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SYSTEMIC INFLUENCES IN IMMUNITY AND CANCER.

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CONTENTS.

INTRODUCTION.

IN continuation of my previous articles[1] on the cancer problem and its relation to general principles of immunology, I propose now to discuss the nature and significance of systemic influences.

First one must form some ideas about them as they exist in the normal body, irrespective of the possible incidence of any pathological condition. The normal mechanism comes first and, whatever changes may be superimposed on it in the course of reaction to abnormal events, it persists throughout life as the essential machinery in the activities of the plasma and the cells which it bathes.

Then it will be desirable to consider systemic influences where normal conditions have been disturbed by some known extraneous agent, as in bacterial infection. What is their significance in natural immunity, in acquired immunity, and in non-specific resistance?

These considerations may then be compared and contrasted with evidence as to the nature of systemic influences in cancer[2], where, according to the view which I support, the essential cause is autogenous. Is cancer due to interference with the systemic influences which regulate normal growth? Is there

[1] *J. Hygiene*, **24**, 255–273 (1925); **28**, 9–32 (1928); **29**, 117–131 (1929).

[2] Throughout this article I use "cancer" as equivalent to "mammalian malignant disease."

a special and abnormal systemic factor which is requisite for the production of malignancy? Though cancer is local in origin, is its incidence due entirely to local causes or to the combined influence of local conditions and systemic factors? These are some of the questions which are constantly being raised; but the answers provided are diverse and often irreconcilable. Some reconsideration of the subject is needed, because the postulate of a systemic influence which does not exist might be as dangerously misleading as the postulate of an unknown virus.

Normal systemic influences.

Distinctive factors.

(1) *Chemical entities.* In one respect the plasma may be regarded as a medium containing distinctive chemical products, which react as such towards the tissues with which they come into contact. The internal secretions which have been investigated by physiologists may be taken as examples. It is often possible to attribute particular systemic influences to the presence of such secretions in the plasma, where they exercise a more or less independent activity, comparable to that of a drug which has been introduced into the circulation. Apart from these special substances which exercise a selective action, there are many other products of metabolism which pass into the plasma as definite chemical compounds and may react as such with the tissues. So far, then, there is a purely or primarily chemical basis for the action of some systemic influences.

(2) *Chemico-physical interactions.* The conception of chemical secretions and chemical entities must not be pushed too far, as it cannot explain all events taking place under the influence of the plasma. In one important aspect, the plasma is not an indifferent medium containing an innumerable array of chemical components which are independent of each other and interact with the tissues like pure compounds in the laboratory of the organic chemist. The plasma is subservient to chemico-physical laws, particularly to laws governing the colloidal state, which are valid for inanimate as well as for animate matter. Owing to the operation of these laws, the plasma acquires many of its characteristic properties. As a system of forces in unstable equilibrium, it exhibits a constancy or consistency in its reactions which helps to constitute its individuality, and may be termed the chemico-physical systemic influences of the plasma as a whole. Such influences are of a different order from those for which discrete chemical entities are solely responsible.

(3) *Vitalistic influences.* I use this term as a convenient expression of the fact that, in living matter, chemical and physical changes are constantly occurring with an extraordinary rapidity and ease to which no parallel can be found apart from vital processes.

The physical explanation of this difference between living and dead matter seems to be that the former contains atoms and molecules which are in a highly reactive condition of unstable energy, whereas in the latter the molecules and atoms have reverted to the rela-

tively inert state. The fact that the cells of the living body possess this vitalistic attribute means that their reactions to systemic influences cannot be fully expressed in the chemical and physical terms which are appropriate to dead matter. The same consideration applies to the circulating plasma which, if not exactly a living tissue, possesses the unstable energy of living matter, associated with constant interaction and change amongst its labile constituents.

This vitalistic property of the plasma may perhaps be said to survive to a slight extent in fresh serum, where it is usually called "alexin" or "complement"; and it is a familiar fact that many biological reactions *in vitro* will only take place in the presence of serum which retains its capacity for "activation." But the true vitalistic property, in its full activity, is only operative in the circulating plasma; and "alexin," owing to its close association with artificial reactions in the test-tube, where chemico-physical rather than vitalistic properties are mainly in evidence, is not an appropriate name for it and is likely to cause confusion. It may, however, be said, whilst postponing any controversial questions about the nature of alexin, that, just as alexin determines certain reactions *in vitro*, so this vitalistic influence of the plasma is a systemic factor which is always present in growth and metabolism.

Correlation.

Systemic influences, then, have three main aspects which are equally important and are supplementary to each other. These are the vitalistic, the purely chemical and the chemico-physical properties of the circulating plasma and of the cells with which it comes into contact. Systemic influences are a complex of these three factors and cannot be expressed as exclusive attributes of any one of them, though sometimes one factor is more conspicuous than another.

About this matter there is agreement. The chemist who analyses dead protein is aware that this is different from living protoplasm, and he also knows that his chemical components are subject to physical laws. The physicist has to admit that specificity is largely determined by chemical factors, and the biologist concedes that no progress could be made in the study of living matter without the data provided by the chemist and the physicist.

But, apart from what is known about the action of hormones and vitamins, the main difficulty, about which there is far from being consensus of opinion, is to decide how to correlate these three factors, how to give the right emphasis to each, without undue exaggeration of its importance in the constitution of those systemic influences in the normal body which are responsible for the stimulation and inhibition of cellular growth and for the control of variation.

Taking the chemical aspect first, one may start with the assumption of ready-made chemical entities. Certain tissues secrete substance A, which stimulates growth, and other tissues secrete B, which inhibits that growth; so growth is regulated by the balance between A and B. This, of course, is hypothetical; but it cannot be dismissed as being *prima facie* unreasonable,

because it is impossible to assert that there are no systemic influences due to unidentified internal secretions which act as hormones.

The next requirement is to explain selective action. Different types of cells differ in their susceptibilities as regards growth; so different stimulant and inhibitory agents must be provided for them. There must, therefore, be a large and undetermined number of different *A*'s and *B*'s, each secreted, presumably, by different types of cells. This is a further advance into the region of speculation, but there does not seem any obvious absurdity about it.

Then there is the question of the mechanism whereby this selective action is regulated, as it cannot be supposed that the postulated secretions are turned out by the cells in an automatic or haphazard sort of way. The readiest suggestion is a mechanism of reflex action. Cells turn out into the circulation certain products of metabolism which differ in the growing and in the resting stage. These products act as stimulants to the appropriate groups of secretory cells, which thereupon produce the required corrective in the shape of an appropriately selective *A* or *B*. This, again, may seem a venturesome suggestion; but is it not, after all, merely an application of the well-known idea that specific secretions may be caused by specific stimuli?

The above propositions are put forward, not necessarily for acceptance but for consideration. Taken collectively, they are intended to illustrate the difficulty of drawing the line between reasonably tentative suggestions and lavish postulates of quite unknown chemical factors.

Now it is time to pay attention to what is going on in the plasma. First, it may be noted that a definite chemical substance of systemic importance which is circulating in the plasma is not necessarily a ready-made product of the tissues. It may have originated in the plasma as a product of interactions taking place in that fluid. Then there are more complex reactions to consider, affecting both plasma and tissues.

I refer to interactions which involve a sequence of events, and are to be contrasted with direct reactions where *A* (a substance in the plasma) acts upon *B* (a substance on the surface of a tissue cell), and at once produces *C* (a changed condition of the cell's surface). In these more complex reactions, to take the simplest instance, *A* acts upon *B* and produces *b*, and it is only after *b* has been formed that the further action of *A* can convert *b* into *C*. In reality, there may be several intermediate reactions between plasma and tissues before the end result, *C*, is attained.

In view of the complex chemico-physical properties of the plasma, it is probable that systemic influences are often of this highly complex nature. Hence the error of supposing that every important systemic influence must be identifiable in the plasma as a concrete entity discoverable by some appropriate method of analysis. No; the influence may be real enough, not as a concrete entity which can be isolated in a test-tube, but as a sequence of events due to the chemico-physical properties of the plasma.

From this complexity of normal systemic influences, an important corollary is to be drawn about disturbances in the normal equilibrium of the plasma as a chemico-physical

system. The change caused by the introduction of a new substance or other disturbing influence, *a*, is not necessarily the mere superimposition of a new factor but may involve much more. The slight "jar" caused by *a* may upset the equilibrium of the plasma constituents as a whole, leading to readjustment in a new condition of equilibrium; and this readjustment of the whole of the forces previously in operation may persist after the relatively insignificant force *a* has disappeared. So the change is not to be identified with *a*, though *a* was the cause of it; and analysis of the changed condition may not reveal the presence of *a*.

Just as the plasma is not a mere collection of chemicals, so also it is not merely a chemico-physical system; it is a vitalistic system. Why does not the plasma behave *in vitro* as it does *in vivo*? The main reason is that when it is removed from the living body it loses the unstable energy of living matter.

There is also another reason, and it is important not to confuse the two. The second reason is chemico-physical. Death causes profound chemico-physical change, loss of complexity, loss of lability and loss of activity (*i.e.* change from the dynamic condition of constant interaction to a static and relatively inert condition); and these changes can be accelerated by artificial means, such as heating.

Even whilst the original chemico-physical condition is partially retained (retention of "alexin"), the plasma or serum does not retain the true vitality of living matter. And so, when the selective activity of the plasma stimulates the growth of particular cells, or inhibits it, or prevents the emergence of a variant, its vital energy is an essential factor, in addition to its purely chemical and physical properties and its general chemico-physical "make-up." A similar requirement is often found in the phenomena of symbiosis, when a cell will only grow in the presence of other living cells; a supply of vital energy is a necessary adjuvant for which there is no substitute.

Another way of expressing the importance of the vitalistic factor is to describe the plasma as a living tissue which possesses a dynamic organisation comparable to the organisation inherent, on the smaller scale, in an individual cell. Very little reflection is needed to realise that the properties and activities of a cell depend upon its internal organisation which, in so far as it is dynamic and not merely structural, defies chemical and physical analysis. The general behaviour of the cell and the substances elaborated by it are the outward manifestations of this organisation; and when some of these manifestations are altered, owing to influences which modify the cell, the characters of the variant are primarily due to changes in the cell's organisation. Similarly, the plasma has its own organisation which is an attribute of living matter and persists as the vitalistic factor, whatever changes may be imposed on it, just as the tissues which it bathes have their own vitalistic mechanism which reacts to the plasma's influence.

The connecting link between the vitalistic and both the chemical and the chemico-physical conceptions is to be found in "stabilisation," *viz.* in the fact that many of the plasma's activities emerge as resultants possessing a greater or less degree of stability either as chemical components or as a chemico-physical complex. This stabilisation characterises all living processes, because their individuality depends not merely on a particular sequence of events, but

also on the precise ways in which reactions are terminated by the formation of components in more or less stable equilibrium.

The complex of systemic influences is not to be explained as a patchwork consisting of substances with certain chemical, certain physical, and certain vitalistic properties. It is to be regarded as a unit, an organisation of living matter; and its chemical and physical attributes are to find their appropriate and subordinate positions as manifestations of a living agent.

Comment.

The main purpose of the above discussion is to show that "systemic influences" are not to be treated light-heartedly, as though the term explained itself or merely implied the presence in the plasma of some more or less mysterious chemical entities.

The chemical factors are not enough, and to treat the subject as though they were gives it a misleading air of simplicity which is unreal. To explain a property as due to a chemical substance is helpful only when that substance actually exists and is capable of doing what it is supposed to do; when it does not satisfy these conditions it is a source of illusion.

The introduction of chemico-physical conceptions adds much to the complexity of systemic influences. It may also be said to cause confusion, because it is a complexity which cannot be defined with precision but can only be indicated in a vague and tentative way. But it is sounder policy to admit that the subject is complex, obscure and confusing than to invest it with an illusory simplicity.

The vitalistic factor, again, greatly increases the difficulty of understanding systemic influences. But there it is; one cannot ignore it unless one refuses to treat the subject seriously.

Systemic influences in bacteriology.

Natural immunity and resistance.

I have given the first consideration to systemic influences in the normal body because they are there to begin with. They form a most elaborate mechanism which the body has built up for the regulation of its own cells, without any purposive preparation for the possibility of bacterial invaders. When this contingency does arise, these normal systemic influences are in possession of the field, and it is upon their activities that the fate of the intruders largely depends. Towards bacteria, as towards normal tissue cells, systemic activities have three essential aspects, the vitalistic, the chemical, and the chemico-physical; and these same three properties are characteristic of the bacteria with which the systemic influences are concerned. There is, again, the difficulty of correlating these three factors so as to give to each its right importance.

Immediately after death and before any gross chemical or physical changes

have occurred, the animal body is invaded by bacteria which were unable to gain a foothold in the tissues during life. For this effective resistance *in vivo* the vitalistic phase of systemic influences is obviously the appropriate explanation. Saprophytes are unable to survive in a medium which is permeated by the unstable energy of living animal matter.

The bacterium, then, if it is to become invasive *in vivo*, must be capable of survival in this medium. This statement would be a superfluous truism if bacteria consisted only of two distinctive classes, the obligatory saprophytes and those which grow readily in the living body. But this is not the case; there is a highly important class which is potentially parasitic but finds difficulties in acquiring parasitic capacities for growth. So these difficulties are worth considering. Not only is the plasma a biological or vitalistic fluid which is alien to it, but the bacterium which has found its way into the tissues is usually placed under conditions of environment and temperature which make the resting stage impossible. It must attempt to grow. But growth, terminating by subdivision into normal elements, is an elaborate series of events, each of which must be strictly suitable to the organisation of the bacterial cell if the result is to be the production of viable daughter cells. It is, therefore, highly probable that bacterial death *in vivo* is often due to a compulsory growth impulse which is abortive, and ends in disintegration because the internal organisation of the bacterium is rendered ineffective by its environment. This feature resembles, but is not identical with, what has been called "antiblastic" immunity.

Here it is to be noted that a new factor emerges. It is the vitalistic factor in the bacterium which is responsible for its own destruction. Disposal of bacteria in this way, prior to stabilised bacterial growth, is important and is to be distinguished from chemical bacteriolysis, in which normally built-up protoplasm is already present, and is then disintegrated by the action of a lysin circulating in the plasma. The vitalistic factor must receive its due recognition as an influence in bacterial immunology which is operative not only in the plasma but also in the bacterial cell.

Closely allied to this subject is that highly useful form of natural resistance which is only effective when the dosage of bacteria is small. This is the usual way in which the animal body escapes infection by many of the common pathogenic bacteria under natural conditions. Some few bacteria have found their way into the tissues, but their number has been too small to set up infection.

How is this natural resistance related to that adjuvant to bacterial growth which the bacterium provides for its own cells? For example, when a suitable liquid culture medium is seeded with a very small inoculum of bacteria, growth may fail, though it succeeds when a larger quantity is introduced. The reason is that bacteria, like animal cells in a tissue culture, often help each other to initiate their own growth by furnishing a secretion which acts as a stimulus; or the stimulus may be derived from the autolysate of some of the bacteria which perish. High dilution *in vitro* is sufficient to prevent this initial stimulus from becoming effective. Similarly in natural infection, failure of the bacteria to grow may be due

primarily to their scanty numbers and consequent inability to produce their own growth stimulus in effective concentration.

In so far as this is the case, there is no operation of a systemic influence. But it is quite possible that the plasma has a more direct influence, not as a simple diluent but as a medium which prevents the bacterial growth stimulus from being adsorbed by the bacterial cells. This influence would be systemic; it might suffice to inhibit a growth stimulus which is relatively feeble, though unable to overcome the quantitatively greater stimulus yielded by well-established bacteria.

If, as I suggested in a former article on bacterial virulence[1], bacterial "aggressins" are not really or directly "aggressive" towards the animal body but are primarily adjuvants to bacterial growth *in vivo*, the systemic influence here suggested would, though not an antibody, be equivalent in its action to an "anti-aggressin."

Now I come to alleged functions of "alexin" in natural immunity and resistance. There has been a very large output of literature on this subject which started by assuming, as though it were an accepted fact, that alexin is a special substance (or complex of substances) with a definite chemical structure, a natural antibacterial entity secreted by some cells of the body and then to be found perhaps in the living plasma and certainly in fresh serum. But this assumption is not an accepted fact, though it has been supported by both Ehrlich and Bordet and by many of their followers; and for a long time the tendency to ignore or to discard it has been on the increase. It remains, however, as a conspicuous example of the desire to seek for purely chemical explanations of systemic influences. So a particular effect, *viz.* "activation," is attributed to a definite chemical component (*e.g.* perhaps a lipase which modifies cell membranes) which is thought to exist as such in fresh serum, though it has not been possible to isolate it in the pure state.

In routine diagnosis with the aid of fresh guinea-pig serum, accurate technique is the main desideratum and questions about the true nature of alexin or complement need not arise. But they do arise and demand definite decisions when one is dealing with "alexin" as a systemic influence. If a factor does not exist as a distinctive chemical entity, the assumption that it does is a serious matter. Adoption of the wrong view is a false step on the threshold of immunological problems; and evasion of the question, by retaining the term "alexin" without attempting to define its meaning, causes ambiguity and confusion.

What I consider to be the orthodox view about alexin may now be stated briefly. *In vitro*, it is a property which is due to the chemico-physical lability and colloidal complexity of fresh serum. Its "activity" means that this chemico-physical condition promotes interactions which would not take place in a more stable medium; but it does not mean that the serum possesses a special substance with the function of generating "activity" in the way in which an engine may activate all the other machinery in a factory. "Inactivation" means change to a more stable chemico-physical condition in which the interactions referred to cannot take place.

About alexin *in vivo* there have been many controversial issues and perhaps these have not yet settled down to any one opinion which will be accepted as orthodox. One has to distinguish, as far as it is possible to do so, between the

[1] *J. Hygiene*, **26**, 263 (1927).

vitalistic and the purely chemico-physical factor in systemic influences. As regards the latter, it appears certain that the colloidal complex of circulating plasma is much more intricate, labile and effective in promoting reactions than is the complex of fresh serum. It therefore seems futile to debate the question whether the activities, called "alexin," of a chemico-physical complex are present *in vivo*. In the next place, the unstable energy of living matter is a very real factor, and is not to be identified with the unstable equilibrium of a chemico-physical system. This vitalistic factor is certainly present in living plasma, and provides an additional reason why the properties of such plasma should not be confused with those of fresh serum. The properties of the serum, it is true, are a survival from the plasma, but they are mainly, if not entirely, a chemico-physical survival; it would hardly be safe to say that "active" serum, as usually employed, retains also some of the unstable energy of living matter.

I take next the specific or selective form of natural resistance for which the term "natural immunity" is usually reserved. How is one to explain the selective action of normal systemic influences on bacteria which are pathogenic for some animal species but not for others? Selection must be due either to particular chemical entities present in the plasma or to the particular chemico-physical complex of the plasma as a whole; and it may be impossible to decide which is the better explanation in any particular instance.

A chemical explanation of natural immunity, in so far as the systemic influences of the plasma are concerned, might postulate the presence in the plasma of special secretions, each appropriate to the animal species. The tissues of species *A* secrete *a*, which is specifically antagonistic to certain bacteria, whilst the tissues of *B* secrete a different principle, *b*, and so on. If *a* or *b* is not demonstrable in the serum, the readiest explanations are that, though effective in the circulation as a chemical entity, it is too labile to exist outside the living body, or it may be sessile on particular cells, or it may be created *ad hoc* as the occasion arises. This view, whatever element of truth there may be in it, seems arbitrary and unconvincing as a general explanation of natural immunity. Can it be made more satisfactory if it is partly supplemented and partly replaced by chemico-physical conceptions?

Reverting to what I have said above about normal systemic influences, the first consideration is the general "make up" of the plasma which constitutes its individuality as a system of forces producing certain stable resultants. For example, there will be something, recognisable antigenically as a precipitinogen, which is very highly specific for the animal in which it is demonstrable, though it was not secreted as such by any particular cells; and there will be other substances, also more or less peculiar to the animal species, which, though not antibodies—as there was no antigenic stimulus to produce them—behave as selective agglutinins or lysins toward certain bacteria or other bodies. Substances such as these may sometimes be formed in the plasma without the aid of the tissue cells, and may constitute antibacterial systemic

influences. Others, again, may be formed in a similar way but may be too labile to survive in the serum.

There are other activities which may be peculiar to the plasma of particular animal species and may be equally real as systemic influences, though they do not find expression in any one resultant which can be defined as a special antibacterial substance. But these other activities may also be protective by constituting a medium in which some particular bacterial species is unable to propagate itself, destruction of the bacteria being due not to any lysin acting upon formed bacterial protoplasm but to the compulsory effort at growth in an unfavourable medium, the consequence being either prompt disintegration or the production of non-viable offspring. It must also be remembered that an antibacterial effect is not always produced by a single cause. As I have indicated in the preceding section, a systemic influence may be due to a complex sequence of events—*a* followed by *b*, which is followed by *c*, and so on—before the critical end-result, *E*, is attained.

In natural immunity, the operation of humoral systemic influences may be summarised briefly as follows. The normal plasma constituents interfere with the vital processes of the bacteria by producing alterations in surface tension, in assimilation of food, in capacity for reproduction or by other change. At the end of these interactions, the plasma constituents remain unaltered, *i.e.* the animal's condition of natural immunity remains as before. This is the primary and most important feature of antibacterial action due to natural systemic influences. The influences which have been discussed are not antibodies in the accepted serological sense, and the destroyed bacteria have not behaved as antigens. I am referring, of course, to true natural immunity, not to immunity which has, in reality, been acquired by subinfective doses of bacterial antigen.

The chemical conception of acquired immunity.

Under "chemical" I include biochemical and serological conceptions, where animal and test-tube experiments are employed for the identification of antigens and antibodies which are regarded as chemical entities.

Antigenic analysis has proved to be of high utility for the routine identification of pathogenic bacteria; and in some instances correlation has been found between particular antigenic attributes and virulence. Work on agglutinins and on their selective absorption has shown that substances in an immune serum with distinctive chemical combining affinities can be separated out; and, though this separation is artificial, it must be based on intrinsic characters of the plasma which are of a chemical nature and are of distinctive importance as such. Recent advances in the analysis of antigens and antibodies have assumed a high degree of complexity, which is always an advantage when it is justified by results, *i.e.* when it is helpful in diagnosis, in tracing an epidemic. in determining virulence, in demonstrating selective capacity for the production of particular types of disease, or in guiding the production of a useful

vaccine or a therapeutic serum. Conspicuous successes have already been attained, particularly in the identification of certain antigens which are directly associated with virulence, and in their distinction from others which do not bear this attribute.

All this work has its justification without reference to any particular chemical explanation of immunity, just as the practical utility of fresh guinea-pig serum does not depend on one's views as to the nature of "complement." Many investigators are content with the facts which they establish, and do not trouble much about the general principles involved.

Coming now to these general principles, the first difficulty is that there is no standard of immunological doctrine which meets with general acceptance from those who adopt the chemical standpoint. But perhaps differences of opinion may be pivoted on a leading question which appeals to all. How far does modern research demand a deviation from the orthodox beliefs of the Ehrlich school? So I propose to approach the subject in this way, by discussing some of the points raised by Kolle and Prigge in their recent article on acquired immunity[1].

These authors declare at the outset that "the majority of all immunologists" now accept Ehrlich's theory as an explanation of "almost all the facts" and therefore earlier views may be disregarded as being of merely historical interest. Then, after reviewing some more recent doctrines, with particular attention to the "antivirus theory," they conclude that "the efforts to establish new theories of immunity have not yet led to a systematic exposition which could replace the side-chain theory." Their great master, it appears, was practically infallible.

I doubt if this is the best form of tribute to Ehrlich's genius, which is appreciated throughout the world. It has been an invaluable stimulus to all subsequent investigators because it has indicated the extremely delicate chemical specificity of biological reactions. But it is idle to ignore the difficulties which have been found in endeavours to substantiate his free coinage of chemical entities. They would explain "almost all the facts" only on the condition that they are true in detail; but that is the hypothesis which cannot be accepted. Hence the great problem bequeathed by Ehrlich is to incorporate really valid chemical data in a wider conception of what actually takes place in the living body. It has not been found possible to elaborate a scheme which will rival Ehrlich's in comprehensive detail; but this admission is no argument for the retrograde step of a return to Ehrlich's position.

After repeating Ehrlich's well-known views about the mechanism of antibody formation as a specific cellular secretion in response to a specific stimulus, Kolle and Prigge lay much stress on the postulate of an Umstimmung (re-tuning) of the cells as a further explanation of immunity. "Active specific immunity is thus to be defined largely as a change in the condition of specific reactivity on the part of cell groups in the organism which perhaps differ for different diseases." This Umstimmung explains why there may be active immunity after antibodies have disappeared from the circulation; infection is immediately checked

[1] Kolle and Wassermann's *Handbuch der pathogenen Mikro-organismen*, 3rd ed. I, 607–62 (1928).

because the Umstimmung of the cells persists, and they respond to the bacterial stimulus by producing at once the appropriate antibody. This property of the cells is compared to the capacity for remembrance on the part of the ganglion cells of the cerebrum.

This postulate, though it cannot rehabilitate Ehrlich's theory as such, is of considerable interest in that it forms one of the ways of explaining active immunity when there are no demonstrable antibodies. Another mode of explanation is to assume that antibodies persist in the body, but are sessile and not in the circulation. Or, as I have suggested previously, it is probable that serological antibodies are merely those antibodies of the plasma which have become stabilised, and that in the living plasma the same antibodies may, whilst in an antecedent and unstabilised form, effect reactions which cannot be reproduced in the serum, because in the latter fluid they have lost their reactive condition.

Kolle and Prigge make brief mention of the view, which is now attracting much attention, that the source of antibody formation is to be found in the cells of the reticulo-endothelial system. They do not receive it very enthusiastically. Whilst admitting that some experiments appear to have proved a relationship between reticulo-endothelium and antibody formation, they point to the conflicting results obtained by different investigators, and deny that this system has been shown to be "the dominant or universal cause" of active immunity or of the production of antibodies. Is this sceptical attitude justifiable?

Bieling, who is the recognised authority on the subject, has defended his position in a recent paper[1] on reticulo-endothelium and immunity. He describes as follows the general properties of the various types of cells found in this tissue: "They constitute a cellular system which permeates the entire body, and is characterised by a particularly well-marked capacity to take up corpuscular and colloidal bodies circulating in the blood, including micro-organisms as well as albuminous material and toxins." These, it is claimed, are the principal cells which produce antibodies. Bieling regards this conception as a great advance in immunology, because it provides a satisfactory reconciliation of humoral and cellular hypotheses. "The combined views of Ehrlich and Metschnikoff form our starting-point, because we see that the vectors of humoral immunity, the antibodies, arise from the co-operative action of the same cell system which is also the vector of general immunity; and so we arrive at a unified conception, since we attach both processes, the purely cellular and the so-called humoral, to the function of the same cell-system."

Here one may remark that a cell which ingests foreign protein may suffer serious, if not fatal, disorganisation and is not necessarily the cell which secretes an antibody to that protein. Upon this point I think there is general agreement. So the hypothesis that the phagocytic cells of the reticulo-endothelium are the source of antibody formation is not self-evident; it requires experimental justification. This Bieling freely admits.

The nature of the experiments employed is now very familiar. An animal is "blockaded" by the injection of some inert material which is taken up by the reticulo-endothelium; in addition, the spleen, which is particularly rich in this tissue, is extirpated. Then suitable antigens are injected into these animals and into normal controls. If the "blockaded"

[1] *Centralbl. f. Bakteriol.* Orig. **110**, 195–210 (1929).

animals fail to produce antibodies, it is assumed that this is because the reticulo-endothelium has been put out of action, and this result is regarded as a proof that the reticulo-endothelium is the source of antibody formation. If the animals produce antibodies, in spite of the "blockade," the reason given is that the "blockade" was incomplete, and it is explained that there are many circumstances under which it is impossible to achieve a complete inhibition of reticulo-endothelial activity.

The obvious criticism, which has often been raised, is that the drastic procedure known as "blockade" is a profound shock to the animal's entire organisation, humoral as well as cellular, and is not confined to the particular cells which store up the injected material. So it does not follow that the interference with these particular cells is responsible for the absence of antibody formation. Nor does it follow that smaller degrees of shock, which cause less or no disturbance in antibody formation, simply mean that part of the reticulo-endothelial "system" has escaped the "blockade." Bieling, indeed, though giving the predominant part to reticulo-endothelium, admits that these may not be the only cells capable of forming antibodies.

Then as regards tissue-culture work, Meyer and Löwenthal are quoted by Bieling as showing that antibodies may be produced by pure cultures of reticulo-endothelium. This is certainly a point in favour of his main thesis. But it remains to be seen how much importance should be attached to these results *in vitro* as evidence of secretory activity *in vivo*.

Meyer and Löwenthal[1] found that their cultures produced agglutinins (against *B. typhosus*) within 48 hours and these attained their highest titre (1 : 320) in 3 days; after that time the titre fell rapidly and after the fifth day agglutinin formation was no longer demonstrable. They conclude that they ought not to form too high expectations of this method as a means of gaining insight into the mechanism of antibody formation.

On the whole, I am inclined to agree with the cautious attitude adopted by Kolle and Prigge. The extensive claims of Bieling and his followers have not been substantiated. The main attraction of their hypothesis, it seems to me, is that it offers a readily available experimental method. One may expect that, for many years to come, there will be investigators who will adopt "blockade" as their method of research on immunological reactions.

It has always seemed to me that passive anaphylaxis gives a better method of demonstrating the site of antibody formation. Anaphylactic antibody (*A*) is injected into a normal guinea-pig; later on, anaphylactogen is introduced and shock occurs. There is strong evidence that *A* was adsorbed by the surface of capillary endothelium, and that the shock originated in this situation. But *A* was adsorbed by endothelium not because it was "ear-marked" by its content of anaphylactic antibody, but simply because it was foreign protein and therefore antigenic. Hence the presumption that, in the usual course of antibody formation, the first step is adsorption of antigen by endothelium.

To review the position as regards the chemical conception of acquired immunity, there are some views which are to be repudiated, others which are frankly matters for dispute, and others, again, which are not exactly contentious but require confirmation before they can meet with general approval.

[1] *Zeitschr. f. Immunitätsforsch.* **54**, 409–19, 1928.

There remain certain predominant ideas which I think are accepted as characterising the chemical position: (1) antibodies are produced by tissue cells in response to a specific antigenic stimulus; (2) antibodies are, of course, subject to chemico-physical laws, which have been studied extensively *in vitro* (inhibitory zone, buffering, law of multiple proportions, etc.); (3) but the predominant feature remains that the essential factor in an immunological reaction is the interplay between two chemical entities, an antibody (agglutinin, lysin, tropin, etc.) and its corresponding antigen; (4) these conceptions are considered preferable to the much less concrete ideas of interactions between systemic influences and living bacterial protoplasm; (5) the vitalistic factor is not ignored; it is accepted as explaining the secretion of antibodies and the building up of bacterial antigens, but attention is then to be concentrated almost exclusively on chemical (including biochemical) analysis of antigens and antibodies.

Systemic influences in acquired immunity and resistance.

Having now made it clear that I have no intention of disparaging the chemical standpoint, I return to systemic influences. I commence by entering a protest against the exaggerated importance which is often attached to the serological reactions following the parenteral introduction of foreign protein. This is not a captious criticism; it provides a reason for a recognised difficulty. The difficulty is that progress in bacterial immunology has been slow and disappointing. The reason is that bacteria are living organisms, not merely parcels of antigens, and the properties of circulating plasma are systemic influences, not merely antibodies to particular antigens. So first I must endeavour to explain the significance of this wider conception.

Acquired immunity does not mean that normal systemic influences have become negligible; these are still the basis of potential or actual antibacterial resistance. But it means a change in them, whereby they become a specifically antibacterial complex. The changed systemic influences still possess a very high degree of complexity, the features of which I have discussed in preceding sections. I need not recapitulate, but only insist that this complexity is an essential factor in acquired antibacterial immunity.

Further, one of the most important features of natural exposure to many forms of bacterial infection is that the individual's non-specific powers of resistance are liable to fluctuation. On one occasion he resists the germs of influenza or pneumonia; on another he succumbs to infection. These fluctuations cannot be explained as due to the possession, acquirement or loss of antibodies. But such modifications of natural resistance or susceptibility are very real factors in immunology and cannot be ignored. One has to assume that they are due to variations in those systemic influences which constitute the general "make up" of the plasma.

On the bacterial side, as I have already intimated under "natural immunity," bacteria may be eliminated, not by the action of a lysin but because

they are compelled to attempt growth in an unfavourable medium. This influence, which cannot be identified with the action of an antibody on a bacterial antigen, is of equal importance in acquired immunity. It may be said that there is a bacterial response to the animal's growth stimulus both in immunised and in susceptible animals, the main difference being that in the latter the growth is viable. In both cases, there is not resistance but susceptibility to the animal's systemic influences. The difference lies in the consequences of this susceptibility. With the bacterium which is virulent for its host, it is not followed by an unfavourable influence on the habit of growth.

Another point of importance is that the disintegration products of bacteria, which perish *in vivo*, may not be identical with those of a killed vaccine (which is supposed to be a mere parcel of antigens) as regards their action on systemic influences.

Now one has to find, within this wider conception of systemic influences in acquired immunity and acquired non-specific resistance, an appropriate place for what may be called the routine production of antibodies by antigens. One needs a scheme which will help to correlate natural with acquired systemic influences, to bridge the gap between specific and non-specific factors, and to replace the conception of an antibody as a special chemical entity, specially secreted by certain cells in response to the stimulus of a foreign protein. No doubt various proposals might be made; I suggest one of them.

In an article on "The capillary endothelium in relation to antibodies[1]," I put forward the view that antibodies are produced by a change which the plasma undergoes when it passes through the capillary endothelium, after this has adsorbed on its surface the specific antigen. Instead of relying on the chemical conception of a special substance manufactured by special cells—just as adrenalin is produced by the suprarenals—I preferred the chemico-physical conception of a modification, by filtration, of the general "make up" of the plasma. Continued filtration would explain, more easily than the secretory hypothesis, why a small amount of antigen may produce a large output of antibody; and differences in the immunological response of animals of the same species may be accounted for as due to individual differences in the general "make up" of the plasma which passes through the filter and is modified thereby. Similar differences may arise through variations in the plasma and endothelium of the same individual. In brief outline, my suggested mechanism of antibody formation is as follows.

Bacterial antigen is adsorbed by the tissues, particularly by the surface of endothelial cells; and the consequent modification of the endothelial filter causes a specific modification of the fluids which pass through it. Hence the plasma constituents become better adapted for forming loose union, often followed by dissociation, with the specific bacterial substance. When this substance is a living bacterium, they become better adapted to interfere with its vital mechanism. This modification in the properties of the original plasma

[1] *J. Hygiene*, **22**, 355–87 (1924).

constituents is something which is acquired not as a new and independent mechanism, but as a readjustment of the natural systemic influences. At the commencement of this phase, the new antibacterial properties of the plasma are too labile to be demonstrable in the serum.

At a later stage, the modified systemic influences behave as before *in vivo*; but the change in the original constitution or balance of the plasma constituents is of a more permanent nature, with the result that the acquired affinity for the foreign protein may survive in the serum and may there become stabilised, though it must by no means be assumed that this serological property represents the whole of the new activity *in vivo*. When the serum is found *in vitro* to make a relatively firm adsorption compound with the bacterial antigen, it has acquired the property of an antibody. To regard such an antibody as the distinctive and essential factor in the process of immunisation would be a gross exaggeration of its importance. It is simply a particular consequence, or an external manifestation, of the complex systemic change which constitutes the true character of the immunisation. Moreover, it is a consequence, or manifestation, which is not always essential, since firm immunisation *in vivo* is not infrequently established without the demonstrable existence of any such antibody.

The above conception, though it subordinates "antibodies" to "systemic influences," leaves plenty of room for the requirements of chemical specificity. There are three types of instance which may be taken as examples. (1) An animal is immunised with diphtheria toxin. Here the new systemic influence is predominantly the combining affinity for toxin and this new factor is stabilised in greater or less degree and then survives in the serum. For most practical purposes, "new systemic influence" may be converted into the chemical term "antitoxin." (2) An animal is immunised with dead bacteria; the new systemic influences are partly stabilised and, to this extent, are demonstrable in the serum as agglutinins, lysins, etc. Here again, there is serological evidence of the specific factor; but it cannot be taken for granted that this factor alone is the full explanation of the new systemic activity *in vivo*. (3) Immunisation is effected without demonstrable serological antibodies. The specific factor must be operative *in vivo*; but here there is very obvious evidence that the ordinary chemical conception of an antibody fails to explain the systemic influences which confer immunity.

This view of antibody production involves the assumption that similar functions belong to the endothelial filter in natural immunity. It regulates the plasma constituents which pass through it and, as its properties probably differ in different species of animals, systemic influences may partly depend on its special characters. In the same animal, also, the degree of its permeability is liable to variation, with consequent variation in the systemic influences. Further, there are reasons to think that the characters of the filter differ in different sites of the body and thus help to account for local differences in resistance and susceptibility, both natural and acquired.

Comment.

What is the use of dragging in "systemic influences" instead of being content with a chemical conception of immunity, either similar to the example I have given in a preceding section or after some other pattern?

For some purposes, there is no advantage. The greater part of the literature on bacteriological research is absorbed in the discovery of new facts. These are intended to form, ultimately, new "building-stones" and, in the better articles, the individual "stones" are trimmed up so as to present no obvious discrepancies. But to the building process as a comprehensive scheme less attention is paid, and sometimes none at all. Probably the reason is that the writers consider very little to be known about the essential principles of immunology and therefore regard it as futile or "merely speculative" to attempt any constructive theory. For all these investigators some form of chemical conception, supplemented by physics, will probably suffice and "systemic influences" are not wanted.

But for the purpose of considering the major problems the chemical conception is inadequate. It does not suffice to explain natural immunity; it does not account for fluctuations in natural resistance; nor does it help to link up natural with acquired immunity. In acquired immunity it is but partially successful, because many of the facts cannot be explained in terms of antibodies and antigens. Even when the defects of Ehrlich's scheme are recognised and excluded, it is still highly "speculative," particularly as regards the marvellous secretory capacities of cells to respond specifically to an unlimited number of different antigenic stimuli.

There are obvious limitations to the information obtainable by antigenic analysis. For example, different strains of virulent diphtheria bacilli are found to be structurally different on serological analysis of their antigenic components; but they all produce the same toxin. The chemical components of pneumococci, apart from their "soluble substance," are found to be very much alike, antigenically, but these components when forming the structure of a living cell behave differently, in that they turn out quite a large variety of different "soluble substances." Again, residence in the animal body may bring about qualitative changes in virulence in relation to different animal species; such changes cannot be attributed to changes in bacterial antigenic structure. Chemical conceptions of antigen and antibody do not completely explain the interactions between bacterium and host.

I may illustrate my last remark by referring to some of the *in vitro* experiments, described by Robertson and Sia[1], on the action upon pneumococci of a mixture of fresh serum and leucocytes derived from normal animals. Here the fresh serum represents the humoral systemic influence, which they regard as "opsonic."

When highly virulent pneumococci were used, "all the resistant animals tested, dog, cat, sheep, pig and horse, showed marked opsonic properties in their blood serum which were not found in the serum of susceptible ones, rabbit, guinea-pig and human. There appeared, however, to be no essential difference in the phagocytic activity of the leucocytes from the various animals." It was, therefore, a property of the serum, a property destroyed by heating, which distinguished resistant from susceptible animals. It was also shown that the inhibitory action of fresh serum was abolished by adding specific "soluble substance" to the mixture of serum and leucocytes. This was demonstrated both for the rabbit (susceptible) and the cat (resistant), the strains of pneumococci employed being avirulent for both species of animals. "It was found that the presence of a very small amount of the purified soluble substance of the homologous type markedly altered the conditions in the mixture, so that even a small number of avirulent pneumococci were enabled to grow in the serum and

[1] *J. Exp. Med.* **43**, 633 (1926), and **46**, 239 (1927).

leucocytes of animals which possess the power to destroy ordinarily such pneumococci in relatively large numbers. The action of the soluble substance was shown to be highly specific to type. A Type II substance assisted the growth of only Pneumococcus Type II, likewise a Type III substance, the growth of Pneumococcus Type III only."

According to my interpretation, the fresh serum—and still more the living plasma—of the animal normally resistant to the strain of pneumococci employed does not contain any special substance (opsonin or specific alexin) but possesses a special and labile chemico-physical complex, in the presence of which the organisation of the pneumococcus is unable to elaborate its "soluble substance"; being devoid of this protective material, the pneumococcus perishes in the living body and succumbs to phagocytosis *in vitro*. In this adverse medium, the task of manufacturing "soluble substance" is more difficult than the assimilation of the appropriate "soluble substance" which is presented to it ready made. The latter task the pneumococcus can and does perform, in spite of the unfavourable chemico-physical complex in which it is placed. Different types of pneumococci (including the heterogeneous Group IV) manufacture many different varieties of "soluble substance"; why does the animal of naturally high resistance antagonise all these varieties with equal facility? I think it would be far-fetched to suppose that the animal's plasma has a special antibody (opsonin) for each "soluble substance" or that it has one antibody polyvalent for them all. On my view, the plasma antagonises not the "soluble substances" but the pneumococcal organisation which manufactures them.

These examples may serve to illustrate the important general principle that a distinction is to be drawn between the structural components of a cell, which are partially amenable to chemical or biochemical analysis, and the living or dynamic organisation of the cell, which is not amenable to such analysis. It is the latter property which is the more important of the two, though it cannot be explained by analysis of the former.

Similar considerations apply to the plasma. Its activities depend, in the main, on its dynamic organisation, and can be explained only to a limited extent by analysis of its antibodies or other chemical constituents.

This principle applies to acquired as well as to natural immunity. When a definite serological antibody does emerge, it is supplementary to this principle but does not replace it. The function of the immunised plasma is not merely to antagonise a bacterial antigenic substance which is requisite for virulence, but to prevent the bacterium from manufacturing this requisite substance.

So I think it is an advantage to approach bacterial immunology by way of systemic influences, because the real problem, which ought never to be lost sight of, is the relationship between (1) the living organisation of the plasma, and (2) the living organisation of the bacterial cell. In the processes of stabilisation which accompany all vital reactions both in the plasma and in the growth of bacteria, selective antibacterial substances emerge out of (1), and specific antigens emerge in (2); but in each case they are the consequences or the products of "organisation," not the cause of it. It is a mistake to regard antigens and antibodies as the foundations of immunity; they take their proper place as manifestations of (2) and (1).

SYSTEMIC INFLUENCES ON CANCER GRAFTS.

Woglom has recently published a lengthy critical review[1] of the work on immunity to transplantable tumours, which has been recorded since 1913. Here I can only call attention to his main conclusions, and must refer my reader to the original article for his evidence, which consists of a highly condensed summary and criticism of experimental work.

"Although," says Woglom, "some tangible basis for immunity, something of the general nature of a specific antibody, has been sought for thirty years, none has yet been discovered, *though the methods employed leave nothing to be desired in the way either of completeness* or ingenuity." Comparing the cancer problem with bacteriology, his opinion is that "except for a few isolated observations which run contrary to the general evidence, no sign of the existence of agents similar to the antibodies so easily demonstrated in the domain of bacteriology has yet been discovered in connection with cancer." In reference to this subject, he quotes my opinion, which I expressed in my first article on cancer, that, whilst a selective cytolysin for the malignant cell might some day be found, the chances of its discovery were remote.

He defines immunity to transplantable tumours as "a generalised refractory condition which appears to be entirely unrelated to other forms of immunity. No single organ has yet been proved responsible for its elaboration, nor is it affected by physiological conditions such as age or pregnancy. In its acquired form it is neither hereditary nor passively transferable through the body fluids." And, since resistance is only effective during the first few days after inoculation, and is entirely powerless against an established tumour, "nothing may accordingly be hoped for at present in respect to a successful therapy from this direction."

The first merit of Woglom's article is that he raises a clear issue and keeps it steadily before the reader. What is the net result of the large output of experimental work on the transfer of grafts from animal to animal? Only too frequently this question is obscured by the introduction of other considerations which are irrelevant, *e.g.* questions about the cause or nature of cancer, its prevention or its cure. When an investigator works with grafts, he is concerned with the conditions which make them grow, with means of preventing a graft from taking, with ways of causing an established graft to retrogress, and so forth. That is all; the study of grafts has no direct bearing on the major problems of autogenous cancer. Woglom clears the ground from much confusion by dealing with the experimental work at its actual value as a study of grafts, and by brusquely sweeping aside all irrelevancies. His criticisms are destructive and his conclusions are pessimistic; but I think most of his arguments are well substantiated, and that pessimism is a more useful stimulus than illusion.

As I do not consider bacteriological immunity to depend entirely upon lysins or other antibodies, I am not in complete agreement with Woglom's view that immunity to transplantable tumours is unrelated to other forms of immunity.

In discussing natural specific immunity, *i.e.* the inability of a graft to grow in an animal of another species, he says that "whatever the nature of the destructive agent, it can hardly

[1] *The Cancer Review*, 4, 129–214 (March 1929).

exist ready made in the blood, for Lambert and Hanes have shown that mouse and rat tumours can be grown *in vitro* in the plasma of all alien species investigated except in that of the goat."

To a large extent, similar conditions are found in natural specific immunity towards bacteria. Though *in vitro* tests in some cases show that the whole blood or fresh serum of the naturally immune animal is more antibacterial than that of a susceptible species, this is not a general rule and natural immunity cannot be identified as a special property or substance present in the serum. For instance, the fowl is naturally resistant to anthrax, but the bacilli grow readily in its blood or serum outside the body; on the other hand, the rabbit is susceptible to this organism but its serum is bactericidal. I have given reasons for believing that antibacterial action *in vivo* is much more complex than the selective action of a special opsonin or bacteriolysin. This is probably also the case in the resistance to a graft which is offered by an alien species. One has to think of the general "make up" of the plasma which constitutes its individuality and forms a medium which, though perhaps not directly cytolytic, interferes with the organised mechanism of cellular growth, and so prevents the cells of the graft from producing viable descendants. For two reasons, then, this resistance to a transplant bears some general resemblance to specific natural immunity towards bacteria. There are systemic influences, in both cases, which are not identifiable with special "destructive agents." And it must be recognised that an animal's natural systemic influences are not divided up into water-tight compartments, one of which deals with bacteria, another with alien animal cells, and so on; they are all part and parcel of one and the same mechanism.

Again, artificial non-specific immunity towards a graft does not appear to me to be altogether unlike this kind of resistance as it is found in bacteriology. It is well known that a graft which will take in a normal animal (*e.g.* a mouse cancer in a mouse), will fail to grow if, prior to inoculation, the animal's resistance has been artificially increased. The acquired resistance is usually produced by inoculation with one or other of a large variety of normal tissues, further requirements being, in the opinion of most investigators, that the tissues must be alive and must be homologous for the treated animal. For this increased resistance, which has to be accepted as a fact, no categorical explanation can be given. It is fairly obvious that it is not due to an antibody or to any special non-specific substance; but I think it is legitimate to appeal to systemic influences and to suggest that the preparatory inoculation has produced a reconstitution of the plasma. This new condition of the plasma need not be directly cytolytic; indeed, it is difficult to see why it should be, as it is non-specific. But, just as in the case of bacteria, acquired non-specific resistance, which involves a change in the constitution of the plasma, may be effective without the aid of a bacteriolysin or a tropin, because it provides conditions incompatible with viable offspring, so the new condition of the plasma may cause the cells in the graft to lose their capacity for stable growth.

The fate of the graft is determined within the first few days; if it survives this period, it settles down to the production of viable daughter cells. Hence the fallacy of thinking that the means which will prevent the starting of a graft provide a clue to the inhibition of an established growth.

I am also interested in what Woglom says about the ultimate fate of a graft after initial growth has been established.

He attaches high importance to the work of Russell, who "showed that tumours could be divided into two main classes—those that did and those that did not immunise the host by their presence, though between the two came others possessing all degrees of immunising power. Yet such were the intricacies of the reaction between tumour and host that neoplasms of the non-immunising group sometimes induced resistance, while those of the immunising class had failed on occasions to elicit the refractory state." He also quotes Bashford's statement that "different strains of the same tumour might fall in different groups in respect to their immunising power."

I think that two comments may be offered on this aspect of grafting experiments.

The first is that they have no evident bearing upon autogenous cancer. With this, I take it, Woglom is in agreement, as he goes further and declares that it has been shown to be impossible for an animal to be immunised against its own tumour cells.

The second comment is that in a general way, though one cannot press for a detailed comparison, there are analogies between these grafts and bacteria as regards their behaviour in the animal body. Particularly amongst bacteria which are pathogenic without being acutely virulent it is found that their interactions with the animal host are varied, complex, and often uncertain, as shown by the variable degree of resistance which is evoked. For these irregularities an explanation in terms of antibodies is generally insufficient. It may, of course, be true that there are fluctuations in the antigenic stimulus of the bacteria and in the capacity of the host to produce antibodies; and it may be said that, on some occasions, the bacterium has produced an effective antibody, and that on others it has failed to do so, or that the bacterium has acquired the habit of growing in the presence of its own antibody. Such statements may certainly contain an element of truth, but they are not the full explanation of the natural or acquired properties of the host's resistance or susceptibility. One has to fall back upon those complex interactions between the bacterium and the host's systemic influences which are not expressible in terms of antibodies. This is also the case with grafting experiments, where, as Woglom says, there is no evidence of what would pass muster amongst bacteriologists as a fully accredited antibody.

So again I come round to the point that, though cancer grafts are not very much like bacteria, they have this in common that they have to deal with the same mechanism, which is to be found in the animal's systemic influences.

Comment.

I have taken transplantable tumours first in order to clear the ground. The subject is relatively unimportant, because it throws no light either on established autogenous cancer or on the genesis of cancer; but, unless it is disposed of to begin with, it is liable to introduce an element of confusion into the more serious aspects of the cancer problem.

Taken for what it is worth, the study of grafts provides evidence of some systemic influences which cannot be explained in simple terms of antigens and antibodies. That is to be expected, on the analogy of similar antibacterial influences which I have discussed in preceding sections. Neither natural nor acquired resistance to the taking of a graft involves anything which has been proved to be a new kind of systemic influence peculiar to cancer.

Systemic influences in autogenous malignancy.

The established disease.

Theoretically, it might seem more correct to commence with the genesis of cancer, and to take the established disease subsequently. The reason why I am adopting the reverse procedure is that misunderstanding frequently arises from the tacit assumption that observations on systemic influences in the cancerous subject are also evidence of a mechanism which was already present in the previous, non-cancerous condition. It is important that this element of confusion should be eliminated.

A mouse has developed cancer either spontaneously or as the result of tarring. The animal is then found to have acquired a considerable degree of resistance against the induction of a second cancer by tarring another site of the body; and this resistance persists after the first cancer has been removed completely. The facts indicate that products of the first cancer made their way into the circulation and, in some unexplained way, diminished the susceptibility of other parts of the body. Here there is a new factor, which may legitimately be called a systemic change. But such observations afford no proof whatever that, prior to this change, there were in the circulation special systemic influences which were favourable or unfavourable to the genesis of cancer.

Similar circumstances apparently account for the rarity of multiple new growths in the human subject. When the disease is once established, some of its products are circulated and diminish the susceptibility of other tissues. Again, the facts afford no indication of special systemic influences in relation to cancer before the disease has developed. It is simply a question of "getting in first."

The same criticism applies to certain statistics which are frequently quoted. Women in this country are very liable both to cancer of the breast and to cancer of the uterus; but the same wŏman does not develop both forms of the

disease, because the organ which first becomes malignant sets up a systemic influence which inhibits the susceptibility of the other organ. In Holland the women are less liable to cancer of the sex organs, and more liable to cancer of the digestive tract, the total incidence of cancer being about the same as in this country. Here, again, the incidence of cancer in one situation prevents its development in a second, owing to the formation of a new systemic influence derived from the site of the disease. The statistical facts provide no indication, still less a proof, that there are special controlling influences which exist before the disease has developed. The distinction between a natural and an acquired systemic influence is surely obvious.

Perhaps this point needs a little more emphasis. A definite condition (*a*), *viz.* the existence of cancer, produces a new systemic influence (*b*). It is certainly natural to discuss the possible ways in which *b* may operate; but all these possibilities assume the pre-existence of *a*. They are not possibilities which existed prior to the creation of *a*; they relate to the consequences of cancer but cannot be accepted as throwing any light on its genesis.

As regards the explanation of *b*, one may first ask if it is an antibody produced by a cancer antigen. No unequivocally accepted antigens and antibodies peculiar to cancer have been found; but this is not a conclusive objection because, if one adopts a reasonably wide conception of antibody reactions, the field for discovery still remains open. There is no overwhelming difficulty about postulating the autogenous creation of a new antigen. Bacteriophage, in the opinion of many authorities, is created *de novo* in the bacterial cell and it has been proved that it exhibits new antigenic properties. A pneumococcus which is devoid of Type antigen may be made to produce a Type antigen; that again is a creation *de novo*. So why should not the malignant variant of an animal cell produce a new antigen characteristic of malignancy? If it does, what is the nature of the antibody evoked in response to the new stimulus? Here a difficulty arises. It may be objected that the hypothetical antibody is not really an antimalignant antibody because it does not interfere with existing cancer cells but is supposed to prevent the change from the normal to the malignant condition; so it is not at all clear how such a peculiar antibody can have been produced by a true cancer antigen. One way out of the dilemma is to suppose that a new cancerous growth has actually been formed but is aborted by the specifically antimalignant antibody already in the circulation. Then why does not this antibody also suppress the original cancer? Because the latter is well established and has become accustomed to grow in the presence of its own antibody, a capacity for which bacteriological analogies are available. And so one may travel further and further into the region of speculation.

There remains the appeal, which I think justifiable, to more complex chemico-physical changes resulting in a reconstitution of the plasma. Bacteria may set up an antibacterial influence in this way, irrespective of the production of antibodies. Probably this acquired systemic influence in cancer is also due to changes in the plasma which, though initiated by the products of cancer cells, are of a complex chemico-physical nature and cannot be identified as any distinctive chemical substance.

On the practical side, this feature of cancer does not seem to be of much importance. It is no great satisfaction to know that a person who is going to die from a particular form of cancer will not contract another kind of cancer. Experimentally, it has not provided any clue either to causation or to cure. Nor has it indicated a useful method of prophylaxis. Vaccination of a normal

animal with cancerous (or with normal) tissue may temporarily prevent the taking of a graft, but it does not immunise against the subsequent development of autogenous cancer.

The genesis of the disease.

The idea that there are some systemic influences which affect the genesis of cancer is often expressed so vaguely that it is difficult either to support it or to dissent from it. I admit that the subject is too obscure to be treated with an air of categorical finality or even with detailed precision; but at least some tentative and reasonably plausible explanations are due from investigators, who claim to have demonstrated systemic influences which are specially concerned with the origin of cancer.

There is sometimes a tendency to make the question of genesis appear much simpler than it really is, by assuming that one-half of it does not require elucidation. I refer to the assumption that normal cells have a "natural" tendency to unlimited growth, which would "naturally" end in malignancy. This being granted, all that remains is to discuss the systemic influence which ought to control this vicious tendency of the cells. Against this assumption a protest must be made before going any further.

In its extreme form, as expressed by some writers, this assumption amounts to the statement that there is no "essential" difference between the cancer cell and the normal cell. Every practitioner and every intelligent layman must regard this view as an outrage on common sense. The cancer cell kills; the normal cell does no harm. What difference could be more "essential" than that? I agree; there is an essential difference, which consists in the fact that the cancer cell is a pathological variant from the normal cell. Such a variant is not produced by growth alone but by some pathological influence. To explain this influence is more than half—it is the major part of the cancer problem. It is certainly not a half which can be ignored.

To deal now with the above assumption in its more usual and less eccentric form, it appears to be thought that unrestrained growth is the cause of variation, culminating in the cancer variant, which is admitted to be a wide departure from the normal. But where is the evidence? In tissue culture, where there is no restraining systemic influence, normal cells may be propagated from year to year; they remain normal; continued proliferation never causes them to become cancerous. And take the cancer cell. The primary focus of true cancer is extremely small; it would be absurd to say that it has been produced by free and unlimited proliferation of cells originally normal. Free growth and independence of systemic control are certainly characteristic of established cancer; but it would be a strange confusion to regard this character as the cause of its own evolution. It is a pathological change due to a pathological condition of the cell's environment. Similarly with bacteria, continued abundance of growth, with repeated subculture on a favourable medium, is the usual means of retaining their normal characters; it certainly is not the means whereby any of the major variants are produced.

So much by way of protest against attempts to simplify the problem by taking the cellular factor for granted as a "natural tendency" to cancerous growth which explains itself. When a writer frankly adopts this method of simplication, as a few do, there is no difficulty about understanding him. But many writers are by no means easy to follow, because their attitude towards this cellular factor is not clearly defined.

The next matter about which ambiguity ought to be removed is the relationship of a true cancerous focus to normal systemic control. Many persons, with whom I agree, say that such a focus is independent of this control; this independence is a characteristic without which the focus would not be a true cancer. This position is adopted frankly and definitely, without any equivocation or reservation. There are other people who favour the suggestion that in the course of a lifetime small cancerous foci may not infrequently arise but are destroyed by a normal systemic influence. This view must be clearly distinguished from the idea, already dealt with, that an individual with an established cancer develops an *acquired* systemic influence which inhibits the formation of a new cancer. The suggestion now under consideration, which is made to fit in with certain general ideas about resistance to cancer, is necessarily no more than a surmise, since it cannot be proved. I think it is an unfortunate and confusing idea, because it is incompatible with an important pathological attribute of cancer, *viz.* its autonomy, and also because it fails to distinguish between cancer and sundry local disturbances, some of which, if not eliminated, may ultimately lead to cancer.

Perhaps I may make this point clear by drawing a distinction between the action of systemic influences in the promotion or inhibition of normal growth and their action in the control of variation. It is the latter activity which is of main interest here. Though there is no systemic control over established variants such as the definitely cancerous cell (*i.e.* there is no evidence of a selective antimalignant influence), there may still be systemic control over the incipient tendency to the formation of any type of variant. This distinction is important. It may often happen, I agree, that there is abortion of a local condition which, if left undisturbed, would constitute the latent period preparatory for cancer. This "abortion," I agree, means that there may often be a time when cells are just emerging as variants of indeterminate character, and that restoration to the full influence of the circulation will then restore the tissue to its normal condition; normal systemic influences promote the ordered growth of normal cells and suppress the variants, because the environment they provide is favourable to the former and unfavourable to the latter. This is a simple mechanism, and I think it may be accepted that it is of common occurrence in clearing up a local condition of semi-stagnation which is the sequel to an inflammatory reaction.

It is desirable that investigators should clearly define their attitude towards this issue. I think they will all agree that there is a conservative influence in the healthy body which corrects various little irregularities of growth, and so

inhibits the emergence of variants. But are they satisfied with this or do some of them ask for something more, *viz.* a selectively antimalignant systemic influence? If they incline to the latter supposition, on what grounds do they support it? I do not think they have proved their case.

Now I come to ambiguities about the relationship of real or alleged systemic influences, not to a true cancerous focus, but to a condition of "resistance" or "susceptibility" on the part of particular cells.

Differences in susceptibility of particular animals of the same species and of particular tissues in the same animal are accepted facts. As the development of the animal body is governed by systemic influences, one may reasonably say that such influences participated in the development of these differences in susceptibility. That may help partly to explain their origin. But, when once established, they are local conditions, *viz.* conditions of particular cells, not conditions directly attributable to the circulating plasma. For example, it would appear paradoxical to say that the susceptibility of the breast or uterus is not intrinsic in the mammary or uterine cells, but is due to "general systemic factors."

This view as to the local factor seems to me both orthodox and reasonable; and it helps to clarify the position. What are the alternatives?

It may be argued that undoubted differences in cellular susceptibility have a humoral explanation, and are due to the permanent influence of special factors in the circulating plasma. Thus, as between one animal and another and between two tissues of the same animal, there are selective differences in the degree of humoral resistance to the emergence of a particular cellular variant which, if left intact, would be the precursor of definitely cancerous cells. (And there might be a bacteriological analogy in the systemic influences which prevent a saprophyte from changing into a parasite.) This would form at least part of the reason why, when a batch of mice are all tarred in the same way, some develop cancer later than others and a few are completely resistant; it depends on differences in systemic resistance to the initiation of a variant. Similarly, varying degrees of efficacy of this systemic influence would be a factor in differences observed in the incidence of spontaneous cancer.

There are, I think, serious objections to this view. It would postulate a vast array of special systemic influences, each selective for a particular type of cell. As it is not known that they exist and as the facts are sufficiently explained by the cellular factor alone, it seems arbitrary and unnecessary to put forward such a postulate. Moreover, it causes confusion in one's ideas about the significance of the latent period in the genesis of cancer. During this stage, certain cells have lost their capacity of responding to normal systemic influences; this is a change in the cell's susceptibility to external influences, a change which, though originated by its local environment, is, when established, a cellular and not a systemic change. Then there is the further change, also cellular in character and local in origin, which converts the potentially autonomous but "innocent" cell into the truly malignant cell. The whole

course of events indicates changes in the characters of certain cells and in their response to pre-existing systemic influences, not changes in those influences. The idea that the efficacy of the latent period is determined by some special systemic factor is an unnecessary complication which it is difficult to understand.

Doubtless there are many other alternative views which might be proposed. The desideratum is that they should be defined clearly.

As Cramer's opinions are often quoted, it is appropriate to refer to his article "On Systemic Factors in the Genesis of Cancer[1]."

Experimenting on mice, he excised and minced up the spleen and then promptly returned this material to the abdominal cavity. After recovery from the operation, a series of these mice were painted with tar and were compared with a control batch of normal mice which were also treated with tar. The first series developed cancer more rapidly than the controls. Cramer writes: "The results indicate that there are systemic factors influencing the genesis of cancer, and that the experimental procedure adopted in this experiment had diminished the resistance against the genesis of cancer."

The natural explanation, it seems to me, is that some of the autolysed spleen tissue made its way into the circulation and behaved as an adjuvant to the irritation caused by the tar, perhaps in the same way as tar cancer has been found to be accelerated by scarification. Though one may speak of the new material passing into the circulation as a systemic influence, the experiments provide no evidence that, prior to this event, the mice were controlled by special systemic influences which regulated their response to a carcinogenic irritant. All that can be said is that the susceptibility of a particular tissue, subjected to irritation, had been increased by an adventitious systemic influence.

Further interesting questions about the nature of "resistance" to the genesis of cancer are raised by Cramer in a more recent article on "Experimetal Carcinogenesis[2]."

Instead of tarring mice over the usual small area of the skin (4–5 mm. in diameter), he painted them over a much larger surface (about 1 cm. broad and 1·5 to 2 cm. long) and observed the results. The development of malignancy was confined to a very small portion of the painted area and, if benign growths also formed in the area, they retained their benign character long after the malignant growth had appeared. He then removed the malignant growth and found that in the remaining non-malignant part of the tarred area "malignancy may develop again in a new centre either beginning at the base of a papilloma which was left behind or starting as an entirely new growth appearing subsequently to the excision of the first carcinoma." The interval between removal of the first malignant growth and the appearance of a subsequent one varied greatly. Sometimes it was so short as to suggest a correlation between the two processes. "In further experiments in which cautery was applied to the base of a papilloma, immediate malignant development was observed in six animals."

Cramer's main conclusion is: "These observations taken together supply evidence that the development of a carcinoma is not dependent entirely upon changes in the epithelial

[1] *Brit. J. Exp. Path.* **7**, 1 (1926).
[2] *Brit. J. Exp. Path.* **10**, 335 (1929).

cells, but that there are *local* inhibitory factors capable of keeping the malignant development in check, so that the immediate cause of the genesis of a carcinoma may be the *local* removal of an inhibition residing in tissue elements other than the epithelial cells." As regards the nature of this resistance of the tissues, he suggests that, in view of its shifting nature, "it is connected with the wandering cells which accumulate immediately underneath the hyperplastic epithelial cells of a skin subjected to tar-painting."

Before proposing an alternative to Cramer's view, it is desirable to clear up a matter relative to "resistance" about which there need be no dispute. A group of cells, with the internal structure and organisation of fully equipped cancer variants, is not always or necessarily in a condition of highly vigorous and autonomous growth. At the site of origin, such cells may need some help from their environment, such as increased vascularity, before they start on their invasive career. And metastases do not always find themselves in situations to which they respond by vigorous growth. This occasional lack of progressive growth is to be admitted, and there is no objection to saying that the unfavourable environment, to which it is due, constitutes "resistance."

But Cramer claims much more than that for "resistance" as a factor in the aetiology of cancer. "The process of carcinogenesis appears, therefore, not as a continuous one but as composed of two phases: a process of long duration which induces in epithelial cells the condition of 'potential malignancy,' which is kept in check by the local resistance of other tissue elements; and secondly, a local breaking down of this resistance, which allows of an immediate malignant development of the potentially malignant cells."

The alternative view is that the cells, in that part of the tarred area which does not show a malignant focus, are not cells with the full equipment of malignant variants. If any of them become malignant later on, it is due to some further environmental change which has altered their intrinsic characters. So the second phase in carcinogenesis is not the breaking down of external "resistance," but the conversion of cells which have become abnormal, as the consequence of irritation, into definitely cancerous cells.

If it were merely a question of interpreting these particular experiments on the skin of mice, the matter would not be important enough for solemn debate on the merits of the above two alternatives, to which others might be added. But Cramer, though not claiming them as crucial and decisive experiments, regards them as evidence supporting a wide and important generalisation about the nature of "resistance" in relation to carcinogenesis.

For example, he suggests that chronic irritation may cause the whole of a human mammary gland to become "potentially malignant," and that complete removal of the only actually cancerous foci present at the time of operation is not enough, because there are other "potentially malignant" areas which will become actually cancerous when the postulated "resistance," which controls them, breaks down. So the general proposition certainly calls for serious consideration.

Turning for the moment to bacteriology, there is a class of organisms which are capable of changing *in vivo* from the saprophytic to the parasitic or invasive condition. There can be no diversity of opinion about the main event. The virulent variant has acquired an internal organisation or capacity for growth

which was not possessed by the saprophyte. Change, of course, implies ability to change, and in this obvious sense the saprophyte may be said to be "potentially" virulent; but that is all. Nor is there any ambiguity about "resistance." Living tissues resist the saprophyte, but do not successfully resist the virulent variant. The change is in the bacterium, not in the resistance of living tissues, though, of course, there must have been some change in the immediate environment of the saprophyte to facilitate its development into a parasite. Here, then, is a simple and unequivocal picture of the cell's capacities and the resistance of its environment.

Tissue cells are not bacteria; but when it is a question of variation there are general considerations which ought to apply to both kinds of cells. In both cases, if the virulent and invasive variant has been actually formed, it is expected to behave as such unless good reason to the contrary can be given. It may be conceded that some help may be needed to start invasion, such as increased vascularity, a damaged or otherwise vulnerable portal of entry, or other conditions which may all be comprised under the general term "opportunity." But it seems to me a perversion of ideas to regard temporary lack of "opportunity" as equivalent to a general defensive mechanism of "resistance," and to interpret the occurrence of an "opportunity" as meaning the breaking down of this hypothetical mechanism. In both cases, again, if the invasive variant has not actually been formed, mere "opportunity" for invasion (or breaking down of "resistance") will not create the variant; there must first be some environmental influence which enables the cell to constitute itself as a variant with invasive capacity.

Comment.

I can appreciate the strong desire to postulate a systemic influence concerned with the genesis of cancer, because, if it exists, it might be amenable to control. But, if the postulate is to be plausible, it should be expounded in a way to provide answers to questions such as the following. Is it an influence concerned with the control of cellular variants in general, or is it specially selective for the cancer variant? Is it a special chemical entity? If so, can it be attributed to any special internal secretion, derived from any particular tissue? If this is not feasible, can it be referred to what I have described as the general "make up" of the plasma, to properties which invest the plasma with its individuality, but do not consist of special chemical substances? Or is the controlling influence local and cellular rather than systemic, a sort of "tissue-tension" between the would-be cancerous cells and the fixed or the wandering cells in their environment? If so, is its mechanism to be explained as merely the opposition of a physical barrier to cancerous growth, or in some other way? These questions raise difficulties which, in my opinion, still await removal.

Systemic influences may be observed experimentally in work on the grafting of transplantable tumours, in stimulating the action of a cancerogenic

irritant, and in the difficulty of inducing a second cancer in an animal already cancerous. There is also evidence that autogenous cancer in the human subject gives rise to a special systemic influence. But data such as these provide no satisfactory reasons for inferring that, in the normal body, there are special systemic influences which prevent it from becoming cancerous, or that there is a special and pathological systemic influence to which the origin of cancer is to be attributed. Nor is there any adequate direct evidence that such systemic influences have been found.

In an obscure subject such as this, a cautious verdict of "not proven" does not amount to a categorical statement that such special influences must be regarded as non-existent. Hence, the main purpose of my article is to urge that the nature of systemic influences needs fuller consideration. They are highly complex and can be analysed only to a very imperfect extent; it is quite possible that further knowledge about them may be of value in the interpretation of cancerogenesis.

If the postulate of a causal agent in the shape of a more or less ubiquitous virus is to be abandoned—as I think it must be, it is natural that search should still be made for some special systemic influence as the explanation of that uniformity of effect which marks the cancerous change.

I refer to the fact that the transition from the normal to the malignant condition is a modification of the cell's organisation, and this change must be of the same character in widely different varieties of cells, because its manifestations, *viz.* the essential attributes of malignancy, are the same. This identity of the new organisation is superimposed upon differences in internal structure which are partially retained; for example, an epithelial malignant growth retains some evidence of the normal type of epithelium from which it originated, and a sarcoma retains evidence of origin from normal fibroblasts. So cells with different chemical structures may undergo an identical change in the reorganisation of their activities. Similarly, bacteria with different antigenic components may acquire the same invasive properties; and the change of a bacterium from the saprophytic to the virulent condition, when introduced into a susceptible animal, might perhaps be attributed to something analogous to a systemic influence.

But the analogy cannot be pressed too far. With the cancer cell, unlike the virulent bacterium, the change of organisation is a degradation; as compared with the normal, the synthesis of its protoplasm is imperfect; there is stabilisation of its protein structure at a lower stage of development and growth reaches its final stage before the elaboration of combining affinities (cf. bacterial haptenes) which would respond to normal systemic control.

On the other hand, it may be said that there is no necessity to search for identity of a causal agent in the shape of some special systemic factor, since identical effects are often produced by different causes and the various local disturbances predisposing to cancer may suffice to explain causation. As the change is intracellular in origin and is propagated only within the descendants

of the affected cells, why be dissatisfied with the view that the emergence of the cancerous variant is entirely due to its local environment?

SUMMARY.

As diverse opinions are held about the significance of systemic influences in cancer, the subject needs some reconsideration. What are "systemic influences"? In the literature on cancer this preliminary question is usually ignored, presumably because it is thought that the answer is self-evident. With this view I do not agree. I think one must begin by forming a general conception about the nature of systemic influences. What are they like in the normal body? What is their position in bacteriological immunity, about which knowledge is more advanced than in cancer? Ideas derived from a discussion of these two questions ought to provide a useful base for approaching the problem as it concerns malignancy.

In the normal body the systemic influences which the plasma exerts upon the tissues form a complex system presenting three aspects, the chemical, the chemico-physical, and the vitalistic. For example, sometimes it may be said that the plasma's activity is due to a special chemical substance, such as a hormone; sometimes the predominant factor is due to the balance of its colloidal constituents; and not infrequently its action can only be attributed to those properties of living matter which cannot be reproduced in the chemical or the physical laboratory. These three aspects of systemic influences are not independent factors but have to be correlated; and the essential difficulty of the subject is to assign to each of them its appropriate significance.

In natural immunity and resistance towards bacteria, these normal systemic influences are in possession of the field and it is upon their activities that the fate of the bacterial intruders largely depends. Where the immunity is non-specific, as in the inability of saprophytes to grow in living tissues, the defensive factor bears a prominently vitalistic aspect. The mechanism of bacterial destruction seems largely to depend on the circumstance that the bacteria find themselves in a living animal environment where they cannot remain in the resting stage; they must endeavour to grow but they perish in the attempt because the medium is unsuitable.

What is the nature of "alexin" as a natural defensive mechanism? The idea that it is a special chemical substance secreted by some cells of the body must be abandoned. *In vitro*, it is a property due to the chemico-physical lability and colloidal complexity of fresh serum, in virtue of which the serum promotes interactions which would not take place in a more stable medium. *In vivo*, the plasma possesses similar chemico-physical properties in a more complex and more effective form, supplemented by its vitalistic capacities as living material. For these properties of the circulating plasma the term "alexin" is not appropriate.

As regards specific manifestations of natural immunity, how is one to explain the selective action of normal systemic influences on bacteria which

are pathogenic for some species of animals but not for others? Selection naturally suggests special chemical attributes of the plasma; but species immunity has not been identified with the presence of distinctive chemical substances and it is not likely that it ever will be. One has to fall back on the chemico-physical attributes of the plasma which constitute its general "make up," as characteristic of a particular species. And these attributes must be regarded not as a system in stable equilibrium but as a dynamic system involving an ordered sequence of reactions.

The most important feature of true natural immunity is that, when the bacteria have been disposed of, the condition of the plasma remains as it was before their intrusion. Its activities have not been due to antibodies, in the accepted serological sense, and the destroyed bacteria have not behaved as antigens.

In most of the literature on acquired immunity the chemical conception stands out very conspicuously. Bacterial protein behaves as an antigen and stimulates certain cells of the host to secrete an antibody; that is regarded as the basis of immunity. After allowing for the operation of chemico-physical laws, the predominant feature remains that an immunological reaction is essentially the interplay between two chemical entities, an antibody (agglutinin, lysin, tropin, etc.), and its corresponding antigen. This conception is considered preferable to the much less concrete ideas of interactions between systemic influences and living bacterial protoplasm.

Whilst appreciating the value of precise chemical data, I consider that this view of acquired immunity is one-sided and inadequate. Systemic influences (other than serological antibodies) cannot be left out of account in the conception of interactions between living bacteria and the living animal body. One needs a scheme which will help to correlate natural with acquired systemic influences, to bridge the gap between specific and non-specific factors, and to modify the conception of an antibody as a special chemical entity, specially secreted by certain cells in response to the stimulus of a foreign protein. Within such a scheme, as I have endeavoured to show, an explanation may be found for what may be called the routine production of antibodies by antigens.

Coming now to cancer, one must first insist on the commonsense view that the transplantation of grafts is a special and relatively unimportant line of experiment which, whatever interests it may possess in other respects, does not help to explain either established autogenous cancer or the genesis of cancer. In these grafting experiments certain systemic influences emerge which cannot be explained as due to the production of antibodies by antigens. This is to be expected, on the analogy of similar manifestations of antibacterial systemic influences. But neither natural nor acquired systemic resistance to the taking of a graft involves anything which may be regarded as a new kind of systemic influence peculiar to cancer.

In the case of established autogenous cancer there does seem to be a new

kind of systemic influence which is directly attributable to the disease. This influence, as is found by animal experiment and by observation on human malignancy, inhibits, or tends to inhibit, the creation of a second and independent malignant growth in the same animal body. Apparently products of the existing cancer pass into the circulation and cause other tissues to lose their susceptibility to influences which might ultimately have produced a malignant variant. The mechanism of this inhibitory action is obscure and is probably more complex than the chemical influence of a particular cancerous product upon normal cells. Whatever may be the right explanation, the observed facts indicate that it is something new, which is created by the cancerous condition; they afford no proof whatever that, before the cancer existed, there were in the circulation special systemic influences which were favourable or unfavourable to the genesis of cancer.

The idea that there are systemic influences concerned with the genesis of cancer has assumed many forms and is often expressed ambiguously. Does it mean that normal cells have a "natural tendency" to malignancy and will actually become malignant if freed from systemic control? I do not accept this "natural tendency"; unrestrained growth does not suffice to explain the origin of cancer. What is meant by "systemic control"? My view is that such control regulates normal cells and that cancer cells are independent of it; I do not agree that there is a special kind of antimalignant systemic control which may destroy the fully fledged cancer cell. What is the nature of "susceptibility" to the change into the cancerous condition? I regard it as essentially a cellular property, not as a humoral or systemic influence, though I admit that irritant material which gains access to the circulation may increase the susceptibility of particular cells. What is meant by "resistance" (either local or systemic) to cancer? Owing to the recuperative powers of the animal body, local disturbances of metabolism are often corrected and there is a return to the normal condition; some of these disturbances, if left uncorrected, might have led to cancer and the fact that they have been corrected may, if one likes, be called resistance to the genesis of cancer. It is also known that true cancerous foci or metastases may remain quiescent for a considerable time. But I do not agree that such quiescence has been shown to be attributable to a specific kind of antimalignant "resistance" (either local or systemic).

Whilst there is no satisfactory evidence, either direct or indirect, of a systemic influence which causes cancer, systemic influences are so complex and obscure that this possibility cannot be definitely excluded. But there does not seem to be any cogent reason for dissenting from the view that the production of the malignant variant is due to its local environment.

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