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The Pathological Signification of Immunity.

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How it is that the human organism is not liable to be invaded by certain infectious and contagious diseases more than once in the lifetime, has occupied the best thought of the medical profession from the earliest of times, and during the last two decades more earnest efforts have been made for the solution of this question than ever before; nevertheless, the pathological, or, if you please, the physiological, signification of immunity has not yet been satisfactorily given. Now here in the beginning of this paper I desire to emphasize the fact, that from all the most recent investigations upon this subject which have been accessible to me, it is my conviction that the facts given us in the various processes of fermentation afford data which are competent to explain how this immunity from the reinvasion of the organism by contagious diseases may be acquired by man and by animals.

What then is fermentation, and how is it accomplished? Fermentation is a certain definite modification which takes place in the chemical constitution of an organic body, and this modification is accomplished by virtue of

a chemical, unorganized and lifeless ferment, which is secreted by a living cell. Fermentations, according to views which now universally obtain, are divided into true and false fermentations; the former are alleged to depend upon the action of living cells, and hence are called organized or living ferments; the latter are made to depend upon unorganized and lifeless substances which these living cells themselves secrete, and are therefore called lifeless or chemical ferments. The transformation of glucose into alcohol and carbonic acid by the so-called yeast cell is an example of the first; the transformation of albumen into albuminose by the action of pepsin is an example of the second. Now I purpose here to take a somewhat different view of the matter and to advance the proposition, namely, that all fermentations are, at bottom, fundamentally one, and that the primary and efficient impulse to these fermentations is impressed, not by an organized or vital ferment, but by a ferment which is chemical, unorganized and lifeless. In venturing to make the broad statement that fermentations, that all fermentations are

due and referable to chemical and not to vital causes, I confess that I have done so with some reluctance, especially as it is in contradiction to the views advanced by such men as Pasteur, Chauveau, Koch, and others whose splendid achievements in these very fields have shed unfading glory on the medical name; yet standing, as I feel myself, behind facts which are incontestable in the support of this view, I will neither hesitate nor waver in defending the position here taken. Let us then take a succinct and cursory review of some of these fermentations, or transformations, as we know them to occur in both animal and vegetable bodies.

Pepsin, for example, which is an unorganized, lifeless ferment, secreted by the peptic cells of the glandular follicles of the stomach, is, "by virtue of its presence," endowed with the capacity of essentially altering the chemical relations and physical qualities of the albuminous substances received by the stomach, and of rendering them diffusible and absorbable in the organism.

The living peptic cells of the stomach are in no way concerned in this transformation, but it is something which these living cells secrete—a pepsin, a ferment at once and forever chemical and unorganized.

The very same thing can be said, and for the very same reason, of all the chemical transformations going on in the organism. It is by a chemical ferment, and nothing more than a chemical ferment, secreted by living cells, by which starch is transformed into glucose, fats saponified, albumens converted into peptones by the pancreas, and sugar into glycogen by the liver. The specific functions of these ferments do not depend, in any way, upon their relations or proximity to the living cells which produced them, but are abundantly able to perform the same offices, as well without as within the organism. Let us now hastily glance at a few of the most common

fermentations as they are known to take place outside of the body, and, in order that I may not weary you by submitting a detailed paradigm of a number of fermentations which are closely allied, as the alcoholic, the acetic, the lactic, the butyric, etc., I shall here, for the purpose of economizing space and time, briefly consider this whole class of fermentations, the so-called true fermentations, under one view, as all of them are held, and I may say universally held, to be set up and carried on by the vital action of micro-organisms. Take, for example, the alcoholic fermentation of glucose. This fermentation has long been held as a notable and convincing illustration of the action of a ferment which is organized, a living micro-organism, the *saccharomyces cerevisia*, the so-called yeast cell. Let it here be particularly noted that glucose, or grape sugar, exists by nature in the expressed juice of the grape, and that it exists by nature nowhere else. For the purposes of nutrition all other forms of sugar, as well as starch and its derivatives, must be converted into grape sugar, for no other is assimilable by the tissues.

Now it is everywhere conceded that in all these transformations of starch into sugar, and of one form of sugar into another form, and of any or all of these forms into glucose, nothing but a chemical ferment is required. It is *certain* that no vital ferment, that the *vital* action of no micro-organism, is required or in any way concerned in these transformations. Bartholot has shown, and he was the first to show, that the conversion of cane sugar into grape sugar by yeast is not done, as it was at one time supposed, by the living yeast cell, "but by a chemical ferment which can be abstracted from the yeast and will still act in its absence." "In fact," says Bartholot, "yeast itself cannot utilize cane sugar, but must first get it changed into grape sugar by this soluble ferment, so that the conversion of cane sugar into alcohol is a double event, and requires

first the action of a lifeless ferment to turn the cane sugar into the more hydrated grape sugar, and second, a living ferment, yeast, to turn grape sugar into alcohol." Bartholot says further: "If yeast can secrete, as it does, a soluble, lifeless substance which inverts sugar, may it not be that it repeats the process substantially in changing grape sugar into alcohol?" In corroboration of this, it may here be stated that wherever yeast cells are found existing together, as at the bottom of vessels where the fermentation of glucose has ceased, there is also to be found an albuminoid, intercellular substance, secreted by these cells, a true chemical ferment, and capable of setting up the vinous fermentation.

Furthermore, it is known that the alcoholic fermentation will not take place in a *pure* solution of glucose, that is, in a solution not containing the albuminoid matter, the chemical ferment native to the grape itself, however favorable the temperature, and however exposed to the air; but if a little of the nitrogenous, albuminoid matter—chemical ferment—which exists by nature in the expressed juice of the grape be added to the solution, fermentation shortly begins, and is carried on to completion.

Parenthetically I must here say, according to the authority of all chemists and chemistries, that, whatever may be the part which micro-organisms may play in the fermentation processes, the alcoholic fermentation of glucose would not be possible without the presence of the vegetable albumen which exists by nature in the grape, so that it is now a chemical aphorism: *No albuminoid (body) ferment, no fermentation.* In the process of brewing also, and in the preparation of spirits from grain, we again meet with this ever-present albuminoid ferment, the yeast, without which, as has already been shown, no alcoholic fermentation is possible. Here in the grain we find this albuminoid ferment in the form of diastase deposited by

nature in the grain itself, just as we have previously found the so-called yeast ferment to exist by nature in the grape under the form of vegetable albumen, which, by the absorption of oxygen from the air, enters into decomposition and becomes the one necessary and universal ferment in all vinous fermentations. Again, in the ammoniacal fermentation of urine, which has all along been attributed to a micro-organism, the *micrococcus urea*, M. Masculus has shown that we can obtain from altered urine, by the action of alcohol, a precipitate, a chemical ferment, which is able to transform urea into carbonate of ammonia. Thus it appears that, as in the alcoholic fermentation of glucose, and as in the fermentation of grain in the manufacture of beer and of spirits, so also in the fermentation of urine the fermenting agent is found to be, not the action of a living micro-organism, but the chemical action of a lifeless, unorganized ferment. In one word, the conversion of sugar into alcohol and carbonic acid, upon the authority of Fown's late edition of chemistry, "*never takes place except in the presence of some nitrogenous body of the albuminoid class in a state of decomposition.*" Now because bacteria are often, perhaps always, present during what are called the true fermentations, that is, in those fermentations which occur exterior to the organism and which are concerned in the regressive or destructive metamorphosis of organic bodies, we must not conclude therefrom that these bacteria are, at least by their vital actions, the cause of these fermentations, and for two reasons: 1st. Bacteria are themselves nitrogenous bodies of the albuminoid class, and when they perish, as they are constantly doing, they at once become the one definite and specific chemical ferment, as defined by Fown—"nitrogenous bodies of the albuminoid class in a state of decomposition." 2d. These bacteria are themselves able to secrete a lifeless chemical ferment which can set in motion the fermentative process. From these

considerations three facts obtrusively present themselves to us: First, bacteria cannot set up fermentation in bodies consisting exclusively of amylaceous or saccharine matter, because, requiring nitrogen as a necessary part of their nourishment, they cannot maintain their vitality upon these non-nitrogenous bodies alone; the second, that these fermenting albuminoid matters, affording all the food elements necessary for their nutrition, would be a sufficient reason to account for the movement of bacteria thitherward in quest of food; and the third, that the selfsame albuminoid matters enter into fermentation in all the so-called false fermentations by the action of a purely chemical ferment alone, and where no bacteria are known to exist. If, therefore, these micro-organisms must be held as standing in any causal relation to these fermentations, they must do so either by secreting a chemical ferment, or by surrendering their defunct albuminoid bodies as a "yeast" for these fermentations.

Now I desire here to signalize the statement, namely: that we violate no law of bacteriology, that we violate no law of biology, in allowing the bacteria the power of secreting a digestive ferment, a ferment that shall be able to perform for them the same physiological functions which this ferment is known to perform in all other living beings, namely: the chemical transformation and digestion of the food elements destined for their nutrition. And if we do not desire to advance the doctrine that these bacteria occupy an unique and isolated position which is not assumed by any other living beings upon the globe, then we must allow that these organisms are endowed by nature to secrete a ferment, and that that ferment shall be able to digest for them their food, rendering it absorbable and assimilable by their tissues, as all other living beings are qualified to do. No, there must be no difference; the fundamental laws of biology, the

universal laws of nature, are over all alike — and just as man would inevitably perish though his digestive cavities were filled with the most nutritious food-stuffs, did not those chemical ferments which Nature has placed within his organism work a chemical transformation upon that food, thus rendering it absorbable and assimilable by the organism; so, too, would the bacteria succumb to dissolution were they not also able to chemically transform by their own ferments the materials upon which they must live. No living being, neither vegetable, bacterial, nor animal, is able to appropriate to its own nutrition the food material in the form, in the chemical and physical form, in which that food is found to exist in nature; but, on the contrary, each must be qualified by nature to transform this material suitable to the physiological requirements of the organism. Now, is there any other power or instrumentality possessed by any being amongst all the living which is able to do this but a ferment, a ferment chemical and lifeless? *Emphatically there is no other.* Then it becomes to us a matter of necessity, we are, *nolens volens*, constrained to accept the proposition, namely: that wherever a bacterion is found to exist and to nourish itself, it must there be found to do this by setting up a fermentation in the organic body or tissue wheresoever it is found.

One word now on putrefactive fermentations. The putrefactive fermentation of albuminous matters, of both animal and vegetable origin, is accomplished by a great variety of micro-organisms. For each step in the downward march of these organic matters a definite and specific micro-organism is required, and their total destruction can only be accomplished and be complete after myriads of these organisms have been employed. The chemical products resulting from these decompositions are so numerous, varied and complex that they have never yet been definitely made out. Among these products are to be found

a great many poisonous substances, pathological irritants, of which recent pathological writers have said so much. Now since we have learned that bacteria have no other way of obtaining their nourishment but by decomposing organic bodies, and that they can only do this by the dissolving power of that ferment with which Nature has beneficently endowed them, the conclusion is imposed upon us, it comes to us by the authority of a voice from heaven, that the molecular edifice of defunct albuminoid bodies, that the organic tension by which these bodies are held in unbroken unity, must be loosened and broken up in these putrefactive fermentations in precisely the same way, and by precisely the same instrumentality by which we have already found this to have been done in the fermentation of glucose, and in the peptic fermentations of albumen in the human stomach; and it may be stated here as a fact, a little remarkable, but no less remarkable than true, that, upon the authority of Flügge, the very first product that appears in these putrefactive fermentations is a peptone in every respect similar to the peptone formed by the human stomach. If, then, the putrefactive process begins, as it does, by a chemical ferment secreted by bacteria, is it not reasonable to conclude, nay, is it not certain, that all other bacteria, in carrying on and completing this process, would do their work by exactly the same means? It is true that beings so microscopically small must be only able to secrete a ferment exceedingly minute, often too minute for chemical isolation, but it has long ago been known that a little leaven may leaven the whole lump, and that the veriest spark may cover a great city.

But, Mr. President, it ought to have been enough to have simply stated, in the beginning of this paper, that Nature sometimes employed a chemical agent in the fermentation of organic bodies, and then to have sat down. It ought to have been enough to have plighted

our undying faith in the veracity of Nature, and in her immutable and unchangeable laws; that yesterday and to-day, from the beginning till now, she has worked according to one universal law, always doing the same thing in the same way. It would be monstrous to suppose that Nature would employ two diametrically opposing agencies to accomplish one and the same specific process; that the living and the dead should be made able to perform the same functions; that now a living, now a lifeless ferment should be employed to accomplish a certain definite and specific fermentation in organic bodies. No, Nature does not abort. Here there is neither variableness nor shadow of change. In all the long cycles of past times her creative and transformative processes have been the same, and the agencies by which these processes began to appear and to continue on in their forward movements are just the same now as in the beginning. Away back in the beginning of the ages, before any organic form was born, before life had appeared upon the globe, before any organism had been fitted up for the reception of a new and most august being, soon to make his advent into the world, a being endowed with sensation, sympathy, and thought, conscious of his own existence, and capable of explaining it—before these appeared upon the globe it became necessary, in the economies of Nature, that a new body should be formed—a body having no prototype or kinship in the then existing nature—a body at once creative and transformative, capable of breaking the bonds which had held for myriads of ages the inorganic world in utter lifelessness—and a body capable of introducing a new and a totally distinct order of being. This was chlorophylle. But what is chlorophylle? It is a ferment; a ferment chemical, unorganized and lifeless, identical in its chemical composition and in its physiological functions to the fer-

ments we have been here considering.

Sir, these most phenomenal and extraordinary bodies, of which chlorophyll is the prototype, have never yet been explained. To the physiologist and to the chemist of this day they are confessedly inexplicable and unknown; hence they are still referred to under the enigmatical and shadowy appellations of "catalytic bodies," of bodies "acting by their mere presence." Although having no life within themselves, they constitute the one sole necessary and indispensable medium by which life began to appear in the vegetable, and by which it now continues to persist in the animal world. Remove from the earth its mantle of immortal green which chlorophyll imparts, take away from the vegetable cell this lifeless ferment, and very soon would vegetable life, very soon would all life, disappear from the earth. The inorganic elements would then cease to arrange themselves into organic forms, and these elements would again become forever fixed and immovably bound down in the inorganic world as they were in the beginning.

Having thus briefly and rapidly touched upon some of the most common and best known fermentations, and having ascertained their cause, we shall now endeavor to show that the pathological signification of immunity is implicitly given in the modifications which occur in the chemical constitution and physical qualities of organic bodies during the process of fermentation. And here I desire to say, and I desire to say it in earnest emphasis, that the pathological signification of immunity is not soluble upon the vital theory of fermentation, and that it will not admit of solution if this theory be true. Hence the most astute men of the profession, who, if I am not mistaken, implicitly subscribe to this vital theory, have yet been unable to give any satisfactory solution of this question. But upon the chemical theory of fermentation the signification of immunity, I must be allowed to say, becomes

natural and easy. Now as a basis to the solution of this question I will here state, what I take to be, a self-evident proposition, namely: *When the chemical relations and the physical qualities of an organic body have been modified by the action of any ferment, the body thus modified will not admit of any additional or further modification by the same ferment, so long as that modification exists.* It will be admitted here as also self-evident that *any body undergoing fermentation must, ipso facto, undergo at the same time a certain definite modification in its chemical nature.*

Now, is it not conceded by the medical profession that infectious and contagious diseases are induced by the presence and action of certain pathogenic organisms received within the system? Yes. Is it not also conceded that these pathogenic organisms, in producing these diseases, act simply in the capacity of ferments, that is, by altering the chemical relations and physical qualities of the tissues? Yes. Is it not admitted, furthermore, that these altered tissues are immune against the bacteria which produced them, and that it would require totally distinct bacteria to re-ferment these altered tissues? Yes. But when we say that such altered tissues of the organism are immune against the bacteria which formed them, do we not implicitly say that the organism itself is immune against a disease of which those bacteria are the cause? Yes. Well, then, is not this immunity? Yes. And when we say that no pathogenic bacteria can re-ferment the product of its own fermentation, is not this the pathological reason of immunity? It is. I will stand to it before the world that the pathological signification of immunity has now been given.

To account for immunity against a second invasion of the system to infectious and contagious diseases many theories have been advanced. The "exhaustion theory," proposed by Pasteur, sets forth that pathogenic bacteria

take up certain elements of the organism for their own nutrition, and when these elements have been exhausted, there remaining no other elements in the organism suitable for their nourishment, the body, by necessity, becomes immune. Then there is the theory proposed by Chauveau, called the "retention theory," which sets forth the notion that certain pathological micro-organisms form special products which are retained by the system, and which are inimical to the growth and development of the organisms which form them; so that a second invasion by the same organism cannot occur. Now if, on the theory of Pasteur, something must be removed from the organism every time it was invaded by an infectious disease, in order that immunity shall be acquired, the body after repeated infections might be subjected to a loss of material incompatible with its physiological functions, and hence this theory must be held as inadmissible. On the other hand, if something must be added to the organism inimical to the microbe which would infect it, the organism, after many of these infections, must become loaded up with a goodly quantity of foreign material; and all this for the sake of immunity, now from this, and now from that infectious disease. Then, also, there is the "tolerant theory," proposed by Sternsbergh, and then the theory of *phagocytosis*, whose most distinguished advocate to-day is Elias Metschnikoff, of the Pasteur Institute, neither of which theories I can here particularly notice; not only for want of space, but also for want of ability to discover their force or pertinency—the former going upon the supposition that one may become so "tolerant," so accustomed to disease germs, that by and by they cannot hurt him; the latter that the *leucocytes* of the organism, like so many hungry terriers, guided on by an inscrutable "*chemotaxis*," keep chasing after these bacteria and devouring them. It must not be forgotten, also, that millions, even billions, of

these germs are able to be produced in the organism during a single day, so that the said *leucocytes* might be kept uncomfortably busy in keeping down the increase.

Now the theory which I have ventured here to propose does not take anything away from the organism, it does not add anything to it, but it simply imposes a change of tissue, as a guarantee for immunity—a change of tissue produced by a cause known to exist in the organism, a cause competent to make a change of tissue and a cause operating according to the principles of a known and well-established law. This theory gives you a ferment as a cause of this change of tissue; it points you to a pathogenic bacterion which forms this ferment, and it assures you, according to the known laws of fermentation, that this tissue, that the organism itself, is not again assailable by the same pathogenic germ. Nor does this theory require you to accept any new, hypothetical or extraordinary law for its explanation, any strange or anomalous process in nature, as a ground and reason for immunity, but it points you to a physiological prototype creating immunity in the same way and by identically the same cause; it points you to the fermentation of albumen by a chemical ferment secreted by the peptic cells of the stomach, to the transformation of albumen to peptone by the action of this ferment, and it gives you a physiological guarantee that this peptone is immune against the action of that peptic ferment, and that this immunity will exist just as long as albumen shall maintain its changed physiological condition under the form of a peptone. It would be superfluous here to argue that the same must be true of the products of all other fermentations; for this would compromise the invariability of Nature; it would tend to hazard the maxim that "the part of a part is part of the whole." If starch is transformed into glucose by the ptyalin of the saliva or by the amyllopsin of

the pancreas, then, by this invariable law, glucose must be immune against these ferments. If the tissues have been transformed by the ferment action of the small-pox bacillus, then these tissues must be immune against the further action of that bacillus. If carbonic acid plus water have been transformed into starch by the action of chlorophylle, then must starch also be immune against this ferment.

But then chlorophylle cannot act by its own unaided power—"of itself it can do nothing. Although the one sole necessary medium by which life and organic forms became possible upon the globe, it is not self-mediated; it is mediated by light; it is quickened and put in motion by the solar rays, which work in it, with it and by it in all the vital operations. It has been eloquently shown by the immortal Draper that "vegetable growth and development is directly as the quantity of light; that for the decomposition of a given weight of carbonic acid and the formation of a given weight of gum a fixed and invariable quantity of light is required; that light really and formally enters into the organic structure and becomes one with it." So that the light of the sun is the veritable life of the world. It is now our life; we are indeed the children of the sun, and are begotten by his rays. So that without any metaphor, without the least imagery of language, we can literally and truly look up upon the face of that great luminary and say unto him, in awe and filial adoration, "Our Father who art in heaven."

But in returning from this digression I cannot better conclude this paper, nor more effectively reinforce what has heretofore been said, than by reaffirming the maxim first formulated by Rudolph Virchow, namely, "That every pathological product must have a physiological prototype." By this maxim we are then entitled to look for pathological immunity just where we have previously found physiological immunity, and if physiological immu-

nity is given in a product formed by a physiological ferment, then we must expect to find pathological immunities in the products given to us in the pathological fermentations; but every physiological immunity is given in a product formed by a physiological ferment—therefore every pathological immunity is given *by a law which cannot be broken*, in a product formed by a pathogenic or pathological ferment.

By way of parenthesis, I may here say that the two classes of fermentations heretofore referred to, the true and the false fermentations, are each of them physiological actions and are at bottom fundamentally one—the so-called false fermentations being progressive and constructive; the true, regressive and destructive; but both are operated according to the same fundamental law.

From the foregoing considerations also it can be seen why it is that there is a fixed and natural limit to the periods of fermentation, just as there is to the periods of disease; why the alcoholic fermentation will cease when the fermenting liquid contains about 17 per cent of alcohol; why the ammoniacal fermentation will cease at about 13 per cent of carbonate of ammonia; why the lactic fermentation will cease at about 1 per cent of lactic acid, and so of the rest. This is not because, as was once supposed, that the bacteria producing these fermentations perish, for they are seen to exist long after fermentation has ceased; but it is because the products of these fermentations are inimical to the chemical action of the fermenting bacteria, and can only continue in the presence of a limited per cent of their products. In putrefactive fermentation, in the fermentation of albuminoid bodies, the inhibiting power, the anti-fermentation power of these ferment products, is exceedingly increased, so that the smallest quantity is able to protect against fermentation on the one hand, and to protect against disease on the other. This is exem-

plified by the principle involved in vaccination, where a particle microscopically small of these (albuminoid) pathogenic bacteria "in a *state of decomposition*" is able to protect the organism against the most active contagion; where the tiniest portion of blood serum of a person made immune, where even the milk of an immune mother, is able to protect against disease. If anything further was required to support the doctrine which this paper proposes, it is given in the fact, now universally admitted, that contagious and infectious diseases can be communicated to a healthy person by the defunct bodies of these bacteria "*when in*

a state of decomposition." Therefore contagious and infectious diseases, all of them, are communicated to men and animals solely by chemical and lifeless ferments.

[This paper was intended solely for a local medical society, and not at all for publication. It must easily be seen that a question so extensive and involved as that of the subject of this paper could not be intelligently treated in so short a communication. I am sensible that not even a summary has here been given—that the question, indeed, has little more than been stated.—CHAPMAN.]

