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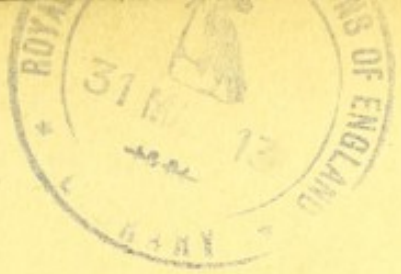

ON HABIT, SYMPTOMS, AND DISEASE *

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It has struck me that it might be serviceable to take up the subject of habit in its relationship to disease: to call attention to the probability that much commonly regarded as symptomatic of functional, not to say anatomical, disturbance may, after all, have no serious anatomical basis, but be one or another manifestation of habit, and, therefore, wholly curable provided the habit can be interrupted; and to indicate how, nevertheless, habit sufficiently long continued may well induce anatomical change, from which stage onward cure can be only relative.

Placed thus on paper there is nothing new in my text. These are truisms which we all must have had impressed upon us in the course of our work, now vaguely, now more clearly. The whole group of tics and hysterical manifestations is immediately called to mind, these affording examples of both stages. But what I want to do is to point out that the nervous system is not alone involved, but that the tissues generally are creatures of habit, and, further, to investigate the principles underlying habit phenomena and the anatomical or histological outcomes of the same.

This matter was brought to my attention years ago in connection with a case of incipient pulmonary tuberculosis. The patient had, shortly after child-birth, gone rather rapidly down-hill, giving the old story of profuse lactation, loss of strength, intractable cold with profuse expectoration, and afternoon rise of temperature. Everything pointed to tuberculosis, and, what is more, our ablest diagnosticians recognized a small area of dulness at the right apex; they were doubtful as to whether there was a still smaller area to the left. But no bacilli could be discovered. The patient was sent to Lakewood and there at last, after two negative reports, a search through something

* An address delivered before the Medical Research Club at the University of Pittsburgh, April 6, 1911.

like seven slides revealed a single definite tubercle bacillus, with a suspicious second. This was years before the development of the finer modern methods of diagnosis, but it has always seemed to me that here was a case in which the disease was suspected and then recognized in its earliest stage. The patient was immediately packed off to Dr. Trudeau at Saranac Lake, and from the first week put on weight, gaining fifty pounds in five months and rising from one hundred to one hundred and fifty pounds in weight. The effect of treatment, that is to say, was immediate. Only once in the first fortnight of her stay there was a doubtful bacillus or two recognized in the sputum. From this time onward the sputum was uniformly negative. That was twelve years ago, and the patient has never shown a sign of setback.

The point that I want to make is this: that here there was undoubtedly tuberculosis, but that of the very slightest we could then diagnose, and, with proper treatment, the bacilli, never present in any number in the sputum, disappeared within a week or two. The fever went down, the weight went up. Notwithstanding this, for more than six months—I do not believe I exaggerate when I say for at least a year—that patient not merely had a cough, but brought up, particularly in the morning, an excessive amount of thin mucoid expectoration. The cough I could understand—the healing of the tuberculous process in the lungs and the formation of fibrous tissue might well set up a certain amount of local irritation, and reflexly in this way induce cough. Nevertheless the cough very soon took on what we term the nervous character. The patient was highly strung, and this might well be a nervous habit. But I could not well explain the abundant expectoration continuing all these months after the evident healing of the lesions, save on the theory of habit, the theory, namely, that a definite irritant had in the first place stimulated the production and discharge of mucus, with associated congestion of the peribronchial vessels, and that the irritant had continued active for a sufficiently long time to set up a habit of heightened activity on the part of the secreting cells, so that when the irritant disappeared and was no longer in action, the congestion remained, and with it the cells continued to secrete abundantly.

A few months ago my colleagues, Drs. Birkett and Meakins, contributed a paper, "Vaccine Treatment in Chronic Inflammatory

Disease of the Accessory Sinuses of the Nose," to a most interesting discussion on "Vaccine Therapy" at the Triennial Congress of American Physicians and Surgeons at Washington. They reported a short series of cases in which from the sinuses a growth of one or other pyogenic organism was obtained prior to treatment with vaccines, and in which, as the result of the treatment, the discharge became wholly sterile. But in the majority of these cases, while the character of the fluid changed under treatment from a mucopurulent to a purely mucoid fluid, the discharge, it is noted, had continued for months, with all the distressing symptoms of hypersecretion and retention. To explain this, Dr. Meakins calls attention, first, to the chronic thickening of the submucous layer of the lining of the sinuses, as the result of continued inflammation; and, secondly, to a partial closure of the ostia by the swollen mucous membrane leading to defective drainage; thirdly, he comes to the same conclusion that I had reached in the case just described, namely, that through repeated stimuli (at first bacterial) hypersecretion has been set up, which after a time has become a true habit, independent of bacteria, as evidenced by its perpetuation after the cavity has been practically sterilized.

As I have already hinted, we are all so familiar with the establishment of nervous habits, with the development of habit tics and those graver habits of lack of coördination, and apparently of arrest of active communication between various centres, which would seem to be the basis of hysteria, that I must not here tire you with an enumeration thereof. It is well recognized that it is easier for nervous stimuli of different orders to travel along well-worn paths, and that thus there may be established a condition in which a minimal afferent impulse, travelling without interruption along a particular path, is sufficient to set in action first one and then another of a group of coördinated centres whereby a minimal stimulus may eventually produce a maximal result; *per contra,* the act of inhibition or arrest of the passage of a given impulse, if repeated, would seem to oppose so strong an obstruction to the passage of impulses along a particular path that soon a maximal stimulus may produce no result. Here there is no anatomical change: it is a matter of habit. Put the patient under an anæsthetic and remove the inhibiting mechanism, and now stimulus is followed by the normal reflex muscular act.

The worst of it is that, too often, the patient is in absolute ignorance of the fact that he or she is exerting this inhibition. I recall vividly a very delightful old lady, a woman of great personal charm, and, if I may so express it, eminently virtuous, who had been in a terrible railway accident on the north coast of Wales in which many people were killed, who received so strong a nervous shock as to be incapable of using her lower limbs and to be bedridden for twenty years. I have said that she was virtuous; that is to say, that within a year after the accident she was awarded by the courts one hundred thousand dollars, and she did not, as is painfully often the case—and that in a way that, perhaps at times mistakenly, makes us contemn poor humanity—recover her powers so soon as the court had awarded her this compensation. No; she remained bedridden twenty years, and then for the first time in her reign Queen Victoria was about to visit a near-by city. The old lady had never seen the Queen, who was just of the same age, so the occasion appealed to her very peculiarly. She longed to see her, and that with a great longing; and, sure enough, the afternoon before the great event she got out of bed and walked, went to the celebration next day, and after that walked until she died.

I do not say that she walked vigorously, but if a long spell of arrested function had some effects, certainly nerve tracts had not been destroyed; or otherwise her paralysis was not due to anatomical changes in the nerve cord. It was an inhibitory habit. But, as I say, I do not want to go into these nervous conditions: these we all accept. The instances of automatic cellular activity are of more immediate interest, and once I mention one or two of these to you, I doubt not that you who are in practice will call to mind individual cases of your own which are best explained along this line. Thus my colleague, Dr. Meakins, has quoted to me more than one case in which a small dose of mercury has induced abundant salivation. We know that salivation is associated in the first place with discharge of the mercury from the system, but all the mercury in small doses must disappear in the course of a few days, nevertheless the ptyalism in some cases persists, and is noticeable for six months or even a year. Some cases, at least, of persistent gastric hyperacidity and excessive secretion would seem to be of the same order, as also, I would suggest, the opposed habits of constipation and looseness of the bowels, the one due to the habit of excessive absorption of the fluid matter of the

fæces, the other to defective absorption. Only this morning Dr. Klotz has quoted to me four cases of obstinate dysentery in which undoubtedly there had been an original bacillary disturbance, but repeated bacteriological examinations failed to disclose anything of the nature of a specific agent. There is also a singularly intractable, obstinate, and elusive intestinal condition which I would suggest is most simply grasped if we regard it as a habit disorder—a condition devoid of indications of bacterial nature, of insidious onset, becoming progressively more severe, unassociated most often with febrile disturbance, most often showing itself in the female, and then in high-strung girls verging upon the hysterical—I refer to mucous colitis. There is something striking in the way this persists once it manifests itself, and that in the absence of sign of any abiding source of irritation. I would suggest that here, following upon a catarrh of moderate intensity in an individual of unstable equilibrium, the cells of the mucous membrane of the colon have acquired the habit of excessive formation and discharge of mucin.*

* After this address had been delivered Dr. Lichty, of Pittsburgh, called my attention to an important paper of his (*American Medicine*, iv, 1902, p. 223) upon the "Etiology of Mucous Colitis," in which he has drawn attention to the intimate association between abdominal ptosis and mucous colitis, and in which he draws the conclusion that with this ptosis and hypostasis and further interference with the blood supply of part, at least, of the large bowel, a condition of chronic congestion of the mucosa is set up, with a disturbance of function and excretion of mucus. Dr. Lichty recognizes fully that not all cases of splanchnoptosis exhibit accompanying mucous colitis, pointing out that 2558 consecutive examinations of men, women, and children afforded 313 cases of splanchnoptosis—41 males and 272 females; but only 21 of these had mucous colitis, and he concludes that ordinarily a condition of compensation is established, such as is so often seen in the circulatory system when there is disease of the heart and the kidneys. When, however, this compensation is lost or disturbed, the symptom-complex of mucous colitis appears, and he gives instances in which, in those affected with splanchnoptosis, mucous colitis showed itself in one case after an attack of acute tonsillitis, in others after typhoid fever. While thus Dr. Lichty affords an anatomical basis for the supervention of mucous colitis, it will be seen that his views are not in opposition to the suggestion here put forth, but, on the contrary, tend to confirm it. Dr. Lichty, that is, recognizes that some active disorder leading to lowered vitality and increased congestion is necessary to originate the condition; that, once originated, the excessive discharge of mucus lasts for weeks and months after the exciting cause has passed away. Accepting Dr. Lichty's views, we may say that the state of chronic congestion of the colon favors the development of the habit of excessive secretion of mucus.

Perhaps here wrongfully I speak for myself, and do not represent the general views of others, but it seems to me that commonly we are apt to regard every functional act of the various tissues as an immediate response to some stimulus and, doing this, to overlook and neglect the abundant cell activities that are truly automatic on the part of individual cells, and cell-collections or tissues; are apt not to realize that according to causation there are three orders of cell activities: (1) those determined by nervous stimulation, which we may term *neurogenic;* (2) those determined by direct stimulus of the individual cells by anything modifying their immediate environment —the *environmental;* and (3) the *automatic,* namely, activities which proceed in spite of or despite absence of sustained stimuli, whether neurogenic or environmental.

Now, it is these last, the automatic activities, to which I would particularly direct your attention—to their nature, their mode of origin, and their relationship to the other two. I believe that when we come to look narrowly we find that they are quite common. It seems to me that the development of cell habit is essentially the development of cell automaticity.

Primarily, as determined by a study of the lowest unicellular form of life, and of isolated cells of multicellular animals, such as leucocytes, it is external agencies that initiate cell activities: the nervous system is a higher coördinating mechanism in multicellular organisms, and so neurogenic cell activities are of secondary and later development. Further, we must regard all automatic activities as not of independent development, but as initiated by the individual cell becoming subjected, in the first place, to either environmental or neurogenic stimuli. To afford a basal instance: the ovum while fully matured lies latent and incapable of growth until such time as a spermatozoön, or, as Loeb has shown, alteration in the tonicity of the surrounding medium, initiates active nuclear changes; and, once initiated, these continue. All cell activities are at bottom chemical or physical changes in the relationships of the cell molecules and their constituents, and so living matter is similar to matter of all other orders in that molecular changes and activities require to be set in motion by the influence of forces acting from without. To this broad statement it may be objected that the remarkable investigations of late years upon radium and allied bodies, notably those of

Rutherford and other pupils of Sir J. J. Thomson, have demonstrated that every individual atom of matter exhibits an inherent activity of its constituent electrons, and, therefore, energy from without is not an essential prerequisite, that in its very essence matter is a storehouse of energy, and that, thus, even inert non-living matter possesses the potentiality of automatic activity. Here, truly, we plunge into very deep waters. To such objections I would reply that the studies upon radium so far only exhibit the possibility of these inherent atomic activities leading to the *dissociation* of electrons and coincident liberation of energy, whereas the striking feature of living matter is characteristically its capacity to *associate,* to build up from its surroundings, other matter like unto itself. Nevertheless my colleague, Professor Barnes, who, as a co-worker with Rutherford at the time when he was making his remarkable discoveries, speaks with high authority, assures me that the activity of the electrons, so far as we can determine with our present knowledge, is wholly uninfluenced by, and presumably, therefore, not initiated by, influences acting upon the atoms from without. Up to the present, the greatest heat and the greatest cold to which radium has been subjected have not been found to influence in the slightest the rate of emanation of the radium rays. In other words, the rate of motion of the electrons is unaltered by extreme temperature changes. It may, therefore, be that in this automatic activity of the atom we have the primal basis of the automatic activities which I wish to discuss to-night; that, just as there are inherent attractions and repulsions within the atom, so there are inherent attractions and repulsions of the molecules that constitute the cell.

If this be the case, how are we to picture the development of automatic activities? In this way, namely, that the cell is not a single substance, but a complex of many, with central nuclear matter, and a cytoplasm of proteid matter presenting within it not only paraplasmic material, *i.e.,* bodies in the process of being broken down to provide food-stuffs, the molecules not yet wholly organized or built up into the cell structure, other molecules which in the dissociation of the food-stuffs are separated off as waste products, other molecules which are the dissociation products of nucleus or cytoplasm, the resultants of functional activity—not only these, but also framework substances, such as fibrils and the striated material of the muscle-cell, developed

as the cell becomes differentiated, the outcome of that differentiation. The activities within the nuclear membrane are, from the nature of that membrane, very different from those outside. Surface tension has also led to the development of a potential, if not an actual, membrane between the cytoplasm and the external medium.

The cell, in short, is a microcosm—a little world in itself.

We in pathology always go back to the cell to determine its elementary properties, and from them to base solidly our views regarding the disturbances that may affect collections of cells, namely, the tissues and organs of the body. Has it ever struck you that we can go much further than this? There is room for a good full essay upon the study of cytology as the essential basis of sociology and political economy. It stands to reason; it is, if I may so express it, a "dead easy" exercise in elementary logic to prove that it must be so. The nation is a collection of allied and similar individuals, and national sentiment, which expresses itself in national action, can only be the expression of the sum of individual sentiments, at most gaining impetus and direction by the interaction of the sentiment of one individual upon the sentiment of the other. It is obvious, therefore, that the political economist in order to understand social tendencies must base himself upon and must first study the individual and his tendencies. But, now, what is the individual but a collection of cells? By a like process of reasoning it is inevitable that to understand the individual we have to get right back to the unit cell, its properties, its reactions, and its interactions with the other cells of the corporation. Wherefore it follows that the only sound method of mastering political economy is through an expert study of cytology.

I might dilate upon this theme; might, for example, point out how a study of the cell throws light upon the existence of two great political parties, and show how the "mugwump" is the outcome of a peculiarly exact balancing in the one individual of those two opposing properties of all living matter: namely, of *heredity* in the strict sense, whereby despite environment the living matter of one generation tends to reproduce with exactitude the characters impressed upon preceding generations, and *variation,* whereby that living matter is keenly responsive to environment and liable to modification. In most of us one or other of these two properties is in the ascendant. In the words of Gilbert (and Sullivan), we are born "either a little liberal or else

a little conservative"; in the mugwump, thanks to the parental amphimixis, the two properties are accurately balanced.

However, this is all parenthetic. What I want to impress upon you is that just as nowadays we have learned to regard the atom not as a solid, if almost infinitesimal, mass of matter, but as exhibiting the active play of numerous electrons, so, taking the cell as a unit, we must realize that it is not merely a mass of homogeneous protoplasm, but it is an extraordinary complex of molecules, a little world in itself.

We have to imagine these molecules as in a state of continuous interaction. Given a stimulus from outside, they set in motion a particular chain of interactions, and we are forced to recognize that, once started, the interaction may continue after the stimulus which has set them in motion has ceased to act. We have, in the first place, then, to recognize the existence of what Dr. Fraser Harris has spoken of as the inertia of living matter, which might perhaps more accurately be spoken of as the momentum of living matter. It is the principle whereby the wheel set rolling continues to rotate until friction brings it to rest. It is the principle that explains the latent period of muscle. If the muscle be resting, as every first-year student knows, a definite period elapses after the passage of the stimulus down the nerve before the muscle passes from the resting to the contracting state. Here it seems to me is the first step; but something more than this is necessary to induce automatic cell action, and to gain an explanation we pass from the cell to the larger world in a search for parallel phenomena, for, as I have laid down, we may safely draw such parallels.

Centuries ago when a comet appeared in the sky it had a profound influence on those who beheld it. It was unusual, therefore it betokened something unusual. It was a portent, but its effect was temporary. People spoke of it after it was gone; as it were, a condition of inertia continued with steadily diminishing force after the stimulus had passed away. Then by chance in the seventeenth century a comet came into the ken of an astronomer who, through his special knowledge, was, if we may so express it, peculiarly responsive; its presence stimulated him to a more than ordinary degree. He looked up the earlier records and found that a similar comet had been reported as flaming into prominence at regular intervals. This led him further

to study the path of the comet, and not merely to determine the course of this one comet, but that of other comets and of meteorites in general. And now everybody knows all about comets, can predict their return; the series of observations of this one astronomer, Halley, has permanently and continuously affected civilized man.

So it is with the cell molecules. One particular stimulus may have but a temporary effect; another, acting upon the cell in a particular state, may initiate a particular recurrent cycle of intracellular changes, may set up a habit.

Not all influences upon cells will set in action these recurrent and cyclic changes, but undoubtedly the dominant constituents of cells, the proteins, by their very nature and complexity of structure, favor the development of cell habits. Let me illustrate: A diffusible foreign body, itself of proteid affinities, gains entrance into the blood —a toxin; and, provided that it be not exhibited in excessive amount, it is in the first place neutralized, and next leads to the presence in the blood of antitoxins. We know that the toxins gain entry into the cells; know that the cells, or certain of them, actively discharge antitoxins. There may have been not a sign of specific antitoxins in the body fluids primarily, but now they are produced in abundance—in amounts far in excess of the amount of toxin introduced. If at first they were modifications of the toxins introduced, brought about by cell activity, certainly the later crop cannot be of this nature. And here is the point: they continue to be produced days and weeks after the original toxins have been neutralized or destroyed.

It may be that our presumption is wrong—that the toxin molecules, once within the cell, persist there, acting as enzymes or ferments, converting one after the other molecular groups of a particular order into antitoxin molecules. These are matters not yet determined. It fits in better with our knowledge to suppose that the toxin molecules determine a modification or rearrangement of certain side-chain molecules, which in their turn lead to the building up of other side-chains of like constitution. But, whatever the exact process, here is an exquisite example of a cell habit of the automatic type. Once started in their new work of producing antibodies, the cells continue to produce them, and this without external stimuli, developing them from the usual food-stuffs assimilated by the cell.

It follows, thus, that we may recognize two orders of cell habit of

the automatic type: first, as afforded in my original instance, the exaltation of a property already possessed by the cells; and, second, as exemplified by this last instance, the acquirement by the cell under abnormal environment of new properties—*an acquired cell variation becoming, if I may so express it, converted into a cell heredity.*

Underlying both we must see a manifestation of that most potent cause of metabolism, namely, enzyme action. In other words, it is the existence of intracellular enzymes that permits both continuous and cyclic automatic cell activities. If the view be accepted which I have put forward elsewhere, namely, that organic enzymes are of the nature of detached side-chains of the proteidogenous molecules—able, on the one hand, to attach themselves to the main ring; on the other, to molecules of food-stuffs, bringing about their dissociation, with eventual building up of like side-chain material in series—then we can realize how, so long as side-chain molecules of a particular order are present in the cell, and that cell possesses its usual nutrition, the enzyme action will continue within that cell until arrested by the concentration of the products of that action; to become active again so soon as those products become used up, diffused out, or otherwise removed. Once enzymes appear or become developed within a cell, we have the conditions most favorable for continuous cell activity, irrespective of alteration in environment or external stimulus save that afforded by the exhibition and regular absorption of food-stuffs. And when abnormal bodies of proteid type—toxins—gain entrance into the cell, I would lay down that they have affinity to side-chains of the cell substance, and either themselves act as enzymes, or more probably form compounds of a new type within the cell which act as side-chains of a new order, and are capable of building up new side-chain molecules in series, the excess of which become discharged as antitoxin molecules.

However, from the pursuit of such ideas I again must desist, for I draw you into the depths. I only wish to impress upon you that the known existence and extent of intracellular enzyme activity and the development of the same afford us a full physiological basis for the assumption by the cell of habits of activity.

Thus far I have discussed only those habits associated apparently with no anatomical or histological change in the parts that are involved in the habit. This is, however, by no means necessary, and

the last few minutes of this discourse may be spent in calling attention to the habit of growth—conditions associated with distinct structural changes in the affected tissues. The whole somewhat limited group of what we term metaplasias are really growth habits. They are conditions in which, always, it would seem, under the influence of altered environment, one or other tissue undergoes a metamorphosis and continues to develop in the metamorphosed state. I had a beautiful example of this only a few months ago in which, apparently under the influence of chronic inflammation, it could be seen that the perichondrium of the tracheal cartilages had given origin to or had undergone conversion into cartilage cells within its substance, which cells, undergoing proliferation, had now projected outward into the submucosa to form small nodular growths, and these in their turn had undergone bony transformation. Here, then, one and the same tissue under different conditions of environment gave rise to connective tissue, cartilage, and true bone. Nor was this all. These multiple bony nodules projected into the lumen of the trachea, and, doing this, interfered with both the nutrition and the function of the overlying epithelium. As a result over each nodule the mucosa, instead of being formed of a single palisade layer of columnar cells, had become converted into a well-formed squamous epithelium, while between the nodules was the normal columnar-celled epithelium.

The cells here under different environment had assumed a totally different habit. It may be asked whether here I am using the term in the same sense as previously—whether what I here term habit is not the result of continued alteration of environment. It may be asked whether in these cases return to the normal environment would not bring about return to the normal type of tissue, or whether this altered habit of growth persists.

To this I would answer that undoubtedly it tends to persist. As evidence I may cite the example of a region in which epithelial metaplasia is not uncommon, namely, the gall-bladder. There, as a result of the chronic irritation set up by the presence of gall-stones, it is not uncommon to find larger or smaller areas of *squamous* epithelium taking the place of the normal *columnar*-celled mucosa, and this more particularly in the region of the fundus. Now, as is well known, 90 per cent. or more of cases of cancer of the gall-bladder are associated with cholelithiasis, and the majority of those cancers originate

in the fundal region; and the interesting point is that I have encountered (and there are several similar cases recorded in the literature) cases in which that cancer, instead of being of the adenocarcinomatous type which one expects to originate from a columnar-celled epithelium, approximated to the squamous epitheliomatous type. They were not absolutely typical epitheliomas; epithelial pearls, for example, have been wanting. My own case, for example,—and others have made the same observation,—exhibited a mixture of alveolar masses of the epitheliomatous type, along with other alveoli of adenocarcinomatous appearance. But certainly these were not ordinary adenocarcinomas. There is no epithelium in the neighborhood of the developing gall-bladder of squamous epithelial nature; no chance, therefore, that these tumors develop from a squamous epithelial cell rest. The only adequate explanation is that the metaplastic squamous epithelium has its characters so firmly impressed upon it that, when it gives rise to a cancer, its cells as they infiltrate into the surrounding tissues do not revert to the columnar type, but give rise to a squamous epithelial new-growth. Again an acquired variation becomes hereditarily transmissible among these cells. They have "got the habit."

Some of you may know that many years ago I applied this habit conception to the elucidation of tumor growth in general, and though in the meantime I have amplified my views, I still believe that my original hypothesis is sound. I would conclude by recalling this to you. There are many examples that I might take as illustrative, but perhaps the best is that worked out by my late colleague, Dr. Wolbach,* now assistant professor at Harvard—his study of the mode of origin of that modern disease, X-ray carcinoma. He had at his disposal material from a long series of X-ray burns, and so was able to follow well all the stages.

Paradoxically, the X-rays have singularly little effect upon the epidermis and epidermal cells, but they influence profoundly the underlying corium. There in the earliest stage there are set up marked lesions, telling especially upon the vessels and lymph spaces—proliferation and desquamation of the endothelial cells, thromboses and other evidence of severe vascular disturbance—and it is secondary to this that the epiderm is affected and tends to ulcerate. Those

* Wolbach: Jour. of Med. Research, 21, 1909, 415.

changes, to be brief, lead to a form of inflammatory fibrosis of the subepidermal tissue, and as a result the nutrition of the epiderm is gravely reduced. In some places the reduction is so great that the cells necrose, and ulceration is the result. In other places the effects are not so intense, and one gets what I would term the " poor curate " phenomenon. You will have observed that the well-fed millionnaire and his wife are apt to be childless, whereas the curate and his wife have a family in inverse size to their capacity to support them. That appears to be a law of nature: there is a certain nutritive minimum at which, it would seem, the preservation of the species becomes of greater consequence than that of the individual, and multiplication ensues, to the detriment of the individual, but on the off chance that a few out of the abundant progeny may survive. And so it is that in these cases where the epiderm is not wholly necrosed, its cells multiply; and now is observed a phenomenon apparently of the same order as that first observed by Bernhard Fischer after inoculating a mixture of olive oil and Sudan III into the tissues of the rabbit's ear (an observation abundantly confirmed), namely, the growth downward of the epithelial cells toward the oil. Now in these X-ray burns the actively proliferating epithelial cells grow downward through the dense fibrosed cutis toward the nearest source of nutrition—the underlying vessels.

But doing this, obviously, they sacrifice their function as epidermal cells. Cells growing down into underlying tissues cannot function as an epithelium. And thus, coincidently, in these cells we have the vegetative powers exalted and the functional activity depressed. Now, while there is a certain mean or level at which moderate function, by stimulating increased assimilation, may stimulate increased cell growth, it must be recognized that growth and function are diametrically opposed states of cell activity. Growth demands that matter taken as food is built up into the cell substance, becomes associated, with coincident storage of energy; function, on the contrary, demands dissociation, with liberation of energy. And, as a matter of fact, your actively functioning cell shows no signs of proliferating. Your actively vegetative cell is of embryonic type, *i.e.*, shows little signs of differentiation, and therefore of functional capacity. We observe, thus, that these down-growing epithelial cells —and the same is true of all early malignant growths—present coin-

cidently depression of function and exaltation of vegetative power. And I would lay down that it is this modification of the cell activities that is the basis of neoplasia; that what is characteristic of the true tumor is that the component cells, from one or other cause,—displacement, irritation and so on,—have lost the habit of function, and coincidently, as the nutritive material taken in needs to be used up, the very accumulation of the newly formed cell substance disturbing, as it does, the surface-to-mass relationships of the cell, becomes in itself the stimulus to cell division, in order that the due relationships may be restored. Thus is developed the habit of growth, replacing the habit of function, and it is, I hold, this habit of growth that characterizes all true tumors. It is at least suggestive that the one non-surgical method of treating malignant growths that is giving definite results at the present moment, when appropriately applied, essentially depends upon a specific reduction in the growing power of the tumor cells. It is now well established that radium and X-rays act especially upon the vegetative cells of the organism, and, characteristically, it is the actively vegetative malignant tumors rather than the benign with their more highly differentiated cell elements, that are arrested and undergo absorption after treatment with either radium or X-rays.