxins, agglutinins, precipitins and coagulins. Antibodies were in turn produced by these, with the exception of the antitoxins.

It was determined that to every cellular group of an animal species there appears to correspond a specific cytotoxin. These various toxins have been termed leucotoxin, neurotoxin, spermotoxin, nephrotoxin, thyrotoxin, etc.

These antibodies have been divided into two groups; first, the antitoxins, which are single bodies; second, the cytolytins, whose antagonistic effects require the co-operation of two bodies.

Of these two bodies, the one which actually destroys the foreign cells is normally present in the cells or fluid of the organism; but it seems incapable of action without the intermediation of a body which is distinguished from it by a greater resistance to heat. The two elements composing cytolytins exist quite independently of each other, so that one may be present without the other, or be artificially removed without affecting the other.

To demonstrate the mode of action and constitution of the specific antibodies, Ehrlich has propounded the theory of receptors or side-chains. The atomic grouping of the toxin molecule, which affects the union with antitoxin as well as with a

particular cell, he has designated as haptophore groups.

In view of the fact that certain molecule groups of the living protoplasm favor the taking up of certain poisons, he has termed them receptors. According to his theory of antitoxic formation, after the introduction of toxins the receptors are produced in excess and finally are thrown off into the blood as useless ballast. The free circulating receptors are the antitoxins, termed amboceptors, intermediary bodies. The action of antitoxins is explained thus: They take charge of the haptophore groups of the toxin molecules and prevent them from approaching the receptors of the tissues.³ There are as many receptors as there are toxins, while almost every day new ones are discovered.

Behring gives the most exact and brief definition of Ehrlich's antitoxin theory: "The same substance which, when incorporated in the cells of the living body, is the prerequisite and condition for an intoxication, becomes the means of cure when it exists in the circulating blood." Every antiserum protects only against substances through which it becomes immunized. Every antiamboceptor protects only against its particular amboceptor.

Ehrlich and Morgenroth found, in experiments with goat's blood, thirteen different new lysins which represent so many receptors. "The receptors are in the cells, not for the purpose of linking poisons to the cells, but to seize certain foodstuffs, particularly proteids, and the toxins, bacterial and other foreign cellular substances, if capable of inducing the immunizing reaction, chance to have the requisite combining affinities for the receptors."

The living body possesses bactericidal and cytolytic substances which may protect it by destruction of invaders or may injure it by destruction of its own cells, according to the mates with which they are paired.

In considering the physiological mechanism of the cells we find that they are designed, primarily, for the assimilation of food, and, secondarily, to meet pathologic conditions, the production of antitoxins, cytotoxins and other similar bodies. The receptors are in the cells for the purpose of taking up foodstuffs, chiefly proteids. The toxins and bacterial cellular substances have combining affinities for the food receptors, if they are capable of inducing an immunizing reaction.

In producing immunization against bacteria, it is the intermediary body (amboceptor) which is generated. It has been found that these antibodies have a specific relation to the substances which caused their formation, as has been shown by the injection of a specific serum into an animal at certain intervals, of toxins, against which an antitoxin is desired.

The specific nature of these antibodies is further shown in their application to serum diagnosis, as shown by the Widal agglutination test for typhoid fever and the serum test in the diagnosis of *B. dysenteriae* Shiga, an organism shown to be the cause of acute dysenteries by Flexner, Vedder and Duval.

When Roux and Yersin discovered diphtheria antitoxin, and Ehrlich the origin and mode of action of antitoxin, a lasting foundation for the study

of immunity was laid. It was positively shown that "soluble toxins enter, as assimilable substances, into combination with constituents of the body cells for which they have an affinity," and are enabled to produce immunity or to exert toxic effects.

The expectations that we should soon be enabled to solve all questions regarding the action of toxins after the discovery of soluble bacterial toxins have only partly been realized, especially regarding the action of the pyogenic micrococci, which concerns us most as surgeons.

However fruitless, hitherto, the practical results regarding toxins of many pathogenic and especially pyogenic organisms, the principle has been established, and it is only a question of method and time when all body toxins and their antitoxins shall be definitely known.

Pfeiffer directed his attention to the bacteria and found substances, toxins, in cholera spirilla, which became free only after the bacteria were dead and which were termed intracellular poisons. This was a most important step in advance, but we must acknowledge that we know as yet very little about the action and nature of intracellular bacterial poisons.

It is interesting to note from the result of Flexner's experiments with venom that its action on red blood corpuscles, leucocytes and nerve cells is like that of duplex cytotoxins, which depend on the combination of intermediary bodies contained in the venom on one hand, with corresponding complements in the cells or fluids acted on. This is shown by the addition of venoms to fresh blood, which brings about the quick destruction of the red blood corpuscles. If the fresh blood has been washed with an isotonic salt solution, so as to remove all the complement, we find that the corpuscles are not dissolved, but agglutinated. It seems that the venom serves chiefly to bring "into necessary relations with constituents of the body cells poisons we already harbor or may generate, but which are harmless without the intervention of intermediary bodies."

Flexner and Noguchi have shown that the leucotoxic, the neurotoxic and other cytotoxic properties of venom depend on combinations of venom, intermediary bodies with complements contained in the cells poisoned by venom, or in the fluids bathing these cells, indicating that the snake venom contains only a part of the complete poison.

Flexner and Noguchi also demonstrated that hemorrhages in various tissues of the body resulting from poisoning from certain venoms is due to the presence in venom of a cytotoxin which has the power to dissolve endothelial cells, which they termed endotheliolysin (hemorrhagin). It causes extravasation of blood through its direct solvent action on capillary endothelium.

The hemolysins have been most extensively studied because of their great pathologic significance, and it has been found that many bacteria have hemolytic power. The secondary anemias, so constant in streptococcus infections, in pneumonia, typhoid fever and other diseases, afford a most striking example.

Normal blood serum contains antihemolysins which protect red blood cells from bacterial hemo-

³ Ehrlich: *Schlussfolgerungen*, p. 176.

lytic agents. Associated with hemolysins are bacterial hemagglutinins, possessing the power to clump red corpuscles.⁴

Heuter and Klebs believed that thrombi were due to the coalescing of red blood corpuscles. Welch calls attention to hyaline thrombi formed by agglutinated red corpuscles. White corpuscles are agglutinated by certain bacteria and also by pus cells.

What is urgently needed is a separation of these poisons and a determination of their source, constitution, mode of action and degree of specificity.

It will not be out of place here to allude to the studies made of the ductless glands, because of their supposed bearing on immunity. Sajous urges that the adrenal extractives have a decided affinity for oxygen, offering a key to tissue respiration and to the functions of all other organs now classed as the ductless glands. It has been found that the red corpuscles are not the only carriers of oxygen, but that the blood plasma contains and distributes this gas. Schmiedeberg, Jacquet, Claud Bernard and others demonstrated the existence of an oxidation ferment in the plasma, and these bodies are now entertained as an oxygen-laden secretion. This secretion is believed to permeate nearly all the body elements. The blood also contains a fibrinogen body which combines in certain quantities with fixed portions of the plasma's oxygen. The changes in the temperature of the blood were traced to variations in the amount of the fibrinogen in the plasma. The adrenals have been shown to be connected with the anterior pituitary body by various sympathetic ganglia. The anterior pituitary body is regarded as the governing center of the adrenal system. Over-activity of this body increases the adrenal secretion, consequently oxidation, therefore vital resistance. Depression of the activity of the pituitary body causes decreased supply of oxygen, consequently depressed vital processes.

The thyroid secretion, thyreoidin, has been shown to sustain the efficiency of the pituitary body. Excessive thyreoidin production stimulates the pituitary body and produces exophthalmic goiter. Deficient thyreoidin production leads to myxedema. The adrenals, the pituitary body and the thyroid gland constitute the adrenal system. According to this line of research, it is believed that toxins act directly on the adrenal system, and, by decreasing or increasing its secretion, decrease or increase the oxidation process. Certain toxalbumins and many drugs stimulate the adrenal secretory powers to a certain limit, and, when exhibited in excessive doses, depress or arrest the functions of this system.

The posterior pituitary body has been shown by Berkley, Andriezen and others to be the chief functional center of the nervous system. It is the center for such emotions as shock, excitement, etc. It governs all organic functions through the nervous system. The secretions of the pancreas and spleen, according to Schiff, and later by Herzen, unite and change trypsinogen into trypsin, a solvent for the albuminous bodies in the pancreatic juice. This ferment performs an important part in immunizing processes, in that it destroys toxalbumins.

Viewing these labors in the light of Ehrlich's researches, the oxidizing substance represents the

amboceptor; the spleno-pancreatic internal secretion, trypsin, represents his complement. To produce a proteolytic action of trypsin, fibrinogen and the oxidizing substances are required. These views are somewhat at variance with those commonly accepted, but are of sufficient importance to deserve consideration in this connection.

From the foregoing it would seem that the doctrine of phagocytosis plays an unimportant rôle. But we find that the French, or phagocytic school, at the head of which is Metschnikoff, recognizes the full significance of acquired immunity and the cytolytic principles represented by the co-operative action of intermediary bodies and complements. The German, or humoral school, led by Ehrlich, recognizes the leucocytes to the fullest extent.

The chief difference between the French and the German schools consists in the belief by the advocates of phagocytosis that the complements reside in the leucocytes, whereas the adherents of the humoral school believe that they exist in the blood plasma.

While, in what has here preceded, we have been concerned in the consideration of chemical problems, we must not overlook the fact that behind all is a governing force which resides in the central nervous system.

The practical outcome of these studies has been found in the production of antitoxic sera, some of which have been proven to have a definite and exact effect under certain conditions. We find these sera divided into two principal groups: (1) those that have an antibacterial action, and (2) those that have a purely antitoxic action. Of all the sera the diphtheritic is best known. According to Welch the mortality of diphtheria has been reduced from 40% to 15% by its use.

Antitetanus serum has been disappointing. Reports coming to us from different sources are conflicting, the mortality ranging from 0% to 70% from practically the same methods, which consist in administering the serum by the subcutaneous, intracerebral and the spinal methods. Antityphoid serum has failed to fulfill expectations even more than antitetanus serum. The antistreptococcus serum of Marmorek, while it seems to have exerted a specific effect in purely streptococcal infections, appears to exert no influence in the presence of mixed infections. The antipneumococcal serum has not yet emerged from the experimental stage. Nothing can be said of its effects. The anti-plague serum of Haffkine and Yersin demonstrated that, as a preventive, it reduced the number of cases to one-twentieth and the mortality in a given number of cases was reduced from 33% to 13% (Calmette). The antitubercle serum has been shown to have a specific effect on tuberculous tissue, but remains powerless in the presence of mixed infections. The antivenom serum has been demonstrated to have a positive usefulness in certain snake bites. Calmette's antivenin has been proven to be of undoubted use in leprosy.⁵

Many other sera have been described, but their usefulness thus far has been shown to be of an uncertain nature. Consequently we will leave them out of consideration at this time.

⁵ F. A. Packard and Robert M. Wilson: *Amer. Journ. of the Med. Sc.*, December, 1900.

⁴ Heuter-Klebs, p. 731.

When we pass in review all that is positively known in relation to the question of immunity, we cannot deny that some of the principles underlying this great question have, in a measure at least, been revealed. The evidence is conclusive that "the same substance which, when incorporated in the cells of the living body, is the pre-requisite and condition for an intoxication, becomes the means of cure when it exists in the circulating fluid."⁶

Ehrlich, in his investigations of diphtheria toxins, demonstrated "that soluble toxins enter as assimilable substances into direct combination with constituents of the body cells for which they have an affinity, and only thereby are enabled to bring about immunity or to exert toxic effects." Further, in connection with Metschnikoff, Bordet, Morgenroth and Ehrlich, it is shown that "the organism possesses a power to produce substances specifically antagonistic to all sorts of foreign cells, cellular products and derivatives. The substances capable of inducing this immunizing reaction appear to be mainly of an assimilable, albuminous nature, or at least intimately associated with such material."

The principle of toxins and antitoxins has become as firmly established as any other in medicine or surgery. We have noted that antitoxins from pure cultures have a certain affinity for and possess immunizing power in specific infections, but fail in the presence of mixed infections. We see at once that failure to immunize does not violate the principle, but that the method of application has been at fault. We know that diphtheria toxin has a specific effect for the products of the Klebs-Loeffler bacillus, and that it controls and cures in the presence of these, but fails when there is an admixture of other forms of infection. This is shown by the 15% mortality which still exists. We have noted that antistreptococcus, tubercular and plague sera have a specific and a decided effect in pure infections, but that they fail in the presence of other specific germs. We observe with satisfaction the certainty of the action of a given antitoxin in its union with the toxin from which it was produced. It at once becomes apparent that, in the presence of several toxins or a mixed infection, it will require several antitoxic substances, a combination of antitoxic sera, or a serum containing different kinds of amboceptors, so combined as to meet and unite with the several toxins in a given case. Coley endeavored to meet such indications by combining streptococcus and Bacillus prodigiosus sera in treating inoperable sarcoma.

These observations presage a revolution in therapeutics, which perforce means a refinement in diagnosis beside which what we do now will scarcely bear comparison.

The inferences to be drawn from the foregoing indicate that the future work will be biochemic. It appears that the solution of cell metamorphosis, as it is observed in pathologic conditions, will be in the field of chemistry. Ehrlich's theory of the side-chains has given us a working hypothesis almost as practical as the atomic theory when applied to chemistry. It is not an idle dream to believe that the revelations of the future will not only consist in a complete exposition of cells and body fluids, or a

perfect understanding of the governing brain centers, but may extend to the life principle itself, although life itself may and will ever belong to the unknowable.

Our chief interest, however, will always center in the cell and its governing influence. Just what influences are responsible for normal cell division may never be known. But it is within the bounds of human possibility to know what influences may be responsible for atypical and excessive cell growth. Excessive cell growth, both in the leucocytes and connective tissue cells in acute infections, we can assume to be due to toxins that are in excess of the amboceptors. The existence of cytotoxins and anti-cytotoxins is now undisputed. The one destroys, the other protects the cells. We have noted that the chief function of a receptor molecule is to combine with nutrient molecules a metabolic, a chemical process. The birth and growth of the cell is restricted within certain limitations and is regulated by chemical law. Now the problem depends on our ability to ascertain the exact influence that carries cell division beyond its normal bounds and causes excessive cell growth as we observe it in malignant new growths. That the process is one of localized excessive nutrition is apparent. The localities of predilection are frequently at points where the cellular elements are exposed to frequent insults, where the tissues are damaged, establishing a *locus minoris resistentie*, as, for example, in the mouth, gastro-intestinal tract and the female reproductive organs. A point of least resistance, damaged tissue, if you please, always offers a soil for bacterial invasion. Cancer very often develops in tissues that have long been irritated, no doubt liberating a complement that unites with a specific infection when introduced under proper conditions. Such is not always the case, however. In fact, we know that in the majority of cases tissues that sustain irritations and almost constant traumatism for many years never become malignant. The simple traumatism does not develop cancer. A specific toxin must be introduced, probably also an intermediary body to complete the side-chain, which increases karyokinetic energy. We have noted in our studies of immunity that the life or death of the cell depends on its intra- and extra-cellular composition, so we may say that the whole process, whether it relates to normal or excessive cell growth, is chemical.

An objection may be urged at this point, which consists of the fact that the propositions of immunization thus far considered affect groups of cells extending over a wide range, that is, the vascular, the muscular and the glandular or cerebrospinal systems. It has been shown that cancer is always at the outset, and often throughout its entire course, absolutely a local disease. It would not seem rational to attempt immunization of the entire system against a strictly local disturbance. We will naturally turn our hope toward a method that will enable us to effect local immunization.

That local immunization is possible has been demonstrated by P. Römer in the following convincing abrinimmunization experiment. As is well known, abrin, which is the toxalbumin of the jequirity bean, will produce a severe conjunctivitis in animals and men. Ehrlich had demonstrated that rabbits' conjunctivæ became immune after the in-

⁶Welch: Behring's Definition of Ehrlich's Theory Concerning Antitoxin.

stillation of abrin. Römer instilled into the right eye of the rabbit weak abrin solutions, the dosage being rapidly increased until immunization was produced. In three weeks the rabbit was killed. It was then shown that if the right conjunctiva, which had undergone severe inflammation, were rubbed and macerated with a certain amount of abrin and injected into a healthy animal, it had no effect. But, if the conjunctiva of the left eye, which had received no instillation, were rubbed and macerated with abrin and injected into an animal, death always followed. Römer concluded from this observation that in conjunctival immunizations a part of the autotoxin existed in the conjunctiva itself. A local antitoxin was produced.

It would seem that these results established definitely the principle of local immunization in indifferent tissues. These observations have an important bearing on the adaptation of these cells in local affections. That local affections of various forms, or general affections with local manifestations, can be best managed by the local introduction of exceedingly small doses of the specific remedy, was shown by Professor Bouchard before a recent meeting of the Egyptian Congress. He found that articular rheumatism disappeared after the injection *in situ* of small doses of salicylic acid, in some cases only half a grain. We must conclude that local cell metabolism can be influenced by local rather than by general diffusion. The inhibition of excessive cell growth must be accomplished in the same way.

It would seem, then, that the cancer question must be solved along the lines of chemistry. Since we know that contagious or infectious energy does not depend on the bacterium itself, but on its products, which are purely chemical, it would seem that it matters little whether the specific parasite is found or not. Since the cancer germ has thus far successfully eluded the most vigilant search, it becomes more and more evident that in the field of chemistry will be found the solution for our problem.

It will be difficult to rid ourselves of time-honored views. Purely theoretical speculation, like the hypothesis of cell proliferation from inclusions of embryonal matrices according to Cohnheim, must give way to the demands of modern science that insist on actual observations and practical demonstrations.

Now, then, will it be unreasonable to hope that when protoplasmic changes are thoroughly understood and when the body sera have given up their secrets and the influences that govern cell growth, we may also find the antibodies which will inhibit cell multiplication beyond natural bounds?

The studies in the field of immunity have, as yet, only assumed the proportions of the initiatory stage. A vast unexplored wilderness lies before us. The pioneers have begun their work well. They have outfitted themselves in a manner that will, in the near future, enable them to throw unexpected light in the pathway of their conquest of discovery. They are only on the verge of this vast domain. What lies beyond the borders we can no more foretell than could Boyer know that in twenty-four years after his death we should have anesthesia and that in fifty years the world would have antiseptic surgery. And yet, in the light of our present knowledge, the hope, amounting to a conviction,

arises in us that even in our lifetime, if we are spared a few years more, we will have an exact bio-dynamic and bio-chemic science that will make diagnosis accurate and precise, and one that will enable us to treat and control all infections with an exactness not now possible. While the surgeon is now constantly encroaching on the field of the internist, the time is not far distant when the physician may not only reclaim his own, but with it that large group of neoplasms known as malignant growths that from time immemorial has been the exclusive property of the surgeon.

REFERENCES.

- Ueber Antikörper gegen die bacteriolytischen Immunkörper der Cholera. R. Pfeiffer und E. Friedberger. Berl. klin. Woch., No. 1, 1902.
 Das Streptokokken-Gift. A. Marmorek. Berl. klin. Woch., No. 12, 1902.
 Ueber die Vielheit der Complemente des Serums. P. Ehrlich und H. Sachs. Berl. klin. Woch., Nos. 14-15, 1902.
 Ueber den Mechanismus der Amboceptor-Wirkung. P. Ehrlich und H. Sachs. Berl. klin. Woch., No. 21, 1902.
 Ueber die Complementophilen Gruppen der Amboceptoren. P. Ehrlich und H. T. Marshall. Berl. klin. Woch., No. 25, 1902.
 Ueber die Receptoren der Mischelweisskörper. F. Meyer und L. Aschoff.
 The Huxley Lecture on Recent Studies of Immunity, with Special Reference to Their Bearing on Pathology. Wm. H. Welch. The Med. News, Oct. 18, 1902.
 The Present Status of Serum Therapy. Frederick A. Packard and Robert Wilson. The Amer. Journ. of the Med. Sci., December, 1902.
 A Résumé of Some Recent Researches Relating to Cytolysis and Immunity. Dr. T. Mitchell Prudden. The Med. Rec., Feb. 14, 1903.
 Experimentelle Untersuchungen über Abrin-(Jacquiritol) Immunität. P. Römer. Archiv f. Ophthalmol., 1-11 Band, 1 Heft, S. 73.
 The Internal Secretions and the Principles of Medicine. C. E. de M. Sajous. The Month. Cyclo. of Pract. Med., January, 1903.
 New Methods of Medical Treatment. Editorial, Med. Rec., March 7, 1903, p. 380.
 Leukämie-Pseudoleukämie-Haemoglobinaemie. Schlussfolgerungen von Geh. Med. Rat. Prof. Dr. P. Ehrlich, Frankfurt a. M.; Privatdocent Dr. A. Lazarus in Charlottenburg, und Dr. F. Pinkus in Berlin. Alfred Hölder, Wien, 1901.
 Ehrlich's Seltenkeitentheorie und ihre Anwendung auf die künstlichen Immunisierungsprozesse. Prof. Dr. Ludwig Aschoff. Vorlag von Gustav Fischer, 1902.
 The Recent Buffalo Investigations Regarding the Nature of Cancer. Address of the President, Trans. American Surgical Association, 1901.

Original Articles.

BRACHIAL PARALYSIS, POST-NARCOTIC.

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THE following instances of post-anesthetic paralysis are presented because the writers believe that such cases should be put on record. Few of the cases are reported, and, as a consequence, the risk we run of having this accident occur is not always appreciated. It is apparently always avoidable, if the etherizer knows the risk and has it in mind.

CASE 1. Miss P., aged twenty-five, healthy, moderately robust; etherized May 6, 1901, for an operation on the hip. The anesthesia lasted a little over two hours. During etherization both arms were raised: the left forearm was on the pillow above the patient's head (but not under any tension); the right arm lay abducted with the elbow flexed, only the supinated hand resting on the pillow. The position was practically unchanged during the whole operation.

After an uneventful recovery from ether, the patient showed a practically total paralysis of both arms.

On the right there was entire loss of power in the extensors of the hand and wrist and of all muscles supplied by the ulnar nerve. There was fair power of flexion in the fingers and good ability to pronate the forearm, but supination was lost. The triceps was paralyzed, the biceps and brachialis anticus only partly so. There was entire loss of power over the deltoid and supra- and infra-spinatus muscles.