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SOME CONDITIONS IN THE GROWTH OF TUMORS.*

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Our knowledge of the conditions of growth of normal and of cancerous tissues is as yet incomplete. We might even say that we are only in the beginning of an exact investigation into the problems of the physiology of growth of vertebrate tissues. Notwithstanding this, it is perhaps not without value, if we attempt from time to time to coordinate the results of various researches in a certain field and to obtain some indication of how far the various facts seem to agree with each other and how a preliminary sketch of the completed structure might appear. Of the subjective and preliminary character of such a synthesis there can be no doubt; and only with these restrictions well understood will I enter into a rather incomplete discussion of the facts underlying tumor growth as they appear to me at the present time.

The tissues of the animal body have each one a definite energy of growth under normal conditions which varies in the case of various tissues and also to some degree in the corresponding tissue in different species of animals. In the large majority of tissues the potential energy of growth is much

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greater than the actual proliferation which takes place under the ordinary conditions of life. How much of the potential energy is transformed into actual growth depends to some measure on external conditions. Changes in external conditions may increase and decrease the energy of growth. The cancer problem can be formulated in the following way:

(1)—Under what conditions does a tissue assume an increased energy of growth? But this question is not sufficiently comprehensive. We notice, for instance, an increased growth energy under such external changes which lead to woundhealing. But in this case the additive proliferative power comes soon to rest. In cancer an indefinite growth is seen. It is therefore evident that one generation of cells must transmit the gain in energy to the following generations indefinitely and we are thus confronted with the second question in the cancer problem,—

(2)—Under what conditions does a hereditary transmission of an acquired increase of growth energy to the succeeding cell generations take place? And lastly, a third question arises in the cancer problem, which however, is perhaps less important than the two prior ones, (3)—Why do we find an infiltrating growth in cancer? Why do the proliferating cells penetrate into adjoining tissues instead of merely pushing them aside? This may be due to an inequality or irregularity in proliferation; it may also be due to chronic inflammatory changes and softening in the neighboring tissues, or to an increased proteolytic activity of the cancerous cells. However this may be, we shall here give our attention only to the first two questions which are of fundamental importance.

An increase in the energy of tissue growth can

be accomplished by wounding the tissue. Such a regenerative proliferation, however, is rather slight and on the whole leads merely to the replacement of lost cells, and ceases as soon as the wound has healed. Separation of a piece of tissue from its normal connections is the cause of regenerative proliferation, but it is in itself quite insufficient to produce tumor growth. Ribbert's hypothesis which assumes as the basic cause of tumors such a disconnection between the cells which later become cancerous and the surrounding tissues, is therefore not an adequate explanation for tumor growth.

In order to obtain a postfœtal proliferation resembling tumor growth other factors have to come into play. Of what character these factors may be is indicated by the following experiments which I carried out in the course of the last two years.

If under ordinary conditions you make incisions into the uterus of the guinea pig the usual wound healing takes place without any noteworthy tissue proliferation accompanying it. If, however, the incisions are made during the first nine days after the rupture of a follicle, each cut, or almost each cut, leads to the formation of a tumorlike deciduoma. During the early period of its existence the corpus luteum secretes a chemical body which unites with the mucosa of the uterus. This chemical substance acts as a sensitizer; it sensitizes the mucosa, and if now an incision is made into the uterus, the freeing of the inner surface of the uterus from the tension of the surrounding tissue acts as an external stimulus which causes the sensitized tissue to react in quite a different way,—leading to the production of tumorlike new formations where under ordinary circumstances the uterus would only have shown processes of wound healing. In order to obtain a tumorlike growth one single factor does therefore

not always suffice. We need a combination of at least two factors, namely, the action of a chemical sensitizing substance and of an external exciting cause which in this case is represented by a trauma. These facts we have to keep in mind, if we wish to interpret the origin of cancer. We must not look for one single cause, but a combination of factors has at least in many cases to be realized, before a malignant tumor is formed. There cannot be the slightest doubt that sarcoma may follow a trauma, but it does so only in a small minority of cases. The character of the external condition, the trauma, may be identical, but in one case the trauma affects an organ which is prepared to a special kind of response, an organ which is sensitized, hence a tumor follows; while in another case it affects a nonsensitized tissue and here no tumor is formed.

Experimentally we have therefore not yet been able to produce a cancer through trauma because of a lack of knowledge of the internal factors. These internal chemical sensitizing agencies which certainly play an important rôle in what is usually called predisposition are as yet unknown to us in most cases; we know more of the external factors and that the latter are of great importance in causing a tumorlike growth is very well demonstrated by the experiments just mentioned. But there exists in all likelihood a correlation between internal sensitizing and external stimulating factors of such a character, that the stronger the one set of factors is represented, the less is required of the second set of conditions, the stronger for instance the influence which is exerted by the external stimuli, the less the presence of sensitizing substances becomes a *conditio sine qua non.* Clinical observation revealed other very striking instances of the importance of external agencies in producing cancer.

In this connection we have to attribute especial importance to cancer of the outer surface of the body. Here the field for ætiological observations is so much more favorable than in the case of tumors in internal tumors. And it is a noteworthy fact in the former the evidence of the action of external factors is undoubted. Hutchinson and others showed the significance of arsenic in the causation of carcinoma; the number of cases of cancer following the long continued use of Röntgen rays is so great that the results are almost as clear as in carefully directed experiments. It is equally probable that in xeroderma pigmentosum the light rays play a similar role as the Röntgen rays in the previously mentioned cases. We have every reason to believe that in cancer of the internal organs stimuli which in many cases have to act during an extended period of time, are of equal importance, and indeed the cases where long irritation preceded cancer of internal organs are well known, but not so clear in their interpretation, because the conditions which precede the formation of internal cancer are not usually accessible to our constant examination. We have to lay much more emphasis on positive observations, where preceding irritation as the cause of cancer can be proven or at least be made very probable than upon negative cases where similar conditions may also have been present but without our knowledge.

Such external stimuli represent therefore one important set of factors in the ætiology of cancer. How do they act? I am very much inclined to believe that they have a direct stimulating effect upon certain tissue cells just as radium has been shown to cause at a certain stage a proliferation of the epithelium of the skin; and it appears to me much less likely that the stimulating action is only an in-

direct one being dependent upon preceding changes in the underlying connective tissues. But however that may be, in the case of carcinoma of the skin the proliferative energy of the epithelial cells is very much increased as a direct or an indirect result of external stimuli and such an increase is hereditary and transmitted to the following cell generations.

Of a similar character seems to be the action of ether upon certain growing tissues according to the observations of Reinke, who found, for instance, a marked proliferation of the cells forming the lens after injection of ether into the anterior chamber of the eye. A temporary proliferation of the epithelium of the skin is also produced through the stimulating action of certain fat soluble stains, as Sudan III.

The importance of external stimuli in causing proliferation of tissue has a still further significance; it does not only apply to normal tissues and to tissues in process of transformation into tumors, but also to cancer cells. A number of years ago I showed that it is impossible experimentally to increase and to decrease the energy of tumor growth. An increase can be produced through mechanical stimuli, for instance, a cut into the tumor or by pulling a thread through its entire diameter. In a similar way I found that in serial transplantations of tumors, usually an increase in the energy of growth, in the virulence of the tumor takes place in the course of the first few inoculations, likewise as the result of the mechanical stimulation connected with the experimental inoculation. On the other hand, I found that this does not apply to all tumors. Not all are equally affected by mechanical irritation. A mixed tumor of the mammary gland of a dog, for instance, could not be stimulated to increased proliferation by any means whatever. These facts

have an especial practical significance and explain certain conditions met with in the operative treatment of tumors. We not rarely find that after an operation the tumor recurs with increased virulence, growing more rapidly and making more extensive metastases. After an exploratory excision the tumor begins sometimes to grow more rapidly. And I believe that an occasional transformation of a benign into a malignant tumor, after an operation, is due to the same factor, namely, to a mechanical stimulation and not to changes in the blood supply. Also the apparently *spontaneous* transformation of a benign tumor, as for instance, of a papilloma into a carcinoma, is not so very rare and is probably due to the cumulative action of certain stimuli. But as I mentioned above, the experimental investigation has shown that not all tumors are equally labile and certain tumors can be attacked without the danger of increasing their virulence, others however, not. At present the experimental pathologist is not yet able to supply to the surgeon definite information which permits him to foresee which tumor belongs to the one and which to the other group. On the other hand through the graded action of heat and of certain chemicals the virulence of tumors can be experimentally decreased and this fact may explain the observation that after extirpation of a primary tumor certain metastases may retrogress, or that after an exploratory laparotomy tumor nodules may occasionally disappear, as certain cases seem to indicate.

But as I stated before, the action of external agencies is only one set of conditions in the origin of cancer. The large majority of internal chemical factors is without doubt quite unknown to us at the present time. But of the importance of

certain other factors we have a more definite knowledge. I have here especially in mind the influence of abnormities in embryonal development which lead to the misplacement of tissue, and to the formation of teratomata and which cause such apparently insignificant conditions as pigmented moles. There can be no doubt that all these structures are especially liable to form cancer, and that the stimuli which in the case of normal tissues would be harmless lead here not infrequently to the formation of malignant tumors. In other cases such a transformation takes place seemingly without any external stimulus.

There are several ways in which the proneness of such tissues to increased proliferation can be explained: in the first place, stimuli are in all likelihood the more effective the more capable a tissue is to respond, the larger its proliferative power is and this is usually greater in the case of embryonal tissues; secondly, some of these structures through their abnormal size and position are more exposed to constant internal or external irritation and this may in part be responsible for their liability to become cancerous; thirdly, it is quite possible that in certain cases a tumor did not develop on the basis of a primary malformation as is usually assumed, but that a cause to a tumor growth was already present during prenatal life as the primary condition and that this led to a teratomatous formation and subsequently to a malignant growth, inasmuch as any stimulus which in the fully developed body affects a specific tissue and causes directly the formation of a cancer, affects in the embryo cells which have larger potentialities for development and which therefore at first develop into a teratoma, and only secondarily into a cancer. This explanation becomes the more likely, if we

consider that experimentally it has been found impossible to produce malignant tumors through the implantation of embryonal cells or tissues.

However this may be, it is certain that there exists a connection between the development of cancer and embryonal malformation, even if, as seems indeed to be the case in a certain number of cases, the existence of errors in embryonal developments has been wrongly assumed, cases in which a more critical study reveals changes due to postnatal inflammatory or degenerative conditions (observation of R. Meyer: Certain Cases of Apparent Chorionepithelioma Malignum).

It is a well established fact that certain developmental abnormities can be transmitted by heredity. It is therefore to be expected that tumors resulting from such embryonal malformations should likewise sometimes be hereditary. This is indeed the case. Heredity is one of the factors in the causation of cancer. Not only the hereditary transmission of anatomical developmental peculiarities but also of invisible metabolic, or functional conditions, may in all probability occasionally lead to the extraordinary frequency of cancer cases in certain families.

So far we have only taken into consideration the first underlying factor in the production of cancer, namely, the increase in the energy of growth of certain cells. In order that a tumor may grow indefinitely, make metastases in the same individual or may be transplanted through very many generations into other individuals of the same species, an hereditary transmission of the increase in the energy of growth must take place. Under what conditions such an inheritance is found, how it can be brought about experimentally—is as yet very little understood and only the beginning of a methodic study into these problems has been made. I have found that the in-

crease of growth energy accompanying regenerative processes is not transmitted into the succeeding generations of cells; on the other hand at least a temporary transmission of the increase in growth energy acquired through stimulation of the lens of certain amphibia by ether takes place according to Reinke. Here is a gap in our knowledge which will have to be filled out in further investigations. From clinical evidence it seems, however, likely that as a result of long continued stimulation or as a result of a strong stimulus of short duration affecting especially sensitized tissues a hereditary transmission can be induced. This is one of the directions in which further work will have to be carried. And until this want is supplied we are not able to absolutely exclude another factor in the production of cancer, namely, the presence of microorganisms.

The presence of intracellular microorganisms could explain very well such a hereditary transmission in the increase in the energy of growth inasmuch as in this case the tumor cells themselves carry with them the agency which causes the stimulus to continuous proliferation. But on the other hand, as we pointed out above, it is by no means necessary to take refuge in such an interpretation for all cases and the appearance of cancer after the use of arsenic, after the long continued application of Röntgen rays and in certain other conditions is in all likelihood not due to the action of microorganisms. There are, however, other facts which can be cited in favor of the causative significance of microorganisms, as, for instance, the production of a sarcoma after transplantation of a carcinoma, first found by myself and by Ehrlich and Apolant independently of each other. As I have pointed out several years ago such a new formation of a sarcomatous tumor might be most easily explained through the transmission

of a microorganism from the epithelial cells to the surrounding connective tissue. But even here other interpretations cannot be excluded.

There remains one interesting condition which seemed especially to call for the presence of microorganisms, namely, the endemic occurrence of cancer which is so very much more striking among animals than among man. But, as I have stated on previous occasions, even in the cases of endemic occurrence of cancer in cattle and white rats hereditary conditions cannot be excluded, and since then further investigation seems rather to sustain the importance of this factor; as the evidence stands at the present time it is very unlikely that such endemic occurrence is due to a real cage infection, to the direct transmission of an organism from the wall of the cages to the animals, or from one animal to another. I am, however, not yet prepared to deny that in certain cases microorganisms might not be responsible for the endemic occurrence of cancer in mammalians or fishes in some way at present unknown to us.

We do not need to come to any premature conclusion in this matter, especially as this problem of the endemic occurrence of cancer is open to an exact experimental solution. But if microorganisms should be present in certain cases, they merely act by stimulating certain cells in a similar way as other physical or chemical agencies.

In this rather hasty review I have endeavored to bring before you what I consider the most significant facts in the investigation of cancer and to indicate in which direction I believe the solution will be found. I have confidence enough to express the opinion that the cancer problem has been solved partially. We have an exact knowledge of various factors which cause a tumorlike and cancerous growth, but very

much remains to be done, and especially the theoretical and experimental workers in this field need the moral support of the physicians who are not only clinical investigators of the cancer problem but who also can influence public opinion and can thus indirectly supply the means without which the necessary investigations on a large scale cannot be carried out.