

FURTHER COMMENTS ON THE CAUSATION OF MALIGNANT DISEASE¹.

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CONTENTS.

	PAGE
SIGNIFICANCE OF INVISIBLE AGENTS	9
True Invisible Viruses	9
Other Transmissible Infective Agents	10
Non-transmissible Stimulants to Variation	12
CONDITIONS PREDISPOSING TO MALIGNANCY	13
Unstable Energy in Relation to Physiological Activity	13
Regulation of Normal Growth	16
Premature Application of Immunological Principles	17
The Latent Period	19
Displacement in Foetal Life	20
Susceptibility to the Precancerous Change	21
THE CRITICAL STIMULUS TO MALIGNANCY	23
Cellular Rejuvenation	23
The Malignant Variant	23
Distinction between Cause and Effect	25
ANALOGIES FROM BACTERIAL VARIATION	26
The Cancer Problem not Unique	26
Loss of Function	27
Acquirement of Function	27
DISCUSSION	29
SUMMARY	31

SIGNIFICANCE OF INVISIBLE AGENTS.

True Invisible Viruses.

UNTIL recent years it was accepted, practically without question, that certain diseases were caused by ultra-microscopic viruses which were as truly specific and individualistic as the ordinary pathogenic bacteria. The plague bacillus, for example, causes a distinctive disease which is only spread by the transmission of this bacillus. Similar characteristics were attributed to the filter-passing viruses. But at the present time, owing to the increasing tendency to regard invisible viruses, which have not been isolated, as the agents responsible for a large variety of infections, confusion has arisen, and it seems necessary to consider more closely the criteria to which these alleged viruses ought to conform.

First there is the question of origin *de novo*. The bacteriologist draws a sharp distinction between theories of evolution and practical problems. He is prepared to admit that, at some remote period in the past, the plague

¹ In continuation of an article appearing in the *J. Hygiene*, 24, 255, 1925.

bacillus may have been developed out of a harmless saprophyte and that, when one goes back to the ultimate origin of life, this saprophyte was evolved out of inanimate matter; and he is not prepared to deny, as a general proposition, that evolution is still possible at the present day. But, when he finds a plague bacillus in a man or a rat, he would regard the suggestion that it originated in its host *de novo* as mere foolishness, incompatible with the elementary foundations of epidemiology. And such a suggestion would appear equally foolish if it were made about some of the diseases, *e.g.*, rabies and variola, which are known to be caused by filter-passers. These diseases do not arise by "spontaneous generation" but resemble bacterial infections; and, for practical purposes, one need not be troubled about the nice question whether their invisible agents are quite as fully entitled as bacteria to be called living unicellular organisms.

Next, there is the theory of ubiquity, which is frequently proposed by persons who would not venture to suggest origin *de novo*. No sensible person would claim ubiquity for some of the invisible viruses, such as those which cause rabies and variola; this would be as absurd as to suggest ubiquity of the bacilli which cause plague, anthrax and tuberculosis. But there are other bacteria which are very widely distributed in nature and are known to be capable of producing disease, though they more commonly continue their existence as innocuous saprophytes. May there not also be filter-passers which are very widely disseminated and are capable, on occasion, of acquiring pathogenicity? The common-sense answer is to admit the possibility but to distinguish between explanations supported by evidence and unsubstantiated hypotheses. The known prevalence of staphylococci, streptococci and pneumococci is a good reason for the occurrence of infective processes due to these organisms, apart from any evidence of transmitted infection. But, until the filter-passers have been isolated and identified in culture, evidence for their prevalence must depend on proof of transmissible infection. When this proof fails, as in the case of cancer, the theory of ubiquity is unsubstantiated; it becomes arbitrary and futile if applied indiscriminately in the explanation of disease.

In conclusion, one may say that the true invisible viruses, in so far as their properties have been established, possess four essential characteristics. They behave like living micro-organisms; they are specific in their capacities for producing disease; they do not arise *de novo*; and they are not ubiquitous.

It has not been shown that any form of malignant disease is attributable to a virus conforming to the above criteria. This is one of the reasons for supporting the "chronic irritation" theory.

Other Transmissible Infective Agents.

I now come to further elements of confusion about the definition of an invisible virus.

If an infective agent is transmissible and is capable of indefinite multipli-

cation, is it necessarily a virus, *i.e.*, a living organism? Many people, with whom I agree, would give a definite answer in the negative. Propagation of an agent is not sufficient proof that this agent is a living cell, though its propagation may be possible only with the aid of living cells. The agent in question may be something similar to such enzymes as are propagated out of substrate.

But the acceptance of the above proposition does not carry one very far towards the simplification of the virus question. It is argued, reasonably enough, that a true virus must conform to other criteria of living matter besides capacity for multiplication; but what these criteria are is a matter in dispute, and the question whether a given infective agent does or does not conform to them has produced controversies which appear to be hopelessly irreconcilable.

I think it would be a good plan to cut the knot in the following way. Satisfactory evidence for origin *de novo* should exclude the true virus; and substitution of "ubiquity" for "origin *de novo*," as an alternative explanation for the appearance of a "virus" disease, is inadmissible in all cases where it is not fully substantiated.

Taking "bacteriophage" as providing the best example of a much disputed question, I accept the experimental proof that this agent can be created *de novo* and I reject, as unsubstantiated, the alternative theory of ubiquity which would imply that it was invariably present to begin with, though undetected. Therefore I regard "bacteriophage" as a transmissible, infective agent which, though requiring for its continued propagation the assistance of living cells, is not itself a living micro-organism.

A good deal has been written about the possible application of "bacteriophage" principles to animal pathology. The subject is highly controversial. There are still several authorities who insist on the "ubiquitous virus" theory of "bacteriophage." As I do not agree with this view, I do not think it can be usefully applied to the animal cell. Turning to the opposite school, who all reject this theory, one finds that individual authorities differ very considerably when they come to explain in detail what they think "bacteriophage" really is. And these differences must naturally influence their mode of applying their principles to non-bacterial forms of life. So, to avoid confusion, I will commence by stating the main facts which, in my opinion, have been established about "bacteriophage."

It is an agent which is frequently created *de novo* by the action of various chemical and physical influences on the bacterial cell. It has been produced experimentally; and it commonly arises "spontaneously," in ways which are not clearly understood. When once created, it is quite independent of the influence to which it owed its origin. It is propagated within living bacteria and is transmissible. It is essentially a stimulus to pathological change in the bacteria, lysis being merely a prominent consequence of the kind of change usually produced.

Taking this view of "bacteriophage" as a transmissible infective agent

which is not a living virus, there are interesting indications that parallel phenomena may be found in other spheres of pathology.

It is not accepted by all authorities that the infective material obtainable from herpes vesicles is necessarily a true virus. It seems not altogether improbable that the "virus" may arise *de novo* in the patient's vesicle, just as "bacteriophage" may in a culture, and that it may then be propagated in the appropriate tissues of animals; just as "bacteriophage" may be carried on indefinitely by cultures of suitable bacteria. This theory, which has already been put forward in the literature in more or less tentative forms, requires confirmation. It has not been proved; but it is a suggestion which, I think, deserves consideration.

One hesitates to compare plants with animal tissues; but it is just worth noting that a similar suggestion has been made about some of the "virus" diseases which affect the former. May not the "virus" be really a non-living, transmissible agent produced *de novo* by some peculiar kind of irritation?

A more convincing example seems to be provided by the peculiar kind of tumour known as fowl sarcoma. According to experiments recently recorded, tumours of this nature have been produced in fowls by injection of dilute arsenious acid together with pulp from chick embryos. Cell-free filtrates of these tumours have been found to produce similar new growths when injected into normal fowls. One may compare the arsenious acid to a non-specific agent which initiates a stimulus to variation in previously normal bacteria (here in certain embryonic cells). These cells grow and propagate this pathogenic stimulus, which is transmissible to the previously normal cells of a fowl. Here there appears an exact parallel with "bacteriophage" as regards (1) initiation, (2) propagation in the affected cells, and (3) conversion of normal cells into affected cells. In the undoubted malignant disease of mammals, capacity (3) is conspicuously absent. This fact alone seems to me a sufficient argument against attempts to explain true malignancy in terms of fowl sarcoma.

There is, then, a highly interesting type of infective agent which is transmissible and, as distinct from living viruses, is readily created *de novo*. The incidence of such an agent does not appear to be confined to diseases of bacteria; it may also be an important factor in human pathology, particularly in diseases where there is doubt as to whether the cause is "an invisible virus of wide prevalence" or "something in the nature of an enzyme propagated out of substrate." But, on this point, available evidence does not justify any definite conclusion.

One fact is clear. There is no plausible ground for believing that an agent of this kind is the cause of mammalian malignant disease.

Non-transmissible Stimulants to Variation.

Invisible agents which cause pathological change may be divided into three classes: (1) true viruses; (2) transmissible infective agents which are not viruses but are created *de novo*; (3) stimulants to variation which are not transmissible or infective, *qua* stimulus.

Class (3) is much the largest and most varied. It comprises most of the usual causes of bacterial variation and, according to the "chronic irritation" theory which I support, it includes the influences which initiate true malignant disease.

As defined above, (3) is in sharp contrast to (2) and (1). Looked at from a different standpoint, all three may be regarded as different manifestations of the same principle, continuity of a vital process. In (1) this is expressed by propagation of a unicellular organism; in (2) it is the propagation within living cells of a stimulus which is transmitted to other cells and again propagated therein; in (3) the stimulus produces a variant, the change is confined to the variant itself, and this change (though not the initial stimulus) is transmitted to its offspring. Or, again, one might express the relationship between (1), (2) and (3) by regarding (2) as the connecting link. (2) can only be produced in living cells and, when separated therefrom, exhibits properties possessing some of the characters of living matter; hence its resemblance to (1). And (2) is a stimulus to variation which is initiated by various extraneous influences; these influences usually disappear when the change is established, though there is continued propagation of the change itself; in these respects (2) is comparable with (3).

So the "virus" and the "chronic irritation" theories have this in common: they are both attempts to postulate invisible influences which will explain malignancy as a vital process. If the "virus" is to be rejected, can the latter theory replace it with something a little more definite than "an unknown disturbance of metabolism"? This is the problem which forms the subject of the following pages.

CONDITIONS PREDISPOSING TO MALIGNANCY.

Unstable Energy in Relation to Physiological Activity.

As the subject of malignancy concerns vital processes, it may be useful to begin by saying something about "unstable energy." This conception has been introduced by physiological chemists with reference to all vital processes. It is intended as a means of explaining the difference between living and dead matter in respect of their chemical and physical activities. It may be regarded as an attempt to bridge the gap between the precision of pure chemistry and physics, where the investigator deals with substances and forces amenable to exact analysis, and the vagueness of biological conceptions which the physiologist is compelled to employ when dealing with facts, too complex for analysis, about vital phenomena.

The suggestion is based on recent physical views about the structure of atoms and molecules. The physicists have not yet come to the end of their problem, which is highly complicated; but the following elementary and imperfect statement may suffice for the present purpose.

According to the electron theory, atoms exist in conditions which differ in their amount of energy. When they are relatively inert, the negative

electron is revolving about the positive electron or nucleus at the centre of the atom in a small orbit. But the atom may absorb energy and then the negative electron moves out to a wider orbit and revolves at a higher velocity. This is the unstable, highly reactive form of the atom. So also the state of molecules may differ in their content of energy, owing to differences in the condition of their component atoms. The molecules which are rich in energy and highly reactive are those which contain atoms with electrons revolving in wider orbits than those of the stable atoms.

Applying these views to physiology, the essential difference between living protoplasm and dead protein is that the former contains molecules in the highly reactive condition, whereas in the latter these molecules have reverted to the inert state. Further, amongst the energetic or highly reactive forms there are differences in degree of activity.

For example, the living plasma, as it circulates in the animal body, possesses a high content of unstable energy, involving a wide range of capacity for chemical union, and thereby effects many changes which can only be produced *in vivo*. When an animal is bled and the serum is collected, this serum, even when fresh, contains only a small amount of unstable energy; and this amount is conspicuously diminished when the serum is "inactivated," *i.e.*, when it no longer possesses any of the attributes essential to living matter. Alexin or complement is to be regarded not as a special substance but as a property of fresh serum, a property which consists in the retention of a small amount of unstable energy; the plasma, in its vital surroundings, possesses this property in a much higher degree. Just as the unstable energy provided by alexin is necessary for the completion of many physiological reactions *in vitro*, so the unstable energy of the plasma is a primary requisite for physiological reactions which are always occurring *in vivo*.

Consideration of the cellular constituents of the body must also start with recognition that all living cells possess unstable energy in greater or less degree, with corresponding extension or diminution in their range of capacity for chemical union, and that there is marked increase of this energy during growth. This is the primary or "vital" aspect of the cellular mechanism which is subject to regulation by stimulative and inhibitory influences. It is the chemico-physical explanation of the well-known fact that in the living body extremely complicated reactions take place with the greatest ease and with extreme rapidity, in ways which it is impossible to reproduce in the laboratory.

Interest in the relation of these matters to the causation of malignancy must depend on the reader's attitude towards this problem. They are negligible if it is thought that the cause is to be found in a special substance—a virus or an enzyme or any particular chemical compound. But, if the problem is regarded as a complex question of the conditions determining cellular variation, then, it seems to me, one must recognise that there are obscure changes of chemical reactivity which differ from the stable reactions of pure chemicals observed *in vitro* and must be taken into account in the explanation of vital

phenomena. For example, there is something "vital" about stimulation or inhibition of growth which is never likely to be expressed in the precise formulae of the organic chemist. Whilst this consideration should not be ignored, it is not suggested that it will yield any wonderful clue to a new theory.

To bacteriologists who are familiar with the fact that many biological reactions *in vitro* require the aid of unstable energy in the form of "alexin," it is not difficult to understand that a similar, though much more complicated, mechanism is operative *in vivo*. This circumstance must also be taken into account in the cancer problem. For example, it is known that some irritants, chemical, physical or parasitic, behave as primary predisposing causes of cancer. And it is concluded from experience and observation that the change is not produced by a simple and direct interaction between the irritant and the cell which is about to become cancerous; it is complicated and indirect, involving intermediate changes which are possible only in a living environment. And in the much larger number of cases of cancer where there is no evidence that a foreign irritant has been introduced, one may imagine that the autogenous irritant produces similar changes with the aid of unstable energy. As to the nature of these changes, one knows from the organic chemist that in a large molecule, and particularly in one containing asymmetric carbon atoms, a relatively slight alteration—or even a merely stereochemical change—in some of the groups which are linked to the molecule may produce a marked difference in the chemical activity of that molecule. This may be taken as an example of the sort of change readily accomplished by the unstable energy of living matter.

I think that this conception of unstable energy should also be applied to the intrinsic factor. I refer to the view which is current in the literature of cancer that there is some "inherent capacity" which enables a cell to change from the normal to the malignant condition. This postulate, it seems to me, amounts to no more than the unilluminating hypothesis that a change must have been possible before it became actual. Equally little is to be gained from the counterpart to this view—the theory of selective action. According to this, the offspring of a particular group of cells are not all alike; some few of them are abnormal; these, under ordinary circumstances, are outgrown by the normal cells; but a selective environment may be more favourable to the abnormal than to the normal, thus paving the way for cancer. I see no reason to cling to this idea that a manifestly new condition is best explained by supposing that it was really pre-existent but latent. Why may not the change be produced *de novo*, frankly and unequivocally? So I should prefer to say that the internal capacities of the cell depend on the chemical and physical conditions of its organisation and that this organisation may be changed, under the influence of living matter, in the way suggested in the preceding paragraph.

Regulation of Normal Growth.

A stimulus to growth results in the transfer of additional unstable energy to the cell. The process presumably begins with a change in the cell membrane, either by physical action or by the adsorption of some constituent in the plasma. The result is an increased permeability or conductivity of the cell for the entrance of the chemical components or physical influences which provide the new energy. It is to be noted that the response of the cell membrane to the stimulative influence implies that the cell has exercised a selective activity, since different types of cells do not react alike towards the same stimulus.

Conversely, inhibition of growth, *i.e.*, the action of a restraining influence on a cell otherwise capable of growth, implies action on the cell membrane which decreases permeability or conductivity and thereby prevents the transfer of energy requisite for growth. Here, again, response to this influence involves a selective action on the part of the cell.

In the above conditions, extrinsic and intrinsic factors are of equal importance, growth or inhibition being dependent partly on the environment and partly on the cell. When a normal cell shows no tendency to growth, this condition also depends on both extrinsic and intrinsic factors; but there is no reason to assume that cells are always being bombarded by two conflicting forces, the one stimulative and the other inhibitory, and that quiescence is only obtained when these two forces neutralise each other. Adaptation to environment is all that one need postulate here about the cell's attitude towards the extrinsic factor; there is no cause for appealing to any sort of forceful "regulation." The point is that, apart from growth, the individual cell is often in a condition of partial autonomy and to a large extent regulates its own activities. This attribute of partial autonomy is an important characteristic of quiescent, normal cells in a multicellular organism and will be worth bearing in mind when considering the much greater degree of autonomy possessed by malignant cells.

This discussion of extrinsic and intrinsic factors is intended to lead up to a consideration of the frequently made statement that normal cells possess an inherent capacity for unlimited growth. This assertion is only true in a partial and unimportant sense and is apt to be misleading when these limitations are not made clear. A tissue culture may remain perfectly vigorous after propagation for a number of years; so there seems no reason why its growth might not be carried on *ad infinitum*. Quite so; but the growing cell does not make its own sources of energy; material for this has to be provided, and the medium has to be such that transmission of energy from the surface into the interior of the cell will be facilitated. So unlimited growth is really dependent on extrinsic rather than on intrinsic factors. Neglect of this point, the requirement for energy, leads to an exaggerated importance of the inherent growth-impulse, with the implication that growth would necessarily run to excess if this impulse were not under constant restraint.

Then there is the contrast between the free growth of cells *in embryo* and their highly restricted growth in later life. The outer membrane of the embryonic cell is particularly well adapted for the reception of unstable energy; as growth advances, this membrane is modified by its environment and receptivity is diminished. This change cannot be satisfactorily described as due to acquirement of control over the intrinsic factor alone (the inherent growth impulse), as this factor is only partially responsible for embryonic growth. Here, again, regulation of growth must take into account regulation of the transmission of energy from the environment to the cell.

Similar considerations apply to stimulation or inhibition of growth by internal secretions (real or hypothetical); they act, primarily, by altering the cell's facilities for obtaining energy rather than by direct modification of the cell's inherent tendency to growth.

I have called attention to the above points because I think they are often overlooked in the literature on cancer, with the result that undue importance is attached to the capacity for unlimited growth.

Premature Application of Immunological Principles.

There can be no question about the existence and the high importance of principles regulating growth. I have been insisting on their relation to the cell's supply of energy because I think that this aspect ought to come first, on physiological grounds. I now come to the distinction between regulation of growth and immunity. "Immunity," I agree, is an elastic term which ought frequently to be stretched beyond the limitations of the orthodox serologist; but I do not think it is a sound plan to make "immunity" the dominant idea in explanation of regulated growth. To illustrate my meaning, I propose to give an example of what I regard as a premature application of immunological principles.

The malignant process is a deviation from the normal; then what is the normal condition in a person who lives to old age without developing malignant disease? In the normal body, according to the type of theory I have in mind, minor disturbances attributable to some form of irritation occur frequently throughout life and cause irregularities of growth amongst small groups of cells. Some of these growths would become malignant if they were not checked by a systemic influence, termed "natural immunity," analogous to another kind of natural immunity which protects the body from invasion by many species of bacteria. In relation to bacteria, the protective mechanism cannot be explained in detail; no specific antibodies are demonstrable and there is often no reason for supposing that the immunity has really been "acquired" by subinfective doses of bacterial antigen; natural immunity is simply a fact which must be accepted as such. Similarly with cancer, the protective mechanism is a natural property of the body and is "non-specific" in the sense that it has not been manufactured in response to the stimulus of cancerous material. Without this natural protection, everybody would die of

cancer unless death from this cause was anticipated by some other fatal disease. Cancer develops when this "natural immunity" is weakened. Its efficacy differs in different individuals and under different circumstances, just as one person may be less highly resistant than another towards a particular strain of bacteria; and the more resistant persons may succumb if some circumstances have delayed the initial reaction of resistance and so allowed the malignant focus (*cf.* bacteria) to gain a firm foothold. The prophylactic and therapeutic problem is to reinforce this protective mechanism.

This type of theory is sometimes elaborated in much greater detail. Sometimes it is not elaborated at all but is put forward for acceptance under the guise of "natural resistance," proof of which is thought to be amply afforded by such simple facts as deaths in old age without cancer and by observations on the resistance of experimental animals to grafting or tarring. In other cases the term "natural resistance," as used by many writers, does not imply acceptance of any particular general principles; it seems to be no more than a convenient way of expressing certain observed facts and it is doubtful whether the authors have any intention of making it the basis of an "immunological theory" of cancer.

I think that cancer investigators might help to clear up this ambiguity. "Immunity," as understood by bacteriologists, means a reaction on the part of the body to foreign protein, living or dead. It may, in the accepted terms of immunology, be "natural," "acquired," "specific" or "non-specific"; so the word "immunity" has been given a generous degree of elasticity. But it has never been intended to include all forms of what may be legitimately called "resistance"; and the use of the two words as interchangeable is the cause of much confusion.

As regards the frankly "immunological" theory which I have outlined, the postulate that minor disturbances readily and frequently convert normal into malignant cells appears arbitrary; it is not supported by experimental work, which shows, on the contrary, that special interference of one kind or another is needed to make a cell acquire malignant characters; still less is there any theoretical justification for the idea that normal cells have a spontaneous tendency to malignancy. Hence I see no support for the second postulate that the supposed malignant foci are suppressed by a mechanism which is analogous to natural immunity towards bacteria.

"Immunity," then, is used in a quite special and peculiar sense; it really means some unknown factor, x , which tends to inhibit malignant growth. Apart from the misleading nomenclature, it does not seem to me that this special x is helpful; everything is referred to x , but this merely amounts to "explanation" in terms of the unknown. This procedure is very different from the "vitalistic" conceptions to which the physiologist frequently resorts. These are admittedly vague, because the causes of vital phenomena are to a large extent unknown; but they do refer to accepted facts. The postulate of a special kind of inhibitory factor in relation to malignancy does not.

Recognition of this distinction will remove confusion and will help to clear the ground for a due appreciation of the systemic influences which regulate normal growth.

The Latent Period.

A striking feature about the abnormal course of events, initiated by some form of extrinsic or autogenous irritant, is that there is usually a latent period which may persist for a remarkably long time. Clinical experience does not support the view that a process of irritation must be maintained throughout this interval. Human cancer may not become manifest until long after the disappearance of an irritant which is known to have had a causative or predisposing influence. And, in cancer produced experimentally, treatment by the application of an irritant may have been suspended for some months before the earliest appearance of the disease. The latent period, during which there is no recognisable continuity of irritant action, is too important to be dismissed as accidental; there must be some reason for it.

Delay may be necessary in order that the cells which are to become cancerous may lose their capacity of response to the systemic influences which would check the growth of normal cells.

On this view, when the primary irritation subsides it is followed by a period of partial stagnation, during which local products of metabolism are not freely carried away into the general circulation. In such circumstances, local growth is determined by local rather than by systemic conditions. Growth is restrained, in general, when the cell membrane adsorbs local products which diminish its permeability; and the cell is quiescent when there is a local equilibrium between its surface and its environment. During partial stagnation, the cell is trained to respond to local conditions rather than to systemic influences. It produces on its surface (*a*) chemical groups which respond to local influences and does not produce, (*b*) the somewhat different chemical groups which would react with a normal systemic inhibitory influence. Eventually, prolonged disuse of a function—the production of (*b*)—results in its complete loss. Evidence of this loss will not be forthcoming whilst the latent period persists; but if the local stagnation is removed, owing to some fresh inflammatory reaction, and the environment is now changed into one favourable for vigorous growth, with free access to the general circulation, the modified cells will be liberated from their local restraining influence and will be incapable of response to systemic inhibition.

These assumptions involve recognition of the difference between (1) change in the character of a systemic influence which is normally inhibitory to growth, and (2) *acquired incapacity to respond to normal systemic inhibition*. Here (2) is postulated but not (1). The inhibitory influences persist in the general circulation and behave in the normal way towards all growing cells except the particular group or groups referred to. The initial change predisposing to unrestricted growth will then be purely local, not systemic. This seems to me

more satisfactory than postulate (1), which is difficult to reconcile with two important facts. The effect of the change is strictly local; if its cause were systemic, one would expect a more general tendency to unrestrained growth. And it is agreed that the general systemic conditions in old age tend to diminish cell growth; but old age is the period when liability to cancer increases.

To judge from the literature on cancer, sufficient attention has not been paid to the significance of the latent period, particularly in regard to the parts played by local and systemic influences during this phase in the development of the disease. I think that the application of deductions made from conditions observed when the disease has become definitely established can only lead to confusion. Here I am confining myself strictly to the preparatory stage of causation, where I think there is good ground for holding that the alteration to which I refer is produced by a local and not by a systemic cause, and that the change consists in an acquired incapacity to respond to a particular systemic influence.

Displacement in Foetal Life.

In relation to the significance of the latent period there is an interesting class of tumours which raise the question whether displacement of tissue *in embryo* is a predisposing cause of malignancy.

During embryonic development, small groups of cells are frequently displaced and may be carried a considerable distance from their original site. These aberrant cells are useless in their abnormal environment and generally disappear early in post-natal life. It is only in rare instances that they survive and, after many years of quiescence, develop into a malignant growth bearing the cellular characteristics of derivatives from the parent organ.

As an example, I may mention a case which I described and discussed in 1902¹. A tumour, together with uterus and ovaries, was removed from a woman aged 48. On histological examination I found that it exhibited the typical characters of malignant suprarenal tissue. It was firmly adherent to the fundus uteri but was separated from it by a well-marked capsule. Uterus and ovaries were normal both to the naked eye and histologically. No abnormalities were found elsewhere at the time of operation. The case was remarkable owing to the situation of the tumour, though it is well known that aberrance of suprarenal tissue is very common in the early stages of development, and that such fragments may be found descending towards the pelvis along the course of the spermatic or ovarian veins and within the layers of the broad ligament.

What is the condition of this displaced tissue, in the earlier stages, when it survives and whilst it remains quiescent? Its behaviour is not in any respect "embryonic," and the retention of this title is only justified as an indication that the displacement occurred *in embryo*. The cells are just as much "adult" as are those of normal, quiescent tissue in any part of the body. These aberrant tumours lend no support to the old theory that all malignant growths are derived from cells possessing embryonic characters and that these attributes have been retained from the period of ante-natal life. Appeals are still some-

¹ *Trans. Path. Soc. London*, 53, Pt. II, p. 153.

times made to an "embryonic" theory of causation, but I do not think that they are helpful. An ordinary embryonic cell is not a malignant cell and it is misleading to apply to the latter a word which is appropriate only to the former. Just as one may postulate an unknown extrinsic factor, x , which prevents cells from becoming cancerous, so one may imagine an unknown intrinsic property, y , to be the inherent capacity for malignant growth. Then normal growth can always be referred to x and malignant growth to y . But these appeals to the unknown do not make for progress. The "embryonic" postulate is really no more than an appeal to y .

There may be said to be two opposite views as to the significance of this displacement of tissue.

(1) The tissue may, owing to its secluded position, behave like adult cells which have been placed in a strange environment as the result of a process of chronic irritation. It may lose, through many years of disuse, its faculty of responding to systemic inhibitory influences. Then a disturbance of environment which stimulates growth will find this tissue in a condition already predisposed to malignancy. The events which took place *in embryo* may thus be regarded as the commencement of the preparatory stage or latent period.

(2) In the very large majority of cases, the displaced tissue either dies out or remains perfectly harmless. This shows that displacement does not suffice to initiate malignancy. The malignant process is usually started much later in life and begins with chronic irritation acting upon cells which, though aberrant, are, to begin with, perfectly normal in relation to systemic influences. The initial displacement has had nothing to do with subsequent malignancy.

Perhaps the truth lies half-way between (1) and (2). Lengthy survival of the displaced cells may not suffice as a preparation for malignancy, *i.e.*, it may not be equivalent to the latent period following chronic irritation. But it is known that some tissues of the body are more susceptible to malignancy than others. This lengthy period of isolation may have had the effect of increasing the susceptibility of the tissues concerned. They would therefore be less liable to make a normal recovery if exposed to chronic irritation, *i.e.*, they would more readily lapse into the condition characteristic of the latent period which predisposes to malignancy.

Susceptibility to the Precancerous Change.

As individuals differ in their susceptibility to particular irritants and in their mechanism of reaction, it is to be expected that they will differ in susceptibility to some of the irritants which are a factor in the causation of cancer. There is ample evidence that this is the case.

In animal experiments on the production of cancer, differences of susceptibility under identical experimental conditions are often well-marked, and in the same species of animal some organs are more susceptible than others. It has also been shown in animal cancer that differences in susceptibility may be enhanced by selective breeding.

As examples of selective susceptibility to foreign irritants, one may mention the production of squamous carcinoma by tar, tumours of the bladder by anilin oil, carcinomata by some parasitic worms and sarcomata by others.

In relation to obscure and presumably autogenous irritants, there may be a selective predisposition on the part of mammary cells, uterine mucosa, squamous epithelium, connective tissue, and so forth. Or perhaps it is more correct to say that the predisposition resides not in individual cells but in particular sites, since the development of the precancerous state of the cells will depend on their environment.

In the above statements, which I think will be accepted without demur, it is implied that certain tissues are insusceptible, or relatively insusceptible, to particular influences; but it is not implied that such tissues are the site of vigorous reactions which may be regarded as "anticancerous." Lack of susceptibility does not necessarily involve active resistance.

Much confusion has been caused in the literature of cancer by the use of the word "resistance" in different senses, the three commonest being resistance (1) to the genesis of the disease, (2) to established, autogenous malignancy, and (3) to the growth of malignant tissue transplanted from another animal. Even when these differences are frankly admitted by the writers, it is often found that relatively little importance is attached to them; and not infrequently there is a free transition from one meaning to another which is responsible for a good deal of obscurity. It has not been proved and it ought not to be assumed that there is a common factor underlying these three expressions of resistance.

Here I am referring only to (1) and only to the initial stages of (1). In this connection one must consider carefully what is meant by "resistance." One may say that the cells of a normal animal respond to systemic inhibition and that the initiation of the precancerous stage is prevented so long as normal inhibitory influences continue to act upon all actively growing cells. In this sense, it may be conceded that the normal body possesses a certain degree of natural resistance towards the preparatory stage of malignancy. But it is of essential importance to recognise that the deviation from the normal occurs not in the systemic influence but in the cells which previously responded to it. In this connection, therefore, the idea of "resistance" as a humoral or systemic property, with varying degrees of intensity, is misleading and should be replaced by the conception of "insusceptibility," in greater or less degree, as a cellular property. The more insusceptible cells are those which, when subjected to chronic irritation, do not readily lose the equipment which enables them to respond to systemic inhibition. The more susceptible cells are those which are more liable to lose this property.

Confusion arises, as I have pointed out in discussing "natural immunity," from misleading analogies with bacteria. Susceptibility or resistance of the animal body towards foreign micro-organisms actually *in situ* cannot be compared, in this simple fashion, with its attitude towards the conditions which

may convert its own normal cells into malignant variants, though, as I shall suggest in a later section, there are other ways in which data derived from bacteriology may furnish suggestive analogies.

THE CRITICAL STIMULUS TO MALIGNANCY.

Cellular Rejuvenation.

In the first place, my hypothesis postulates the following sequence of events. One starts with cells in their normal condition (*a*) and in their normal environment (1). Chronic irritation changes the environment into (2), which, during the latent period, changes the condition of certain groups of cells into condition (*b*), the precancerous state. A subsequent change (3) in the character of the environment stimulates active growth; its effect is to change the condition of those groups of cells from (*b*) to (*c*), the condition in which they take on active growth with incapacity to respond to systemic inhibitory influences.

Up to this point, analysis of the conditions may be taken as referring alike to the causation of both innocent and malignant new growths. The important difference between the two seems to depend on the nature of condition (*c*). With the former, the change to (*c*) is a rejuvenescence after the semi-starvation of the latent period and is associated with partial reversion to (*a*); with the latter, this change involves a wide departure from (*a*), leading to a degraded and definitely abnormal type of cell.

I think this distinction is of primary importance and I disagree with the view that innocent and malignant growths are to be comprised within the same pathological group or to be regarded as manifestations of the same process. It is true that malignancy not infrequently supervenes in a tumour originally innocent; in ovarian new growths, for example, I have occasionally found definitely innocent and definitely malignant tissue in sections from the same tumour. But the characters of the cells are essentially different. The change to malignancy cannot be explained by a natural or inherent capacity of a rapidly growing cell but demands an extrinsic influence which converts the cell into a variant, possessing characters which are not found in the rejuvenated cells of the innocent tumour. All that can be conceded is that, owing to its irregular and disorderly growth, the tissue of an innocent tumour is more susceptible than normal tissue of the same type to the initiation of those further changes which lead to malignancy.

What, then, is to be said about the further conditions which are requisite for the production of the malignant variant?

The Malignant Variant.

The cause of that more profound change which constitutes malignancy is the mystery about which nobody can offer more than conjectures. The field for speculation is wide and indeterminate. There are two lines of thought which, in my opinion, are unpromising, though there is no likelihood that they

will be abandoned. One is the theory of the invisible and more or less ubiquitous virus. The other is the idea that certain cells have an "inherent tendency" to malignancy and will become malignant if "freed from restraint" or surrounded by an environment which favours their growth. I think that those who are prepared to reject these two ways of explaining causation will find that the ground is then cleared for presenting the problem in a more hopeful form.

In giving more definite shape to the conditions requiring explanation, probably no two persons will express themselves exactly in the same way. The main features, as they appear to me, are: (1) there is an extrinsic cause which is autogenous and is created *de novo*; (2) this agent is highly specific for specially predisposed cells and produces an intrinsic change in them; (3) the cause disappears after the change has been effected, and the cells are left with the property of transmitting their new condition from generation to generation.

These three events are all compatible with what is known about vital activities; so the problem of explanation is at once brought into range with the general subject of biological variation. It is always possible that analysis of the conditions which determine variation in other kinds of cells may throw some fresh light on the malignant variant.

As regards the last, I have stated the position in a way which, to my mind, indicates that some peculiar kind of selective action is a necessary part in the process. Reactions of the antigen-antibody type form the best examples of highly selective activity which is created *de novo*. One does not expect to find them in the perfectly normal body, when no "foreign" element has been introduced parenterally to play the part of antigen. But pathological conditions, it is admitted, may change the character of selective reactions which normally took place; and it does not seem impossible for abnormal substances, though produced autogenously, to function as antigens in their own host.

If one examines more closely the conditions under which this development of anti-substances, or specific reactive agents towards constituents of the body itself, may occur, it appears, in the first place, that the local condition of the capillary endothelium is a factor of importance. In the latent period this adjacent endothelium may be liable to modification by adsorption of material derived from the modified cells which are conveniently called "precancerous," though a tumour subsequently developing from them may not necessarily be malignant in character. If, however, this endothelium is modified in the way suggested, it will be capable of modifying the plasma which passes through it; in immunological terms, the adsorbed material may act as an antigen and may produce in the plasma an antibody selective for the "precancerous" cells. Whilst the latter cells are quiescent and their environment remains in a condition of local stagnation, nothing happens; but, when they are stimulated to active growth under the influence of a new local inflammation, free access of the plasma with its locally acquired antibody may act upon these cells as a selective stimulus to variation. The stimulus may behave like an anaphy-

lactic reaction of "reversed" type, *i.e.*, a union between circulating antibody and antigen present on the surface of the "precancerous" cells. The result of the "shock," which may be conceived as a sudden liberation of unstable energy, is to effect a radical change in the cell's chemical constitution.

Whilst the primary mechanism of the critical change must be left as a matter for conjecture, the immediate results of it may be discussed with a little more confidence.

The immediate effect of the critical reaction which takes place at the surface of the cell is that the cell's permeability is increased. This is in accordance with the view, which I think is fairly well accepted, that the permeability of malignant tissue is greater than that of normal cells. The consequence is that, on the initiation of the changed permeability, chemical components which were previously excluded make their way into the interior of the cell and are dealt with by the cellular mechanism which has been modified by the critical or "shock" reaction. One feature of this change is probably a process of "cannibalism," *i.e.*, the precancerous cell is now enabled to feed on the disintegrated protein of dead, normal cells in its environment and to reconstruct this material into a new type of cellular equipment. Then the fully fledged cancer cell perpetuates its own characteristics as regards permeability and internal organisation, whilst it may retain the "cannibalistic" habit when growing in the living body, *i.e.*, the habit of utilising, as food, protein derived from normal cells of its own animal species.

For evidence of the profound change in internal organisation which differentiates the malignant cell, it will suffice here to mention two obvious facts. The capacity to form metastases distinguishes it from other cells which only exhibit a tendency to localised, excessive growth. And the general histological characters of malignant cells are distinctive. They are not "embryonic" but, as contrasted with non-malignant cells, they may be described as "immature" and they are generally more perishable than normal cells. Probably the reason for their immaturity is that the balance between catalysis and synthesis which regulates normal growth has been disturbed. As compared with the normal, the cancer cell subdivides prematurely, before firm synthesis has been accomplished. The balance between catalysis and synthesis is new and abnormal, though just sufficiently stable to enable the cancer cells to produce viable offspring.

Distinction between Cause and Effect.

On this hypothesis, the stimulus which produces the malignant variant changes the conditions under which, in the economy of the growing cell, the catalytic enzyme activity is subordinated to the process of synthesising the material prepared from substrate. In the cancer cell, the change results in less effective synthesis and an important consequence of the alteration is a change in the character of the enzymes themselves. New enzymes appear which are able to break up normal cells into material suitable for synthesis. A still more

conspicuous feature about some of the new enzymes is that they derive energy from glycolysis, *i.e.*, carbohydrate is split up without the aid of oxygen and yields lactic acid as the final product. This is in marked contrast to the behaviour of normal tissues, which cannot survive without oxygen and break up carbohydrate by a pure oxidation process into carbon dioxide and water.

Whilst recognising the importance of recent discoveries about enzymes peculiar to malignancy, one must not confuse cause with effect. The new enzymes are the consequence of the cancerous change, not its cause. Their detailed investigation is admittedly of great interest, but it does not help to explain the biological change which is the origin of cancer. It has been suggested that some local chemical condition, such as oxygen deficiency, is the primary cause, the consequence being that only those cells which have marked glycolytic capacity can survive and produce a malignant growth. This reminds one of the old embryonic theory, with which I do not agree. It postulates that certain cells retain, for some unexplained reason, an inherent capacity for malignancy, *i.e.*, for growth under chemical conditions which are impossible for the majority of normal cells. It seems to me that the capacity must be regarded not as inherent but as acquired at the onset of the malignant change.

The distinction between cause and effect must also be remembered in dealing with possible modifications of "virus" theories, when the conception of an enzyme is substituted for that of a virus. The idea of a virus as a living agent, foreign to the body, is readily understood, whether one agrees with it or not; it is put forward definitely as the cause of malignancy, or as an essential part of the cause, and there is no danger of its being confused with the consequences of malignancy. But if one goes on to suggest, first, that the "virus" is really an enzyme which propagates itself out of substrate and, secondly, that the enzyme is not derived from external sources but is autogenous in its origin, then the question of causation assumes a different aspect. The proper view, it seems to me, is to regard the local factors which gave rise to the enzyme as the cause and to treat the enzyme itself as one of the effects of the malignant change.

ANALOGIES FROM BACTERIAL VARIATION.

The Cancer Problem not Unique.

In trying to understand the change from a normal into a malignant cell it is some consolation to realise that equally puzzling mysteries are encountered in the field of bacterial variation. Changes in the direction of degradation may perhaps be explained in a relatively simple way as loss of bacterial equipment due to growth in adverse environment; it is the acquirement of fresh characters which presents the main difficulties, the conversion of a harmless saprophyte into an invasive parasite, the origin of epidemic virulence, the qualitative change of virulence in relation to particular animal species. Satisfactory explanations, when forthcoming, may throw some indirect light on the cancer problem.

Both with bacteria and with animal cells, variation is due to some subtle change of cellular constitution, which may arise from conditions, not altogether dissimilar in the two cases, involving a complicated succession of interactions between the cell and its environment. The matter cannot be simplified by ascribing the change to a special physiological agent, such as an invisible virus or an enzyme; an explanation of this sort seems to me equally untenable for the acquirement of new bacterial characters and for the production of the malignant variant.

Loss of Function.

Bacteriologists are familiar with loss of a function, *e.g.*, virulence or capacity to form a protective capsule, owing to disuse or relatively long exposure to an unfavourable environment. Something analogous seems to occur in the latent period preceding malignancy. The cells which are becoming "precancerous" lose the capacity to form on their surface the chemical attributes which would enable them to respond to a systemic inhibitory influence. This, it seems to me, is a more reasonable explanation than the postulate that the systemic influence disappears or is neutralised in some mysterious way.

I do not think that this analogy is vitiated by the fact that the consequences of loss of function are dissimilar in relation to capacity for growth. The conditions under which growth is possible are different. The degraded animal cell in its normal host is capable of becoming virulent or invasive because it is insusceptible to a restraining influence and also because its increased permeability facilitates acquirement of energy. The degraded bacterium is found to be avirulent because it has lost the protection of its outer membrane which is requisite for its survival and growth in the animal body. So the analogy may still hold, though loss of a certain equipment favours virulence in the former case and is detrimental to it in the latter.

With bacteria, loss of some attribute may be a preparatory stage towards the acquirement of a new property. It seems as though the fully equipped micro-organism cannot acquire something new *per saltum* but must first pass through a preliminary phase of degradation, as evidenced by the loss of some function. This implies that the internal organisation of the cell must first be disturbed before it can be reconstituted in a new way. Similarly, the change in the precancerous cell of the latent period may not be confined to loss of an attribute (responsiveness to systemic inhibition); a partial disturbance of the internal organisation of the cell may also be involved, thus facilitating a reconstitution of this organisation when the critical stimulus to malignancy supervenes, a stimulus which, I have suggested, may possibly be comparable to an anaphylactic shock.

Acquirement of Function.

To begin with, certain bacteria are growing in the saprophytic condition (*a*) and their environment is the surface of a normal, or relatively normal, mucous membrane (1). The character of this environment is then changed to

that of a congested or otherwise abnormal mucous membrane (2). This new environment (2) modifies the permeability of the bacterial surface and thereby leads to internal changes which modify the constitution of the bacteria and affect their capacity for synthesis, the result being the production of a less saprophytic type (*b*), which is more or less capable of assimilating the unstable energy available from living material. Then the first steps of bacterial invasion take place and their environment is changed to living tissue (3). Bacteria in condition (*a*) would perish in (3), but when they are in condition (*b*) they are capable of survival. Perhaps they at once adjust themselves to (3) or, more probably, under the influence of (3) their condition is modified from (*b*) to (*c*), which is still more completely adapted to (3). The cycle of changes may in reality be much more complicated; the main point is that it is due to a series of events, not to a single causative substance.

The above scheme, I think, provides a rough resemblance, though not in every point of detail, to what may be imagined as being the evolution of a tumour cell (not necessarily malignant). It is due to a long series of events, not to a single factor, "freedom from restriction," however prominent this characteristic may be in the final stage.

There is another aspect of bacterial activity which is still more suggestive, the production of local immunity. The example of this condition which is usually quoted is the production of localised lesions by staphylococci or streptococci. After passing through an inflammatory reaction, the infected sites make a complete recovery and are then found to be highly resistant to re-infection; that this resistance is local and not systemic is shown by the fact that fresh sites become infected from time to time. The accepted explanation is that antibodies are produced locally in the infected areas.

I have suggested above that the critical stimulus to malignancy may be due to a local immunity reaction. The precancerous cells of the latent period may be compared to the cocci which are capable of evoking antibodies *in situ*. The results, of course, are different. The immunity reaction does not invest the cocci with a new function but inhibits them; in the other case, it causes the precancerous cells to acquire the new function of the malignant variant.

In his work on the rejuvenation of pneumococci which had become "rough" and avirulent, F. Griffith has shown¹ that restoration of virulence and "smoothness" can be effected by inoculating mice with the degenerate strain together with killed culture of a virulent strain. The special feature to which I call attention in the present connection is that he has produced something more than a restoration of virulence; the Type characters of the rejuvenated strains were not necessarily (*a*) the same as those possessed by these strains prior to degeneration, nor were they necessarily (*b*) the same as those of the killed, virulent strains which assisted in the rejuvenation, though they were always either (*a*) or (*b*). Thus a pneumococcus, as well as re-acquiring virulence, can also develop new Type characters. There are two other points to be noted. In

¹ *J. Hygiene*, 27, 113, 1928.

order to initiate the change, the growing pneumococcus behaved as a "cannibal," *i.e.*, it required killed, non-degenerate pneumococci as food material or as adjuvants for the construction of its new equipment. Growth *in vitro* of the degenerate strain together with killed virulent culture produced no change in the former; the experiments were only successful *in vivo*, *i.e.*, the change was only accomplished when there was a supply of unstable energy which is only obtainable in the living animal body.

Simple rejuvenation of pneumococci (restoration of virulence) may be compared to the change, taking place at the end of the latent period, which gives rise to an innocent tumour. Change of pneumococcal Type involves a more profound modification of bacterial constitution; and a still more definite creation *de novo* is involved when a precancerous cell becomes truly malignant. "Cannibalism," aided by the unstable energy available only *in vivo*, seems to be requisite for this change in both instances, though, with the bacteria, its continuation is not requisite after the change has been initiated.

It is a curious and interesting fact that growth of micro-organisms in the animal body sometimes results in loss of virulence for one animal species together with gain of virulence for another species. This is another example of modification which is more radical than mere rejuvenation; it results in a fresh equipment of the cell which is qualitatively different from the previous equipment.

Perhaps capacity of the malignant cell to form metastases is evidence of a similar radical change. The critical stimulus to malignancy, arising from abnormal conditions of growth, has altered the relations of the cells to their host, *i.e.*, they have acquired an invasive property which they did not possess previously.

DISCUSSION.

In a preliminary note on immunology and malignant disease¹, I started with acceptance, in general terms, of what is currently known as the "chronic irritation" theory, but went on to point out that its adherents differed widely in their detailed interpretation of it. There was much diversity of opinion about the nature of resistance to the onset and to the progress of malignancy; and the discordance was still more marked when one came to the question of applying to malignancy immunological principles expressed in terms of antigens and antibodies. These opinions could not all be sound; but I wished to avoid adverse criticism, because there was no clear basis for a settlement. In this preliminary survey I merely attempted to broaden the outlook by calling attention to the discrepancies. It seemed desirable that individual investigators might help each other by explaining more fully not only their own ideas about immunological principles but also their reasons for dissenting from the more important alternative views which others had put forward. Differences of opinion might then assume less irreconcilable attitudes and the way might

¹ *J. Hygiene*, 24, 255, 1925.

be paved for a more constructive type of criticism, leading to gradual abandonment of claims which could not be substantiated.

On returning to this subject now, I still accept the "chronic irritation" theory and do not think that its validity has been shaken, as regards mammalian malignant disease, by recent attempts to discover a filter-passing virus. But work on the latter type of theory must be recognised and appreciated as a persistent and concentrated effort to explain causation. It serves as a reminder, if not as a reproach, to believers in "chronic irritation" that they should make equally strenuous endeavours to explain causation from their point of view. The postulate of a mysterious perversion of metabolism following chronic irritation is not enough; effort must be made to penetrate the mystery, at least far enough to provide some sort of reasoned explanation. In the present article I have confined myself to this question.

In concentrating on this problem of causation, it is impossible to preserve an attitude of easy tolerance towards the many individual differences of opinion expressed by upholders of the "chronic irritation" theory. It is necessary to attempt the development of a consistent line of thought and this must involve frequent rejection of ideas which appear to be incompatible with it. In taking this course, one has to make arbitrary decisions, whilst remaining conscious of the fact that the subject is too full of obscurities to justify dogmatism, and that an apparently unsound working hypothesis may, incidentally, lead to a useful experimental discovery.

It is easy to emphasise the dangers of arguing back from effect to cause, *i.e.*, from the conditions found in the established disease to the conditions which initiated it. But the cause, in this case, is highly mysterious; one must think of the effects in order to form some idea of what the cause is likely to have been. At the same time it must be recognised that, in many instances, interpretation of an effect as a cause has undoubtedly been a source of confusion. On this matter each writer must adjudicate for himself; he will accept some data as throwing light on causation and will reject others. And, whatever his decision may be on any particular point, he must be prepared to find that there are some dissentients.

Another matter about which every writer on cancer theories has frequently to make a decision is the value of analogies taken from other fields of immunological enquiry. If actual discoveries relative to the malignant process were sufficient for the erection of a substantial theory, analogies could be dispensed with. But, as this independence is not yet within sight, the provisional hypotheses which have to be utilised are frequently borrowed from other sources where there has already been a copious output of immunological work. Such analogies may be either helpful or inappositive or actually misleading. The writers have to discriminate and must be fully aware that there are certain to be some authorities who are not prepared to accept their decisions.

Much has been borrowed from the branches of immunology which interest the bacteriologist. Here it is obvious that there is necessity for caution and

discrimination, partly because the conditions of bacterial life are very different from those of animal tissues and partly because there is great uncertainty about immunology in relation to bacterial growth, which is the aspect where helpful analogies are most likely to be found in relation to the problems of malignant neoplasms. Some cancer investigators make the mistake, in my opinion, of borrowing immunological principles too freely and of taking too much for granted about their validity.

I am not suggesting that the cancer worker should disregard the bacteriological side of immunity. On the contrary, I think it would be advantageous if he became more closely acquainted with it, just as it would be helpful if more bacteriologists took a serious interest in the cancer problem. It is not desirable that the two sets of investigators should work in "water-tight compartments." They have much ground in common, particularly as regards the causes of variation in cells which reproduce themselves asexually.

SUMMARY.

Invisible infective agents may be divided into: (1) true, ultramicroscopic, living viruses, which do not arise *de novo* and, so far as is known, are not ubiquitous; (2) transmissible infective agents which arise *de novo* and are propagated through living cells, but are not themselves living organisms; (3) stimulants to variation which arise *de novo*, are not transmissible, and are not living organisms.

Class (1) is not represented in malignant disease. "Bacteriophage" is a representative of class (2); very probably the infective agent of fowl sarcoma comes under the same category, and possibly some important human diseases of doubtful aetiology. There is no satisfactory evidence that mammalian malignant disease is related to class (2); its causation, according to the "chronic irritation" theory, must be attributed to influences comprised within class (3).

The stimulants to variation in class (3) depend for their effectiveness upon the unstable energy of living matter. The changes which they produce are "biological" in the sense that they are changes of chemical constitution which could not be obtained without the aid of vital processes.

Regulation of normal growth in the animal body means regulation of the cell's facilities for obtaining energy. I think it is misleading to regard it as a forceful restraint (or stimulus) upon the cell's inherent capacity for unlimited growth.

The assumption, borrowed from "natural immunity" towards bacteria, that there is in the animal body a natural principle which destroys frequently occurring foci of incipient malignancy is also unsubstantiated and misleading.

During the latent period, certain cells, which subsequently grow into a neoplasm, lose their capacity to respond to inhibitory systemic influences. This change is brought about by local and not by systemic causes.

As regards the special class of tumour derived from cells which have been displaced in foetal life, long residence in an abnormal situation does not appear

to be equivalent to the ordinary latent period; but it may have had the effect of increasing their susceptibility, so that, if exposed to chronic irritation, the cells would more readily lapse into the latent period predisposing to malignancy.

It is known that the various tissues of the animal body differ in their degree of susceptibility to the precancerous change. This is a cellular characteristic; so also is the difference in the susceptibility of one animal as compared with another. It is not a question of difference in a hypothetical humoral property of "systemic resistance."

On the termination of the latent period by a fresh stimulus to proliferation, certain cells commence active growth and are incapable of responding to systemic inhibitory influences. These conditions seem sufficient for the origin of an innocent neoplasm. But something more is required to explain malignancy, because the malignant cell is essentially different from the cells in a benign tumour.

About the actual cause of the change to malignancy one can only offer conjectures. I have suggested a way in which the change may possibly be produced through the agency of the local endothelium and the autogenous formation of antibodies.

On taking a broad view, the change into the malignant variant is not something unique; equally remarkable changes are to be found in the properties of bacteria. In both cases the facts have to be accepted, at present, without satisfactory explanation of the conditions which gave rise to them. One finds with bacteria that degradation or "roughness" may be a phase preparatory to the acquirement of new properties, just as the degradation of cells in the latent period seems to be a requisite preparation for acquiring the new property of malignancy. But the actual steps involved in the change from a bacterial saprophyte to an invasive parasite are as difficult to understand as are the processes involved in the conversion of a normal animal cell into its malignant variant.

Throughout the study of cancer it is very desirable to maintain a clear distinction between cause and effect. For example, the enzymes peculiar to cancer are not the cause of cancer but the effect of the biological change which produced the cancerous cell.

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