# A NOTE ON IMMUNOLOGY AND MALIGNANT DISEASE.

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## Introduction.

In discussing stimulants to bacterial variation[1], I called attention to the probable influence on parasitic bacteria of stimulants derived from the animal body and noted, incidentally, that such stimuli must also be of primary importance in the animal economy, as regulating the normal activity of tissue cells and, abnormally, as determining the fate of incipient pathological changes in such cells.

I have subsequently been led to consider whether my references to stimulants in relation to the growth of tissue cells are worth following up as part of wider questions concerning the possible utility, in the study of malignant disease, of those immunological principles which bacteriologists are endeavouring to elucidate.

The relation of immunology to malignant disease is an obscure subject, to which no important clue has yet been found. In the first place, there is need of further determined effort to realise more fully the nature of the difficulties for which an explanation is sought. I am therefore attempting to discuss the question with this object in view.

When dealing with bacterial variation I followed the view, which I see no reason to modify, that the type of transmissible stimulant which has been

[1] *Journ. Hyg.* XXIII. p. 317, 1924.

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termed "bacteriophage" is not a living virus but consists entirely of material derived from the bacterial cells. Similarly, I think that the stimulant to malignant growth, in the natural disease as it occurs in mammals, is derived entirely from the animal cells of the host; and the present article is based on this view. I am aware that it is not in accordance with Dr Gye's theory, published in the *Lancet* of July 18th, 1925, which regards cancer as due to the combined operation of two agents, a virus and a "specific factor." As it is impossible, at present, to foretell how far this theory will be confirmed by other investigators, I think I ought to postpone the question whether the view which I have adopted requires modification.

## The Theory of Chronic Irritation.

I propose to accept, in its general outline, that theory of cancer which is one of the oldest and is still the best accredited. Malignant cells develop out of normal cells as the final outcome of a long succession of events which are associated with some perversion of the normal reactions of tissues during chronic inflammatory conditions and the repair of injuries. These changes seem to take place in a series of stages, each phase being the requisite precursor of the next in order that attainment of malignancy may result. Why this pernicious sequence should be consummated in some instances but not in others is a biological problem about which nothing definite is known.

One has to be content with provisional hypotheses. Of these there is a large number, and I do not think that any one of them can be selected as pre-eminently the best or as justifying the exclusion of others. The choice depends on the personal equation. My own bias is towards economising in hypotheses as much as possible, by taking what appears to me the simplest and following it up as far as it will go. This method is reasonably safe, provided that the chosen hypothesis is not allowed to become an obsession which obscures one's vision in regard to the merits of others.

In the simpler field of bacteriology it is known that individual members of a culture help each other to grow until a certain optimum is reached and that, after this point, they exercise a retarding influence on growth. Normal animal cells exert a similar influence on each other, promoting growth up to a certain limit and then restraining it. In the mammalian body, stimulation and control of growth are highly complex, since the circulation which bathes each tissue contains products from other tissues and these products participate in the regulatory mechanism of orderly growth. Thus the individual tissue is not autonomous; it is kept in equilibrium, in respect to its growth, by the complex of influences circulating in the plasma.

This equilibrium may be disturbed. A particular site in the body, though not cut off from an adequate supply of nutrient material, may be temporarily excluded from the normal action of those constituents of the plasma which regulate growth; and this change may be due to chemico-physical disturbances in its environment which are not demonstrable by histological methods. Perhaps

scarification, for example, may have this effect when it is found to accelerate the production of tar cancer. Scarification alone would not produce cancer, but it may interfere with the action of the normal growth-regulatory impulses and thereby facilitate the incidence of further changes.

Within an area which, in one way or another, has been partially freed from normal control there may be expected to be a more abundant growth of cells. This may be analogous, in some respects, to cases where bacteria become capable of growth in a naturally immune animal, when they occur in sites partially occluded from the free circulation and so escape the normally inhibitory action of the animal's plasma.

This secluded proliferation will be associated with an excess of local growth impulse, as distinct from the growth-regulatory impulse in the free circulation.

The next events may be of two kinds: (*a*) a slowing down of growth, this being a self-regulatory mechanism due to the accumulation of "growth stimulants" beyond the optimum; (*b*) the formation of products which may act as a stimulus to variation, just as stimulants to variation may be formed in cultures of bacteria which have been allowed to age.

This partial isolation of the cells need not be regarded as a permanent condition but as one which will break down sooner or later in the ordinary processes of tissue repair, thereby bringing the cells once more into intimate contact with the regulatory influences of the circulating plasma.

It may then be found that the cells referred to are amenable (as before their partial occlusion) to the normal regulatory growth impulse of the body as a whole. The pathological process is then terminated by reversion to the normal condition.

Or the cells may have retained a local growth impulse which is excessive but otherwise normal; this condition may lead to non-malignant hyperplasia.

Or the local growth impulse may have acquired the abnormality which gives rise to malignant proliferation. This change, whether initiated by products of metabolism or by the action (probably indirect) of a foreign substance, is autogenous in the sense that it is due to a reconstitution of the normal cell's protoplasm. Though it leads to abnormal growth and abnormal products of secretion or disintegration, it is not due to incorporation within the cell of any material which is foreign to the host.

The malignant growth impulse is selective for the cells through which it is propagated. This transmission of an acquired characteristic may be compared with the behaviour of trypanosomes which have been trained to resist atoxyl and then transmit this property from generation to generation.

The influence of the new growth impulse on the malignant cells either overcomes the restraining action of the normal growth impulse or makes them independent of the latter; just as, in partially susceptible animals infected with bacteria, the favourable growth impulse which the bacteria derive from each other may overcome an adverse impulse derived from the animal body or may make the bacteria independent of the latter impulse.

The malignant cell, being unstable or immature, has a natural tendency to autolysis, and its dissolution yields a fresh supply of the abnormal growth stimulus. Thus the fate of the new growth depends on the relative rapidity of these two processes, reproduction and autolysis. Usually the former is somewhat in excess of the latter and growth is progressive, perhaps because the cells have gradually become habituated to growth in the presence of an abnormal stimulus which tends to increase in potency when fresh autolysate is added to it.

But, when cells with incipient propensities for malignant growth have not been accustomed to the influence of a strongly developed stimulus to immature proliferation, the result of such an influence may be subdivision into forms which autolyse before they can again reproduce themselves, and thus the growth will be aborted. In this way, perhaps, induction of a second cancer (*e.g.*, by tarring) in an animal already cancerous (spontaneously or by tarring) may be impeded by the action of the powerful circulating stimulus to malignant growth derived from the established disease. Analogous examples may be the elimination of bacteria which are more sensitive than resistant to a "lytic principle" or the failure to produce a tuberculous local lesion by injecting culture of tubercle bacilli into an animal previously infected with tuberculosis.

On this view, the stimulus to growth and the influence causing death of the malignant cells by autolysis are not "antagonistic principles"; they are two phases of one and the same principle, viz., an abnormal growth stimulant derived from the malignant cells.

*Comment.*

The above suggestions are admittedly vague, because there are not sufficient data to support them in detail; and it is quite likely that they would need modification if further data were available. I think that similar difficulties are encountered in other methods of attempting to formulate a reasoned explanation of the "chronic irritation" theory; one cannot escape from the region of inadequately substantiated hypotheses.

Perhaps I have been building too much on one idea, variation of the growth stimulus as an automatic mechanism, and have neglected factors, attributable to particular substances derived from special tissues, which may explain the normal condition when they are properly balanced and the malignant state when the balance is upset.

For example, it may be thought that there is an inhibitory substance, derived by secretion from some special cells of the body, which restrains a natural tendency to unlimited growth on the part of normal tissues; then local inhibition of this restraining influence would lead to malignancy. Or there may be two substances in the circulation which are normally in equilibrium, one stimulating growth and the other inhibiting it; malignancy may arise by a local increase of the former in relation to the latter. Or, again, the

malignant growth stimulus may be some special substance which is not manufactured locally at the site where the new growth originates but arises from some general perversion of metabolism. Then there would be three distinct factors to consider: (*a*) the malignant stimulus, (*b*) substances normally inhibiting growth, and (*c*) substances promoting growth as in normal repair of injuries. It may be thought that (*a*) is independent of the other two and that it may act locally on specially susceptible cells without postulating that these are cut off from (*b*) by some mysterious barrier.

I have no desire to disagree with explanations which tend in these directions. They introduce complicating factors and it is difficult to be confident that evidence of stimulating and inhibitory substances in the cultivation of tissues *in vitro* indicates the occurrence of similar conditions in the living body. But, if simpler ways of explanation prove unsatisfactory, it may be necessary to postulate some such complicated mechanism which involves the interplay of distinctive factors instead of variations in the influence of one factor. There would be no advantage in pretending that the problem is simpler than it really is.

On the contrary, it seems better to accentuate the present limitations of knowledge.

In instances which are rare when compared with the majority of cases of the spontaneous disease, some known irritant, such as the growth of an animal parasite or the continued application of a chemical compound, is recognised as instrumental in the production of cancer. This information is, in some degree, a simplification. It introduces a known factor and is of obvious utility for prophylaxis. But its value is limited by the fact that it has not provided an explanation of the way in which a normal cell is converted into a malignant cell.

Then there is the histological method. A series of sections taken, for example, from different stages in the production of tar cancer show that certain changes in the morphology and arrangement of the cells occur in a certain sequence. But they throw no light on the biological problem of causation.

It is naturally thought that more information about the chemistry of the tissues would be helpful; but that long succession of events, which affects the tissue and its environment and culminates in the malignant phase, is not at present amenable to biochemical analysis, and, owing to the intrinsic difficulties of the subject, there is no immediate prospect that it will be.

Three main difficulties, then, must be frankly recognised. (1) When, as is most frequently the case, there is no recognisable irritant to remove, it is difficult to see what means can be taken to prevent the pernicious sequence of events leading to malignancy. (2) If the biological mechanism producing the malignant variant were discovered, it does not follow that prophylaxis would be possible, because the causes which initiate the mechanism might not be preventable. (3) Nor does it follow that this discovery would indicate the way to control the established disease.

There are two corollaries. (*a*) No possible means of investigating causation should be neglected; light may be thrown on the subject in unexpected ways, and the difficulties raised above may not be insuperable. (*b*) At the same time, the established disease has to be accepted as a fact which at present is inevitable; possibilities of its cure must be considered without waiting for a thorough elucidation of its cause.

### Initiation and Propagation of Variants.

The distinction between the initiation of a variant and its continued propagation is sometimes overlooked.

With bacteria and also with tissue cells, the initial stimulus to variation may be due to one or other of various conditions which are quite different from each other and are generally non-specific; the propagation of the variant is, in a sense, automatic and must depend upon a complex and perplexing interplay of specific and non-specific factors, involving adaptability to environment and transmission of specific characters from generation to generation.

In all studies of cancer it is important to keep in mind a clear distinction between conditions which are likely to give rise to malignancy and conditions which may have a favourable or an adverse effect upon an established growth.

In this connection I may make some reference to experiments on the transplantation of malignant tissue from animal to animal.

These take the fully developed malignant variant as their starting-point; so one cannot expect them to throw any direct light on the mechanism whereby such variants originate. They provide, however, wide opportunities for studying the characters of the malignant cell as it grows in the living body; and discovery of any means for bringing such artificial growths under control would probably be of value in dealing with the spontaneous disease.

At the same time it is generally recognised that much caution must be exercised in drawing conclusions about the latter from the former. For example, various agents may stimulate or (in larger doses) depress an animal's resistance to the taking of a graft; but it cannot be concluded that such influences have a similar effect upon its susceptibility to spontaneous (or tar) cancer. And, when the latter disease is established, increase of resistance is not effected by means which might render a normal animal insusceptible to a graft. A distinction has also to be drawn between the latter kind of insusceptibility and resistance to the production of a new tumour in an animal already bearing a spontaneous growth.

I do not wish to exaggerate the distinction between the initiation of a variant and its continued propagation. It may be argued that the distinction is not an absolute one. Cancer, it may be suggested, is due to the production of a mysterious substance, $x$, which persists in the fully developed disease; the study of $x$ in the established disease may throw light on its nature and thereby give a clue to its origin. For example, $x$ may be responsible for the

special "systemic change"; and, if this could be identified before established malignancy, a mode of treatment might be discovered which would remove the cause.

## THE RESISTANCE OF THE HOST.

Under this heading I propose to raise some preliminary questions of a general nature concerning one's ideas of natural and acquired resistance in relation to autogenous cancer.

### *Natural Resistance.*

There are two alternatives which may be put forward.

(1) As regards natural resistance or susceptibility of the host there is no proved analogy between parasitic infections and the autogenous development of malignant disease. It has been suggested above that the incidence of a malignant growth is probably the final outcome of a long series of events taking place in the tissues and following each other in a particular order; and the continuity of this pernicious sequence may be largely a matter of chance, with the odds against its occurrence in any one individual. On this view, there is no need to postulate any sort of "resistance" in explanation of the fact that many old people die without having developed cancer; it may be simply what one would expect from ordinary laws of probabilities; and a comparison with resistance to bacterial or animal parasites, known to have been introduced into the body from without, would seem quite irrelevant. All that can be said is that, when cancer does not occur, there is absence of any effective interference with the forces[1] which regulate normal growth of tissues; but this state of affairs cannot accurately be described as "natural resistance." Still less can the body be regarded as "naturally resistant" when a new situation has been created by the development of fully virulent malignant cells. Against these the normal constituents of the body possess no selective mechanism of defence (as distinct from the customary and non-specific inflammatory reactions); and, in this respect, all persons and animals are equally helpless.

(2) The alternative view is that the normal animal, though susceptible in greater or less degree, has certain natural powers of resistance against the incidence of autogenous cancer, and that these natural powers still exist as a factor of importance when malignant disease has developed. For many infections there are arguments in favour of this latter conception. I refer to those parasitic diseases towards which there is always some degree of natural resistance, though it varies, for different individuals and for different species, within a wide range which sometimes extends from almost complete susceptibility to a degree of resistance approximating to a high degree of immunity. Then one of the main problems of therapeutics may be concerned with efforts

[1] On the other hand, greater susceptibility in old age may simply mean that the circulating substances which constitute these forces have become less potent or are more easily cut off from an area of chronic inflammation.

to increase these natural powers of resistance. There would be several advantages in the adoption of a similar attitude towards cancer if it be permissible to do so. It would, to some extent, bring under the same general principle resistance or susceptibility towards the initiation of a new growth (spontaneously, by tarring, or by grafting) and towards the progress of an established tumour. Resistance might be interpreted in terms of natural "antibodies," or, if preferred, in terms of normal regulatory "growth impulses." On either alternative, it might be said that, under normal conditions, these influences preserve a proper equilibrium between the growth of the different tissues of the body and thereby help to prevent the normal person from becoming cancerous, and that there is no reason why they should not persist as a restraining force (occasionally effective though more frequently not) in established malignant disease. Then the problem of increasing natural resistance, or of reinforcing it by some subsidiary means, would be of primary importance as a therapeutic measure.

### *Acquired Resistance.*

There are two aspects to the question whether, in established or incipient malignant disease, there is spontaneous development of any specific or selective substances which may retard or even suppress the new growth. Are such hypothetical substances manufactured (*a*) by the malignant cells themselves or (*b*) by the normal tissues and fluids of the host? It is convenient to take (*a*) and (*b*) separately, though possibly the correct answer may be that both participate in their production.

(*a*) There is nothing unorthodox or intrinsically improbable in the idea that the malignant tissue itself may be the source of substances which are detrimental to its own growth. This need not be inconsistent with the view that this tissue is also the source of a selective stimulus which promotes the growth of the malignant cells. The same stimulus may differ in its effects according to its intensity, in relation to the susceptibility of the cells on which it acts; it may cause the rapid production of temporarily viable cells or, if more intense, may lead to the formation of daughter cells which are more immature and non-viable; in the former event, there will be progressive growth; in the latter, elimination of the growth by autolysis. Or perhaps some investigators prefer to postulate that the malignant cell produces variable proportions of two distinct substances, the one stimulative to growth and the other inhibitory. In either case, the hypothetical substance or substances might be associated with the "systemic change" which is a stimulus to the development of malignancy and also offers resistance to the induction of a second new growth.

(*b*) The products of the malignant cells may not be directly inhibitory to their own growth in the living body but they may stimulate the normal tissues of the body to produce antagonistic substances, thus investing the host with "acquired resistance" as a new mechanism of defence.

*Comment.*

The above ideas about some possibilities of natural and acquired resistance to cancer have been expressed in the form of alternatives; but it does not follow, as regards either type of resistance, that selection is limited to full acceptance of the one alternative and complete rejection of the other.

On the contrary, I think that, at this stage, it is better to keep an open mind about these questions. It will be useful to remember them, without being in a hurry to settle them, when entering into further details of immunology.

## ANTIGENS AND ANTIBODIES.

*Elementary Ideas.*

It is often thought that the main problem of immunity is to find the right antibody to the right antigen.

In dealing with antibodies to the constituents or products of infective bacteria, it is usual to quote diphtheria as an instance in which this problem has been solved. Diphtheria toxin is neutralised by antitoxin; hence the therapeutic value of antitoxin obtained by immunising horses. Persons in whom there is an adequate supply of circulating antitoxin are immune. In susceptible persons it is found that there is little or no circulating antitoxin; but a susceptible person may be rendered immune by administering suitable doses of toxin and thereby causing him to increase his supply of antitoxin.

One would like to think that this is an example of the utility of antibodies which will ultimately be found to be the general rule, extending beyond the neutralisation of bacterial toxins by antitoxins. Infective bacteria of various kinds contain foreign protein which behaves as an antigen, and union of this with its specific antibody may, directly or indirectly, lead to the destruction of the bacteria. This antibody, it is hoped, may be produced (if not already present) in the human or animal body by suitable dosage of the antigen and may thus provide the means of active or passive immunisation.

It is admitted that the conditions in malignant disease are not strictly parallel with the above, particularly when one adopts the view that malignancy is not due to foreign material introduced from without, such as bacteria or other parasites, but is autogenous, *i.e.*, is attributable to a perversion in function of certain cells of the body which were originally normal.

But this, it may be thought, is not a serious objection, since one may find suggestive analogies in established data about antibodies to constituents or products of the animal body. On examining the antigenic properties of closely allied animal proteins, it is found that extremely minute differences exist between them and that these differences are reflected in the specific properties of the antibodies to which they give rise. Therefore, it may be believed that malignant tissue, which is certainly abnormal, ought to differ antigenically from the corresponding normal tissue of the animal in which the new growth has developed.

Certain observations on bacteria lend support to this view. For example, a particular strain of bacteria (*e.g.*, pneumococci) may be either (*a*) virulent or (*b*) non-virulent; a slight modifying influence may convert (*a*) into (*b*) or *vice versa*; but (*a*) and (*b*), though derived from identical bacterial protein, possess recognisable differences in their antigenic properties. Then may there not be differences (though probably not quite of the same nature) between the antigenic properties of the cancer cell and the corresponding normal cell?

Hence the above elementary considerations suggest that it may be an important problem of cancer research to "find the right antibody for the right antigen."

*Some of the Difficulties.*

However much one would like to assume that immunity is an affair of antibodies, it must be recognised that the earlier expectations of bacteriologists have not been realised. In the greater number of bacterial infections it cannot be shown that specific antigen-antibody reactions are the mechanism of resistance, either in natural or in acquired immunity. One can only postulate an unknown "something" which is antibacterial in one way or another; but obviously this vague conception is not equivalent to an antibody which can be demonstrated as such by immunological criteria. This is particularly the case when the problem is to influence capacity for bacterial growth in the animal body, as distinct from either neutralisation of a bacterial exotoxin or selective combinations between antibodies and dead bacterial proteins. But these obscure influences on capacity for growth are by far the most important considerations, both with parasitic bacteria and with malignant cells.

Hence bacterial immunology, when one takes into account the many limitations to its success, does not provide any firm ground for believing that the hypothetical mechanism which is supposed to resist cancer will ultimately be found to be an antibody, even in the rare cases where cancer disappears or spontaneously "cures" itself.

Is there a valid analogy between this exceptional event in cancer and disappearance of the parasites on recovery from a bacterial infection? One would like to think that there is, particularly because elimination of the bacteria is attributable to acquired resistance on the part of the host and is sometimes associated with the production of antibodies. Then may not a spontaneous cure of cancer be similarly attributed to an acquired antibody? If this view be accepted, there is the hope of coping with the progressive disease by artificial means which would enhance the output of these antibodies. The primary difficulty, of course, is to demonstrate the existence of these postulated substances.

But the real analogy with bacteria may be quite different. An old culture dies out, owing to accumulation of toxic products of metabolism or for some other simple reason. May there not be an equally easy explanation for the eventual disappearance of a sluggish cancer? If there are only a few cancerous foci and if the centre of each is dead, why should not the necrotic process

spread to the peripheral cells and, if these are temporarily quiescent, overcome them before they are able to renew their growth? What need is there to postulate antibodies or any other sort of antagonism on the part of the host?

One hesitates to compare autogenous cancer with experimental grafts, but it may be noted incidentally that, when a graft first develops into a tumour and then retrogresses (either of its own accord or after injection of tumour autolysate), the latter condition may perhaps be explained in the above simple manner; there seems no cogent reason to postulate the action of exceptionally effective antibodies.

If, however, one concedes that the simple explanation is reasonable, the consequences of its acceptance are rather serious. It implies that the spontaneous cure of autogenous cancer is due to natural causes which afford no clue to the treatment of the progressive disease.

Malignant cells, though abnormal, are still strongly characterised by the specificity attributable to the normal cells of the animal (*A*) in which the new growth has originated. Hence, when an animal of different species (*B*) is "immunised" with the malignant tissue, the antibodies which are formed are usually antibodies to the normal cells of *A* and not to the special characteristics (if such exist as antigens) of *A*'s "malignant" protein.

Why should the abnormality of malignant tissue be antigenic any more than the abnormalities associated with other non-infectious diseases of the animal body? When serum, tissues, or tissue products of animal *A* (suffering from some autogenous disease other than cancer) are injected into animal *B* (of another species), one does not usually expect that the antibodies produced in *B* will reflect the particular abnormality present in the serum or tissues of *A*. In other words, the principles of antigenic specificity have not been found applicable to pathological attributes of the cells and fluids of the body.

This being the case, why expect that pathological attributes (malignant or of other nature) should act as specific antigens in the body of their host and so produce auto-immunisation? No doubt they often produce systemic changes in their host; but, even if such changes appear associated with increased resistance to the morbid process, this circumstance is no proof that the changes can be described as antibodies in the immunological sense.

The above, then, are some of the difficulties—I do not call them insuperable objections—in the cancer investigator's search for the right antibody to the right antigen. Is there any possibility of overcoming them?

### *Hypothetical Antibodies.*

It is a trite saying amongst bacteriologists that what is at present known about antibodies by no means exhausts their possibilities; and one notes that, at the present time, search for new kinds of bacterial antigens and antibodies is being pursued with much vigour. One has certainly no right to exclude this possible field for enquiry in the still more obscure subject of cancer immunology.

There may be natural antibodies to cancer and these may be subject to circumstances which increase or diminish their potency.

Or there may be acquired antibodies, formed as a new mechanism in the course of malignant disease.

There may be antibodies which exist and are effective *in vivo* but are too labile to survive in the serum and therefore are not demonstrable *in vitro*.

There is the possibility of employing chemical, physical, or biological methods for the separation of new antigens which are purer and more specific; and such products may be employed for the production of more distinctive and more effective antibodies.

If an antibody is produced by the antigenic stimulus of the malignant cells upon the body, failure to arrest the growth may be due to its feeble powers. It may be strong enough to inhibit the induction of a second new growth in the same animal or even to arrest a slow primary growth of weak activity, but not to check an established tumour which is growing vigorously.

But why should not a vigorous growth produce more potent antibody than a feebly growing tumour? One can always fall back on the hypothesis of antagonistic principles. There may be two "somethings" in the body of the cancerous individual, one which promotes the new growth and another (the antibody) which tends to inhibit it; progressive disease may mean production of the former in excess of the latter.

There is another point of view in connection with the endeavour to express the position in terms of antibodies. An antibody reacts with its antigen, but it cannot be assumed that this reaction is always and necessarily unfavourable to the living material from which the antigen is derived. Why may not the antibody neutralise some toxic product of metabolism which is injurious to the growth of the malignant cell? It is found, in work on tissue culture *in vitro*, that the malignant cell gives off some product which is specifically toxic for itself but less toxic for normal cells; therefore it is at least conceivable that neutralisation of such products by an antibody is part of the usual mechanism for promoting the growth of malignant cells *in vivo*. And it is theoretically possible that the antibody, instead of being antitoxic, promotes malignant growth by entering into some other kind of union with the malignant cell or with its environment. On this view, it would be the more vigorous growth which causes the body to produce the more potent antibody.

Thus, in the search for the hypothetical cancer antibody, it may be just as well to bear in mind this possibility—I do not say it is a strong probability. If the antibody is found, it may not prove to be something helpful to the host (like a selective cytolysin) but may be helpful to the new growth and therefore injurious to the host. Then, I suppose, the next problem would be the discovery of an "anti-antibody."

MODIFICATION OF STIMULANTS TO GROWTH.

It will be seen that the attempt to think out the subject in terms of antigens and antibodies is by no means an easy task. I do not think that it presents fewer complexities or difficulties than the consideration of influences which may modify the character of the growth impulse. Each line of thought is equally puzzling; and discussion of what may be said in favour of the latter does not imply rejection of the former.

I return, then, to the conception of a stimulus to the production of unstable variants, the degree of instability being variable but resulting, as a rule, in a preponderance of temporarily viable over non-viable malignant cells (progressive growth); the problem then will be to produce a preponderance of the latter over the former (retrogression).

When bacteria exhibit variants, as they usually do, there is the question, perhaps mainly or merely academical, as to which is the normal and which is a variant; and the answer may differ in respect to different bacterial species. With tissue cells there is no difficulty, because the malignant cell is obviously the variant. So, if one wishes to find analogies between tissue cells and bacteria, I suppose one must select the types of bacteria which commonly live as harmless saprophytes on a mucous membrane but occasionally acquire invasive powers; in the former condition they may be called "normal," like the normal tissue cell; in the latter they may be regarded as "variants," like the malignant cell.

Using the terms in this sense, bacteriology affords plenty of instances where the variant can be brought back to the normal, either in the living body or in the test-tube. But there seems no likelihood that the living body can make a malignant cell recover that internal organisation which was characteristic of the normal condition; the only probable way in which it may control such variants is by causing them to die out.

Hence, it seems to me, one line of speculation may perhaps be excluded. There may, as I have suggested above, be some analogy between malignant cells and bacteria which are partially sensitive and also partially resistant to that type of modifying influence which is known as a transmissible "lytic principle"; and such bacteria may sometimes be made to revert to the normal condition. But the circumstances under which such a change may take place hardly seem worth considering in this connection, since there is no good reason for anticipating that a similar change from the variant to the normal may occur in malignant disease.

Thus one is thrown back on an alternative consideration. Bacteria may die out through becoming hypersensitive to a "lytic principle"; is there any hope of finding a similar influence which will cause the death of cancer cells?

I think that this idea is worth considering, though one cannot anticipate the establishment of anything like a close parallel.

In the case of bacteria it is known that subtle differences exist, even in

strains of the same species, as regards susceptibility to a "lytic principle," capacity to propagate it, and the selective properties of the particular "lytic principle" which is obtained. Why there should be these differences is not very clear, but advantage may be taken of them in experimental work with suitable strains. The production, *in vitro*, and final elimination of a hypersensitive strain of bacteria is certainly interesting; and, though it is brought about by artificial selection and other arbitrary influences, it may throw some light on the conditions under which bacteria are modified in the living body.

Amongst malignant cells similar differences as regards susceptibility to modification may occur, and it may be theoretically possible to induce a condition comparable to bacterial "hypersensitiveness." But, when one asks for detail, I think it is doubtful whether much of the laboratory work on "bacteriophage" can be applied usefully to conditions affecting growth stimulants in cancer.

But I may remark parenthetically, though parasitic theories do not directly concern me in this article, that discussions which have taken place as to whether "bacteriophage" is a virus or an enzyme may possibly be correlated with the question of extracting a living virus from cancerous tissue, particularly if the so-called "vital" properties of "bacteriophage" are no more than those of an enzyme which may be propagated out of substrate. In the present article I am assuming that, in cancer as it occurs in the human body, the stimulus to malignant growth is entirely autogenous, though foreign irritants sometimes operate as predisposing causes. In certain observations on animals it seems that the effective stimulus may be extracted from malignant tissue and may be split into two components, each inactive *per se* but capable of being reactivated by the other, the one (*a*) being specific and the other (*b*) non-specific; (*b*), moreover, may be replaced by something which is not autogenous. Is (*b*) comparable to "bacteriophage"? And, if so, is it necessarily a virus? Or is (*b*) comparable to the non-specific property of fresh serum which may "activate" an immune body?

Perhaps it would be better to start afresh, ignoring the assumed origin of the cancer cell as a variant derived from a normal cell and regarding it simply as a special type of abnormal micro-organism.

Though the malignant cell is autogenous and not a foreign virus, one cannot avoid the admission that the course of malignant disease presents a strong resemblance to certain parasitic infections which, when once established in a susceptible host, show a natural tendency to progressive infection, exceptions being so rare that the possibility of either natural or spontaneously acquired resistance may be disregarded, and recovery, when this rare event occurs, may be attributed to some accident such as unusually feeble vitality on the part of the virus.

This analogy might seem a particularly uncompromising way of expressing the difficulty of the cancer problem, were it not for the fact that the introduction of a particular chemical compound may completely change the situation in the case of experimental infection with some of the parasites referred to. Unaided, the animal is helpless; after administration of the drug, the animal survives and the parasites are eliminated.

For some trypanosomes and spirochaetes, for example, drugs have been

found which are highly selective, and it is now known that their action is generally of a complex nature and not an immediate union between the parasite and the unaltered chemical compound. Amongst various possibilities there are: (*a*) modification of the drug by the tissues or fluids of the body, followed by its combination with the parasite; (*b*) combination between the drug and some substance provided by the host and then union of the parasite with this compound; or (*c*) the drug, perhaps after attachment to an endothelial surface, may convert some constituent of the host's plasma from *a* into *b*, and then *b* may be the active principle which unites with the parasite.

It is interesting to note that the ultimate effect (by direct or indirect action) of the drug upon the parasites depends upon dosage. If the initial amount administered is adequate, the parasites are eliminated; if the dose is too small to produce this result, the parasite continues to multiply and it may be found that its descendants differ from the normal in that they are unusually resistant to the action of the drug.

For these two phenomena various explanations might be offered, though I do not think that any one of them can be regarded as definitely proved.

To bacteriologists who are interested in stimulants to growth, irrespective of laboratory details about "bacteriophage" phenomena, it is a natural suggestion that the active principle initiated by the drug resembles a stimulus which, if sufficiently intense, leads to the production of a strain highly sensitive to lytic influence and therefore perishable; if the stimulus is less intense, its effect is to increase the strain's resistance to this particular type of lytic action.

The former contingency is of main interest here, as it suggests the possibility of a similar result being obtained with cancer, by means of an artificially created stimulus which would overcome that partial resistance to autolysis apparently acquired by the cells of an established tumour in the natural process of their growth. Numerous attempts to find a suitable chemical compound have already been made and the outcome has not been very encouraging; but these disappointments do not justify abandonment of this field of enquiry.

As the drugs of known efficacy require the active co-operation of the animal body, the idea that some substance, which is not manufactured by the host, may induce a selective action on malignant tissue does not imply that acquired resistance would be independent of biological products derived from the host.

## GROWTH STIMULANTS AS IMMUNOLOGICAL PRINCIPLES.

The primary object of this article has been to consider whether the line of thought suggested in my former discussion on stimulants to bacterial variation can be followed up in relation to malignant disease. This point of view is not intended to replace but only to supplement other aspects of the immunological problems which interest the investigators of cancer.

As regards the initiation of the disease, it is generally conceded that some particular form of growth stimulus must be operative. Since precise data are

not available, there must naturally remain differences of opinion as to the way in which the stimulus acts. But I think the evidence is sufficient to exclude the view that the malignant stimulus is simply the normal growth stimulus inherent in cells and operative owing to a release of the cells from normal inhibitory influences. The cancer cell is not a normal cell in a changed environment; it is distinctly a variant. Changes in the modifying influences of its environment are very probably necessary for its evolution; but, when it is evolved, it is no longer normal in its growth or other main biological properties. The initial stimulus, therefore, which gives rise to the cancer cell, must, I think, be regarded as a special kind of influence which is abnormal in character.

On coming to the question of the immunological significance of growth stimulants when once the disease has started, one must go back to the old distinction between dead protein and living protoplasm.

This distinction is of considerable importance in bacteriology. The main reason why the progress of immunology is so slow is that antibodies to dead bacterial protein, though easily produced, frequently fail to modify the living bacterial protoplasm in such a way as to inhibit its growth. The bacterial cell is not merely a sum total of chemical constituents with particular physical properties but is an organisation; its life depends upon a constant succession of events following each other in a particular way which is determined by the internal machinery of the cell, machinery which is characteristic of the individual cell and is transmitted, with only minor variations, from generation to generation. Immunology cannot afford to ignore the fact that the individual bacterium is a highly complex organisation with elaborate differentiation and co-ordination of its ultramicroscopic constituents.

Evidence is increasing that bacteria in the living animal body cannot always be destroyed (or be made amenable to phagocytosis) by the direct action of something, *e.g.*, an antibody or a known chemical, which combines with the bacterial protein and does not damage the animal host. But their elimination may sometimes be brought about in another way, by causing some derangement of that internal organisation on which the life of the bacterium depends. This derangement may, with some parasites, be a sort of "shock," resulting in paralysis of reproductive activities and ultimate death. But it seems to me much more likely that, with bacteria, the change is not a paralysis but a perversion of activities and that it occurs when the bacteria are most susceptible to change, viz., when they are in a state of active division. This is known to be the case in the induction of "transmissible autolysis." Therefore I think the most satisfactory hypothesis is to assume not a direct act of destruction but a stimulus to variation, with the further consequence that the variant which is evolved perishes because it is not fully equipped with the internal organisation necessary for life. This is probably an important part of the mechanism in both natural and acquired immunity, in cases where antibacterial antibodies are not demonstrable in the serum.

Similar considerations apply to animal cells. Though it is not theoretically

impossible that an antibody may some day be discovered which acts directly as a cytolysin, selective for malignant cells and innocuous for all other tissues, the probability is remote. Hence one is induced to consider not a direct act of destruction but some method of disturbing the internal organisation of the cell which will lead to the production of non-viable variants, as in the case of bacteria.

It seems, theoretically, that this might be possible. The malignant cell, though usually constant in its main characters, is presumably less stable in its organisation than the normal cell from which it was derived; so it should not be less susceptible to modifying influences than the latter.

What one has in mind is a further change in the organisation of the nucleus and cytoplasm, including, perhaps, a change in the functions of the chromosomes which regulate growth. If some change of this nature converted a normal into a malignant cell, some further influence on the new organisation might make autolysis outstrip proliferation. The important point is that the functions of living protoplasm are concerned, and these are not necessarily reflected in the biochemical properties of the dead constituents of the protoplasm.

To take an example from what may be considered to be the most pessimistic view of the situation. Cancer, it may be imagined, is due to a local perversion of metabolism which, when there is no foreign irritant associated with it, is accidental and unavoidable and causes the affected cells to be independent of the normal mechanism which inhibits growth; there is no systemic resistance on the part of the host when once the disease has been established. Owing to this absence of resistance, there is no prospect that malignant tissue can stimulate the host to produce specific antibodies. Passive immunisation is not feasible, because the immune substances are antibodies to the host's normal protein and are not selective for the protein of the malignant cells. As the situation cannot change automatically, there is need of artificial intervention with something alien both to the host and to the tumour, in order to modify the growth of the tumour either directly or by modifying the relations of the host to the tumour. Perhaps the introduction of some chemical compound or other agent (not yet discovered) may initiate a stimulus causing the production of non-viable variants of the malignant cells.

How are ideas about growth stimulants to be correlated with other immunological principles?

Before entering into this question I should like to refer to the difficulty of using terms which appear to be more or less concrete, such as "stimulants," "antibodies," or other "antagonistic forces," in substitution for more general conceptions which are less definite.

A good example of the latter is to be found in those chemico-physical conceptions of equilibrium and of disturbance and re-adjustment of equilibrium which are of undoubted importance in regulating vital processes. It is not clear how far they may be expressed legitimately in terms of special secretions or special functions. For instance, it may not be true that there

is a natural tendency for normal cells to become cancerous, which is held in check by some special internal secretion; nor is it proved that some perversion of metabolism gives rise to a secretion which passes into the circulation and stimulates to cancerous growth cells "predisposed" to its influence by some local irritation.

It must be admitted that ideas of balanced mechanisms and disturbances of equilibrium are vague and therefore unsatisfactory. But physiologists find it necessary to employ them as expressing facts, the details of which are unknown, in the organisation, metabolism, and growth of the cell. Immunologists and bacteriologists are under the same necessity; and it is sometimes dangerous to try to fill up gaps in knowledge by coining too freely "antagonistic forces" which, though apparently more concrete, may be imaginary and unreal, and may therefore raise issues which are misleading.

I now return to the correlation of growth stimulants with other immunological principles.

Opinions differ about the existence of cancer antigens, the possibility of producing antibodies, the validity of applying to the cancer patient those conceptions of susceptibility, resistance, and immunity which are derived from bacteriology, the relative value of discordant theories about natural and acquired immunity, and so forth. This certainly seems confusing, but I think some common ground may be found.

On every aspect of the problem, questions of specificity are involved. How can one explain that extremely delicate selective action which changes the characters of a cell from the normal to the malignant? Then, assuming no explanation to be needed for the fact that the cancer cell "breeds true," how is one to find an equally delicate selective action which will remove the malignant character? However these questions may be answered ultimately, reactions between antigens and antibodies afford some of the best examples known of extremely delicate selective action; and the significance of this fact must not be lost sight of. Such reactions, however, do not appear to be exclusively entitled to the term "specific" but rather to be members of a much larger group of reactions which are highly selective for the individual characters of the reacting agents. Moreover, reactions are not always separable into specific and non-specific; there are degrees of specificity which might be arranged on a scale passing by slight transitions from the exclusively selective to the less and less selective and down to the vanishing point of specificity.

This idea, then, of a stimulus to the production of non-viable variants is one of the many possible aspects which are presented in dealing with a much wider subject—the significance of specificity in the immunological reactions of the living body. Regarded in this way, the question of stimulants as immunological principles is, I think, worth considering. It would be reduced to an absurdity if one attempted to make it the basis of a theory intended to replace better established data about the principles of immunity.

SUMMARY.

The "chronic irritation" theory still retains its interest, though it has not yet provided a thoroughly satisfactory explanation of the origin of that stimulus to growth which causes normal tissue to become malignant. If employed with caution, ideas borrowed from bacteriological work on "transmissible autolysis" may be contributory in the search for the explanation which is desired.

It is important to maintain a careful distinction between the initiation and the continued propagation of the malignant variant.

It seems hazardous to assume that one can apply as immediately valid for cancer those ideas about the natural and acquired resistance of the host which are current in bacteriological literature. On the other hand, it is not suggested that such ideas should be discarded but rather that they should be regarded as suggesting alternative possibilities, none of which can be definitely excluded.

Analogies with immunological reactions to foreign protein (bacterial or animal) certainly suggest the possibility that the cure of cancer may be found in discovery of "the right antibody for the right antigen"; but it is not clear how far such analogies can be accepted as being entirely appropriate; still, owing to the likelihood that new kinds of antigens and antibodies will be discovered, continued search for these factors in cancer is of high importance.

In the present article, which is a sequel to a former discussion on stimulants to bacterial variation, I have considered whether the idea of a stimulus to the production of non-viable variants may be regarded as of immunological interest in relation to the therapeutic problem of cancer.

I have endeavoured to show that this idea is worth consideration, provided that its importance is not exaggerated and that it is correlated with better established data about the principles of immunity.

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