The bearing of immunity reactions on the nature of cancer / by E.F. Bashford.

XVIIIth International Congress of Medicine
London: 1913

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Chemical Pathology

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BY

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London

LONDON
HENRY FROWDE HODDER & STOUGHTON
OXFORD UNIVERSITY PRESS WARWICK SQUARE, E.C.
1914

[Friday Morning, August 8]

SUB-SECTION III (a)

CHEMICAL PATHOLOGY

DISCUSSION No. 2

(JOINTLY WITH SECTION IV, BACTERIOLOGY AND IMMUNITY, DISCUSSION No. 2)

CANCER

REPORT BY E. F. BASHFORD, M.D., LONDON

The Bearing of Immunity Reactions on the Nature of Cancer

THE early experience gained from the grafting of cancer of the mouse has been amplified in the laboratories of the Imperial Cancer Research Fund by many experiments on other animals, especially the horse, dog, rabbit, guinea-pig, and rat, in all of which, except the first, true tumours have been transplanted. In consequence, sharp distinctions may be drawn to-day with great confidence, between heterologous, homologous, and autologous inoculations. Moreover, the employment of the term immunity with reference to cancer has been found subject to very narrow limitations, since, as will be demonstrated, it signifies nothing more than the exemption—under clearly defined circumstances—of one individual from the consequences of *transplanting* a tumour from another individual of the same species. The employment of the term immunity with reference to cancer in the present state of our knowledge is really wrong, because, as pointed out in 1906, the resistance which can be induced artificially to the continued growth of grafts does not create any exemption from the liability to the development of cancer. It is also certain that cancer is rarely, if ever, communicated naturally or spontaneously from one individual to another by transplantation, and that its great frequency cannot be explained in this way. The mechanism of its natural development therefore differs fundamentally from transplantation, and the use of the term ' immunity ' can only be justified by convenience.

Resistance to the transplantation of cancer comprises a large number of phenomena which are of the nature of hindrances to the continued growth of the already fully developed cancer-cell. The analysis of these phenomena has permitted of the discovery of some subtle properties of the cancer-cell, as well as of some of the relations obtaining between it and the animal in which it grows, both in the case of the natural and of the transplanted cancer-cell.

I propose to consider 'immunity' to cancer in the light its study has brought upon the nature of the tumour-cells and their relation to the individual serving as food purveyor. Throughout, sharp distinctions will be drawn between heterologous, homologous, and autologous inoculations, whether employed for the purpose of inducing or of testing resistance. Notwithstanding these distinctions, it will be shown that the results converge upon conclusions of importance.

The reason of the unsuitability of a species for the progressive growth of cancer of a strange species was raised in 1904 in the First Scientific Report of the Imperial Cancer Research Fund, and explained as probably due to an active immunity leading to the development of cytotoxins analogous to the hæmolysins, and other antibodies which are developed against tissues of heterologous origin. Subsequently Ehrlich (1906) sought to explain the transitory growth, first noted by him for mouse tumours implanted in rats, as coming to an end in consequence of a starvation from lack of special food-stuffs or of stuffs inciting growth—atreptic immunity. Subsequent investigations have confirmed the explanation originally given, and I do not propose to elaborate Ehrlich's additional form of immunity.

In the Second Scientific Report, in 1905, a parallel was fully demonstrated between the processes occurring during healing under the action of radium and adrenalin and those occurring in the spontaneous healing of transplanted tumours, particular attention being directed to the occurrence of hæmorrhages under all of these three conditions. At that time it had been ascertained already that the absorption of tumours under the action of radium was followed by protection to re-inoculation, but the number of re-inoculations (16) did not justify publication of this result, and Clowes first published evidence that mice in which tumours had been absorbed were resistant to a second inoculation. He explained the phenomenon as due to the production of antitoxins as in infective diseases.

The first years of the investigations of the Imperial Cancer Research Fund and of Ehrlich and Apolant led to marked distinctions being drawn between the origin and the continued growth of tumours as well as between the behaviour of the spontaneous tumours of the mouse in their hosts of origin and when transplanted into other individuals of the same species. It is well to emphasize that these differences were recognized thus early by experimenters themselves, since in more recent times much has been made of them.

Resistance to Heterologous Inoculation

Heterologous inoculation may be practised in two ways. One species of animal, say a rat, may be inoculated with the tumour of another animal, say a mouse, and the rat may then be tested as to resistance to an inoculation of its own kind of tumour or for resistance to mouse tumour. In the first there is no resistance induced, in the second there is.

Apart from a few observations which do not carry conviction but awake mistrust, there is general agreement that the normal tissues or tumours of one species of animal are incapable of progressive growth or even of continued existence in another species. Very extensive investigations have been made into this subject, and the few positive results cannot be set up against the enormous preponderance of negative results obtained. The conclusion has also been arrived at that the few experiments showing that resistance to the inoculation of the tumours of one species has been induced by the immunizing effect of the tumours of a strange species are quite unreliable. The fallacy of too small numbers explains some of these results, and it must be admitted that inconstant results can be obtained which appear to support the view that resistance can be induced in this way; but the explanation has usually been found in illness of the animals often due to enteritis, or in consequence of bacterial infection through the agency of the material inoculated, or when an operation was performed. Such apparently positive results have also been claimed after the strange tumour has been thoroughly crushed, the method even being recommended in order to secure success. In such experiments there lurk fresh sources of fallacy, since tumours are robbed of all immunizing power even for their own species if mechanically disintegrated. Similar fallacious and equally inconstant results can be obtained by the normal tissue of a strange species, and for similar reasons. The failures to induce resistance by heterologous inoculation against a subsequent homologous inoculation are independent of the doses employed either to induce or to test it, and also of the interval before testing and the age of the animals employed. In view of the strict limitation of progressive growth after transplantation to animals of the same species,[1] it is obviously quite erroneous to interpret such occasional and in all probability fallacious results as bearing on the resistance which can be induced against the inoculation of a species with tumours or normal tissues of its own kind. On the contrary, by far the greater mass of the accumulated data shows that tumours of one species are both incapable of progressive growth in another species, and of power to induce resistance to tumours of the species inoculated. These two lines of inquiry therefore agree in bringing out general exemptions which can only be explained on the basis that the tumours have a specificity analogous to that distinguishing the organisms from one another as zoological species. These two groups of phenomena of themselves have no bearing upon the resistance which can be induced against the inoculation of tumours into other individuals of the same species. In conjunction with other studies they do have a bearing upon the question of whether an immunity is induced analogous to that against infective diseases, by

[1] It is not proposed to discuss growth *in vitro* and in the plasma of strange species, or the analogous growth of mammalian tumours in chick embryos. These methods have nothing common with growth in animals capable of the vital immunity reactions.

showing that when induced it does not depend on a virus common to cancer in whatever species of animal it occurs.

Induced resistance to a repetition of the heterologous inoculation has been demonstrated to occur and to give reactions identical in nature both *in vivo* and *in vitro* to the well-known hæmolytic and cytotoxic reactions induced by immunizing with antigens from strange species. The doses used to induce and to test resistance are important, as is also the time interval before testing. The age of the animals should also be uniform. It is possible that the tumours and tissues of nearly related species, e.g. the blood of the rat and of the mouse—as pointed out in 1906—do have a slight reciprocal influence ; but, if so, its existence only serves to emphasize the importance of blood-relationship rather than the intervention of a cancer parasite common to the different zoological species.

The absence of progressive growth after heterologous inoculation, and also the non-production of resistance to subsequent homologous inoculation, may be illustrated [1] by charts of experiments for the mouse, rat, and rabbit.

The tissues need not be alive in order to induce the hæmolytic, cytolytic, and heterologous cancer-immune reactions, but retain this power, e.g., after mechanical disintegration.

Heterologous Immune-sera

One of the hopes awakened by the knowledge of the cytotoxins was that of a further development of a rational organotherapy. In the promotion of more accurate diagnosis and in forensic medicine the methods relied on have yielded advances of prime importance ; but the hope of fresh therapeutic triumphs has not been fulfilled. The sharp specific distinctions which may at times be drawn *in vitro* between normal and cancer immune-sera do not necessarily, if at all, obtain also *in vivo*. In the test-tube they present in varying degree hæmolytic precipitin and cytolytic reactions which as yet have not been shown to have any distinctive characteristics. Notwithstanding all statements to the contrary, ' cancer-immune ' sera must to-day be regarded as devoid of all action in the living body. As vehicles for the communication of passive immunity such heterologous sera have proved valueless, and likewise they have not been demonstrated to possess qualities which can be relied on for the purposes of diagnosis.

Under this category there also fall the results which have been interpreted as toxic or anaphylactic phenomena after a repetition of an inoculation. On the basis of careful and numerous repetitions of the methods on which such observations have been advanced, the conclusion has been arrived at that they are due, not to anything specific to cancer tissue, but rather to accidental bacterial contamination.

[1] This reference and all others to illustrations, figures, or experiments apply to the diapositives exhibited at the reading of this paper.

Homologous Immunization and Resistance

In contradistinction to heterologous immunization the effects following homologous inoculation are markedly influenced by the age of the individuals, the site of inoculation, the doses used both to induce resistance and to test it, the time interval before testing, and the vitality of the tissues.

Homologous resistance may be considered from the standpoint of whether it is pre-existent and natural or induced by active changes following on various procedures.

Natural Resistance

Natural resistance played a much more prominent part at the beginning of the investigation of immunity to cancer than it does to-day. Many of the earlier observations could not be otherwise than tentative during the period when an appropriate technique was being developed. For example, under one form of technique, the primary transplantation of certain hæmorrhagic mammary growths of mice succeeded not more than once in 500 attempts. With a different technique these growths were as easy to transplant as other mammary tumours. Naturally the appearance of 499 resistant mice out of 500 was calculated to give great importance to natural resistance, the real explanation being, however, the employment of such large doses for inoculation that auto-immunization was induced and put a stop to growth; perhaps also the greater suitability of young mice than old mice for growth was not fully recognized at that time. The existence of a certain amount of natural variability in power of reaction from animal to animal cannot be denied, and account must also be taken of age, site, dose, time interval. Although some tumour-strains are relatively indifferent to age, no strain has been found which grows better in old than in young animals. Young animals are as a rule more susceptible than old, whether they come of normal or of cancerous stock, the latter not offering a more favourable soil. In primary transplantation a small dose, or minute intact fragment, as a rule gives a higher proportion of takes, than does a large dose of emulsion or a large graft, and the same holds for a good proportion of propagable tumours. The loose subcutaneous tissue of the flank is more favourable for inoculation than the dense tissue of the back or the peritoneum in most cases.

Since young animals are more suitable for inoculation and continued growth than old animals, the rarity of cancer in the young is not due to constitutional resistance to growth and its frequency in the old is not due to a constitutional change occurring with senescence, favourable to the growth of cancer in general. This conclusion led to determining whether animals naturally suffering from the disease offered a more suitable soil than others for the growth of cancer in general. It was found that they did not do so. Whereas the re-inoculation of an animal with its own tumour is always successful (apart from accidents which may reduce the percentage to about 90), the success of the primary trans-

plantation on inoculating other cancer-animals is on a level with that for normal animals. Thus the strict individuality of spontaneous tumours has been demonstrated by the resistance which the majority of strange hosts offer to the introduced cancer-cell. How far the resistance to a single inoculation, without any previous procedure, is pre-existent or actively induced will be considered after regard has been paid to the varying proportions of successful takes for different propagated strains.

Active Resistance induced by Tumours

Active resistance can be induced in a variety of ways—by inoculating with spontaneous or propagated tumour without obvious growth following; by inoculating with propagated tumours, which after a considerable amount of transitory growth become absorbed; by inoculating with normal tissues. It is not advisable to aim at too great refinements in dosage of tumours. Owing to the variability both in the nature of the tumour material and in the amount of growth supervening on inoculation, comparisons are permissible only with extremes. If the dose of spontaneous tumour inoculated without giving rise to daughter-tumours in normal mice has been sufficiently large, they will exhibit resistance to a second inoculation of a propagated tumour taking in maximum percentage and of extreme powers of growth. The extent of the resistance is not uniform for all such negative inoculations with spontaneous or propagated tumour; if the dose be too small, resistance may be practically absent and the animals react almost normally by giving a number of tumours approximating to the control. Conversely, the dose used to test the existence of resistance may be so large as to overcome it, if present. Spontaneous tumours also vary among themselves in the extent to which they induce resistance against the same test tumour-strain.

Propagated tumours exhibiting the phenomenon of transitory growth followed by spontaneous healing induce resistance to re-inoculation whenever this results. This resistance is usually absolute for a secondary inoculation of the same tumour-strain, but may be only partial or altogether absent in the case of different tumour-strains. There is thus a degree of resistance common to all tumours. The explanation of this common property and of these diversities is obtained by studying in more detail the induction of immunity by normal tissues and the phenomena of double inoculation as described below.

Active Resistance induced by Normal Tissue

Normal tissues induce a high degree of resistance: defibrinated blood, erythrocytes, liver, spleen, testis, mammary gland, kidney, placenta (freed from blood), entire embryos, embryonic skin, &c. The most convenient tissues to work with are blood and embryonic skin, especially the latter, because of the great uniformity that can be obtained, both technically and in the results; it is also the most potent. Spleen,

while giving a high degree of resistance, is apt to be infected. Liver is also liable to be infected, and is not so good an immunizing agent. Serum and plasma do not induce any resistance. In the case of normal tissues dosage can be more accurately adjusted, both because of the uniformity of the material and of the amount of growth they exhibit on transplantation, a variable factor which can be excluded in the case of blood.

The power to induce resistance varies from one tissue to another, and the same tissue does not induce the same degree of resistance against all tumour-strains. Thus blood produces a high degree of resistance against Strain J but not against Strain 32 or 50. Embryonic skin produced the highest degree of resistance against a squamous-celled carcinoma, giving rise to the surmise that histological relationship might have some specific influence, although the possible influence of a high and pure dose of epithelium could not be excluded. Further experience has not yet tended to confirm this view as to histological relationship, and the results may be explicable rather by the varying qualities of the tumour-strains rendering some more susceptible to resistance, as described below.

The high degree of resistance induced by spleen is remarkable and has attracted particular attention, owing to the apparent rarity of metastases in this organ. Testis was stated not to produce resistance, but has also been found to do so.

The Parallel in the Onset, Duration, and Distribution of the Resistance induced by Tumour and Normal Tissue

There is no advantage in repeating an immunizing inoculation. One adequate dose suffices, and thereafter the parallel in the rise, duration, and disappearance of immunity induced by normal and tumour tissue, as shown in the accompanying curves, is of great importance. Of normal tissues skin always induces a higher and kidney a lower level of resistance against Strain '63' than does spontaneous tumour, but there is throughout a parallel course for all three curves, the maximum being attained at about ten days and the normal level returned to after about 80 days. This parallel would of itself serve as evidence that the resistance is identical in nature whether induced by normal or cancer tissue; an extraneous agent or virus cannot be made responsible for the resistance induced by embryonic skin, and there seems no reason to suppose that the resistance induced by cancer tissue is due to any property other than that of cancer *qua* mouse tissue.

The resistance conferred by a single inoculation is distributed all over the subcutaneous tissues of the body, the peritoneum, internal organs (kidney), and extends even to the blood. If a tumour-strain naturally giving rise to metastases be injected as fine emulsion into the tail vein, metastases in the lungs can be simulated, but in immunized animals the number falls far behind that in the control. The wide distribution of the resistance throughout the body almost makes the

assumption of the presence of some substance in the body-fluids a necessary postulate, and the indications of quantitative relations point in the same direction.

Distinction between Living and Dead Tissue

The tumour tissue and normal tissue must both be alive if they are to call forth resistance. If killed or disintegrated so that no intact cells remain, no resistance is induced, whether the means employed be chemical, mechanical—as effective crushing at or below 0° C.—or actinic, such as heat or exposure to radium. The absence of immunizing effect cannot be overcome by enormously increasing the dose. Even red blood corpuscles, if completely ground at the temperature of ice and salt, lose all power to induce resistance. Although it would appear that growth following inoculation must contribute to the production of resistance by actually increasing the dose of the effective substances, mere growth of itself would appear to be non-essential, since growth of the inoculated red blood corpuscles can certainly be excluded. Some subtle product of metabolism of the living cell would appear to be essential in consequence of whose action a change is effected in the body-fluids of the resistant animal.

Homologous Immune Serum

The serum of immunized animals has not yet been shown by *in vitro* experiments to differ from that of normal mice. Nothing of an antitoxic or cytolytic reaction has been discovered. Neither has it been shown to possess curative powers, nor has passive resistance been conferred by its means. The milk of highly immune mothers conveys no resistance to their offspring. Nevertheless, the change effected by immunizing is so very marked that its full nature must ultimately be revealed by refined technique. Meanwhile, this problem can be approached by indirect means.

Nature of the Change

The nature of the change effected by immunization is elucidated in part by studying the processes of spontaneous healing of tumours, by examining the site of grafting in normal and in immune animals, by searching for histological evidences of reaction throughout the body, by analysing the results of double inoculations of different tumour-strains, and by observing the effects of progressive and of transitory growth of tumours on the relative weights of the several organs of the body, and lastly by observing any changes which may occur in the metabolism.

Spontaneous Healing

The phenomenon of spontaneous healing can be obtained with any desired frequency from a sufficiently representative series of differently

propagated tumour-strains, but it is extremely rare in spontaneous growths not occurring so often as once in every hundred of the spontaneous tumours observed.

Very characteristic histological pictures are to be seen when a tumour undergoes absorption after growing for a time and it may be attaining huge dimensions. There are hæmorrhages; the tumour-cells vary in their staining capacity so as to exhibit light and dark areas, or they are more obviously degenerating; aggregations of plasma-cells are more frequent than in growing tumours; later, the tumour-cells are cut up into groups surrounded by a large zone of phagocytes, and ultimately scar-tissue forms. The conditions obtaining between the connective tissue and the cancer-cells are obviously quite the opposite from those obtaining in a growing tumour. The primary change appears from the histological investigation to arise probably in the tumour-cells themselves, but of course this cannot be determined by direct microscopical observation. That this is the case, however, is shown by the fact that while one tumour goes on growing, another tumour in the same host is being absorbed. That the primary change is in the tumour-cells has been determined by studying the site of inoculation in normal and in immune animals, and by investigating the resistance which tumours induce against themselves, as described below under auto-immunization. The histological appearances are exactly analogous in the rare phenomenon of the healing of spontaneous tumours, and in their case also changes in the tumour-cells themselves play the determining rôle. As in transplanted tumours, one spontaneous tumour may be absorbed whilst another continues to grow. Whether or not constitutional hindrances to growth also develop, as in transplanted tumours, has not yet been determined.

Examination of the Site of Grafting

When a minute graft is made into a new host the carcinoma-cells persist and grow progressively. The supporting scaffolding of blood-vessels and connective tissue degenerates and is supplied afresh by the new host reacting to the chemotactic powers of the cancer-cells in such a specific manner that the structure of the mother-tumour is exactly reproduced, it may be after years of continued propagation. In animals immunized by normal or tumour tissue this *specific* reaction does not take place. Superficial examination may lead to the conclusion that the reaction is the same, but the careful examination of serial sections shows that neither the connective tissues nor the blood-vessels of the immune host penetrate the graft in the same way as in normal animals. There is a reaction in immune animals, but it is of a different nature. The cancer-cells in the immune animal are lying in a single layer against a solid wall of the host's tissues, at a time when the graft would be developing into a well-reorganized miniature tumour in a normal animal. They are as near the food supply as they can get, and

are not immediately or directly killed by some potent cell-poison. Their architectural powers of moulding a new stroma of blood-vessels and connective tissues from the host appear to be paralysed, as shown in the accompanying figures for the mouse and rat, and ultimately they are so injured as to die or succumb to the formation of scar-tissue. In its essence the process is the same as in spontaneous healing. It is more acute because the immunity reaction was existent before the graft was introduced, whereas in spontaneous healing it is induced concomitantly with the growth of the tumour and has to overtake the latter.

It is possible to proceed further by applying the information thus gained to an analysis of the difference obtaining when inoculation is successful and when it fails in animals already bearing tumours. The method now is to inoculate two tumour-strains, either simultaneously or one at an interval after the other, and then to examine the site of the graft: the same histological differences as described above are thus again found between the two cases, and the same mechanism of active resistance may be inferred.

Reaction throughout the Body

Apart from the fact that the resistance is disseminated throughout the body, it has been found that the connective tissue contains an excess of plasma-cells during the time when the resistance is developing.

The Relative Weights of the Several Organs

The growth of a tumour leads to hindrance to the growth of the animal bearing it, so that very young animals may remain dwarfs as compared with others of the same age that have remained free from tumours. When the several organs of tumour-bearing animals are weighed and expressed as ratios to the total body-weight (minus tumour), it is found that there is a relative hypertrophy as compared with the normal. This hypertrophy is most marked for the heart, lungs, liver and kidney, and spleen. Owing to the great fluctuations occurring in the weight of the spleen from other causes the interpretation of the figures for this organ may only be made with caution. From the standpoint of immunity it is of importance to determine whether this hypertrophy is due to supplying the needs of the tumour or concerned in the development of resistance. In this connexion the heart, lungs, and kidney need not be considered. The spleen is particularly interesting, owing to the apparent rarity of metastases in it, and the prominent part the liver plays in dealing with all intoxications also claims attention for it. It is necessary to consider the effects produced by tumours which always induce resistance and strains which never do so. The ratio of the weight of the spleen to the body-weight varies in normal animals from 1 : 54·4 to 1 : 81·4, the body-weight being reckoned after removal of the alimentary canal plus contents. Similarly the liver varies from 1 : 12 to 1 : 14·4. The following figures show that the hypertrophy

of the liver and spleen is greater in animals bearing progressively growing tumours than it is in animals in which tumours are undergoing absorption or have already been absorbed. It follows, therefore, that the hypertrophy of the liver and spleen occurs independently of the influences proceeding from a tumour and calling forth active auto-immunization. The hypertrophy is concerned in promoting growth and not in hindering it. The tissue of the hypertrophied organs (liver) has undergone no modification in its immunizing property.

ABSORPTION TUMOURS—RATIO OF ORGAN-WEIGHT TO BODY-WEIGHT

Batch.	*Tumour.*	*Mouse.*	*Spleen.*	*Liver.*
5 mice— 63		1 : 20·65	1 : 70·2	1 : 12·04
4 mice—Jensen	1 : 55·4	1 : 14·13	1 : 64·2	1 : 9·6
18 mice— 37		1 : 15·34	1 : 65·62	1 : 12·08
7 mice—206	1 : 145·2	1 : 13·07	1 : 52·59	1 : 10·4

PROGRESSIVE TUMOURS—RATIO OF ORGAN-WEIGHT TO BODY-WEIGHT

12 mice— 63	1 : 2·9	1 : 14·29	1 : 43·2	1 : 10·3
10 mice—Jensen	1 : 2·99	1 : 13·07	1 : 40·4	1 : 8·19
16 mice— 37	1 : 2·6	1 : 13·1	1 : 48·3	1 : 10·2
4 mice— 91	1 : 1·9	1 : 12·7	1 : 47·5	1 : 9·4
2 mice—349	1 : 14·8	1 : 23·7	1 : 48·8	1 : 11·15

AUTO- OR CONCOMITANT RESISTANCE

From the preceding results it was possible to advance yet deeper into the biological properties of the cancer-cell and to determine the nature of a difference between tumours growing progressively and those exhibiting only transitory growth.

The behaviour on transplantation of propagated tumour-strains differs greatly from one to another. In a representative series of eighty-six strains of different primary origin there are at one end strains which take in 100 per cent. of all animals, grow rapidly, and always progressively, and under suitable conditions exhibit metastases in a high proportion. At the other end there are strains which, although they take in 100 per cent., grow only transitorily and all become absorbed. Between these extremes there are series exhibiting all possible combinations of rates of growth, proportions of takes, and of absorptions. To explain this differing behaviour five main methods of investigation have been resorted to—the influence exerted by varying the dose of material inoculated, the re-inoculation of the animals after the primary inoculation had shown growths, the simultaneous inoculation of a strain showing progressive growth and of one that is always absorbed, the surgical removal of the first set of tumours prior to a secondary inoculation, the microscopical examination of the site of inoculation. All these methods lead to the same conclusion. The reason for the difference is to be found chiefly in the varying degree to which the tumour-cells are able to elicit an active reaction against themselves and are susceptible to it. The susceptibility of the animal plays a minor part; although

natural resistance cannot be altogether dismissed theoretically, practically it can be left out of account, and the conception of variability in power of reaction from animal to animal substituted for it. There are tumour-strains which induce a powerful auto-immunity or concomitant immunity in every animal, which, within limits, is more rapidly effective and of higher degree the larger the dose. There are strains which induce no such reaction whatsoever, so that an increase of dose merely leads to bigger tumours in a shorter time. Between these two groups there are all gradations. The effect of the primary inoculation on a secondary inoculation is the same whether the latter be practised with the primary tumours present or after their surgical removal; according to the nature of the tumour first inoculated there will be respectively no resistance to the secondary inoculation or an active resistance to it. In the latter case the examination of the site of the secondary inoculation shows changes identical with those found when early grafts are examined from animals which have been actively immunized by normal or tumour tissue, viz. absence of the *specific* blood vascular and connective tissue scaffolding on the part of the host.

Autologous Inoculations

It has been determined that mice in which tumours had originated presented—as regards their reactions to tumours other than their own—no deviations from normal mice, either as regards suitability for inoculation or for being immunized. Against the re-inoculation of their own tumours all methods of immunization are powerless. While resistance is effectively present against a strange tumour, an autologous inoculation will always overcome it, if indeed it intervenes in any way at all, of which there is no evidence. Conversely an inoculation of an animal's own tissues is equally incapable of protecting it against the growth of a tumour from another individual.

Since an animal's own normal tissues do not induce resistance to a homologous cancer inoculation, there is no reason why its own cancer tissue should do so, and tumour-cells on autologous inoculation into immunized animals naturally subject to cancer probably do not even require to overcome the homologous resistance. The tumour-cells are indifferent to the existence of resistance when replaced in their natural hosts. This fact possibly gives us an insight into the relative importance played by the changes in the cells confined within the circumscribed area in which cancer develops, and general constitutional conditions existing at the time of such changes.

Loss of Power to induce Resistance and Acquisition of Powers of Continuous Growth

Tumour-strains which although taking in a high percentage only exhibit transitory growth and produce active resistance present exactly

the same features as do normal tissues on transplantation. There is, of course, the difference that although normal tissue cannot be grown in an indefinite succession of hosts, such tumours can be, if transplantation is performed sufficiently early. Of great importance is the observation that from mother-strains exhibiting these phenomena there can be obtained daughter-strains with better powers of growth and even possessed of progressive growth in every animal and able to produce metastases in a high percentage of them. Such altered daughter-strains have not become insusceptible to the immune reaction, or ' serumfest '. As grafts, they remain susceptible to resistance induced by normal tissue or tumour, but they have lost the power to induce resistance to their own growth and to the growth of other tumours. The change must be of great fundamental importance, since before its occurrence a dose of cells able to render absolutely resistant an animal 200 to 400 times their weight, and evident even if it be only 1/1300 of the weight of the animal, loses this power entirely. They no longer induce hindrance either to their own growth or to the growth of other tumours, and therefore they behave in this respect in normal animals in the same way as autologous inoculations of spontaneous tumour. It would appear that a new fact bearing on the correlation of growth has been brought to light by showing how progressive powers of growth have been acquired in the case of such daughter-tumours.

Hypersensitiveness

The use of this term, as of ' immunity ', can only be justified by convenience. The condition has nothing in common with anaphylaxis, and only implies an alteration in the soil in consequence of which tumours grow better.

This phenomenon has been described after the inoculation of tumour tissue or normal tissue either undamaged or treated in various ways, e. g. by heat or crushing. It is not an antecedent stage in the production of resistance, but rather a later phenomenon. The subject is not thoroughly cleared up. Apparently it is of the nature of a neutralization of the power to react with active resistance and not a persistent stimulus to growth, since it has not been possible to get clear evidence of the abolition of immunity by inoculating crushed material into an actively resistant animal.

Possibility of applying Results to explain Nature of Cancer

Active resistance is effective against grafts and emboli, and hardly effective or not effective at all against well-established tumours, except such as are liable to spontaneous healing in consequence of auto-immuniza-

tion. A slight effect of active resistance, never amounting to cure or persistent holding up of growth, can be obtained on strains which do not induce auto-immunity and grow progressively in consequence. A problem of great interest centres in the difference between the great susceptibility of grafts to active resistance and the relative or absolute insusceptibility of established tumours. This contradiction is of primary importance in any discussion of the nature of cancer immunity. This contradiction has not yet been completely resolved, but the conclusion has been drawn that something circulating in the fluids and acting on the cancer-cells is responsible for the histological pictures observed (1) for grafts in immunized animals, (2) for secondary grafts in animals in which the primary inoculation has led to tumours which ultimately are absorbed, and (3) for those seen during spontaneous healing. The part played by changes in the cancer-cell itself is brought out by the fact that while one tumour is absorbed another continues to grow in the same host.

Some facts of great importance stand out as having possible bearings upon the nature of cancer. Tumours vary in all degrees in their power to induce resistance and in their susceptibility to it, however induced. From mother material able to induce resistance there has been derived material which has lost this power, and while retaining susceptibility to resistance as a graft has acquired powers of progressive growth for established tumours. The normal relation between the cancer-cell and the connective tissues has been shown to be distinct from that obtaining in immune animals and when healing is taking place, either of transplanted or spontaneous tumours. It must not be forgotten that, with the exception of healing, these phenomena have only been observed on homologous inoculation, and that to consider their bearing upon the behaviour of cancer in its native soil is to leave fact for the realms of speculation. Nevertheless, the purpose of all these experiments is ultimately to find an application to spontaneous cancer, and, since the differences are probably in degree rather than in kind, speculation along the following lines may promote the discussion which it is the object of this paper to open.

The difficulty is that the loss of power to induce resistance on homologous inoculation is not combined with a loss of susceptibility to resistance. Loss of power to induce resistance, while having also local, has constitutional consequences. Insusceptibility to resistance would have similar consequences. Loss of power to produce resistance combined with insusceptibility to resistance would also have local and constitutional effects. Absence of power to induce resistance is combined with insusceptibility to it when the autologous inoculation of cancer is practised in immunized animals. This combination apparently does not hold for normal tissue, which on subcutaneous autologous inoculation is absorbed after transitory growth, even in non-immunized animals.

In connexion with this loss of power to induce a reaction of resistance, perhaps mention should also be made of those epithelial tumour-strains which lead to the production of sarcoma, and for two reasons. First,

because this change may be effected both in the animal in which such tumours arise and in normal animals. Secondly, because the power to produce sarcoma in this way may be as completely lost, in the course of prolonged propagation, as is the power to induce resistance in the case of other strains. Like the power to induce resistance, the power to elicit sarcomatous reaction cannot be separated from the vitality of the cells. In each case some subtle metabolic product appears responsible. The reaction which leads to the supply of a fresh connective and blood vascular scaffolding must be a closely allied phenomenon. In its beginnings it may be protective in nature, but ceases to be so on account of the influence proceeding from the cancer-cells. The paralysis of this influence is the essence of active resistance.

With reference to the loss of the two distinct powers to induce resistance and to induce sarcoma, it should be pointed out that while the first is the loss of a power to produce a constitutional change of fundamental importance, the second is the loss of power to induce a purely local change confined within a minute circumscribed area, but nevertheless of equally fundamental importance. Both have reference to a change in the relations obtaining between the cancer-cell and the connective tissue due to activities of the cancer-cell itself, only revealed secondarily by changes in the host. In the first it has been determined that a loss of a power to induce a reaction of resistance has taken place, but in the second it is not known whether a power to stimulate the connective tissue, or a power to neutralize hindrance to the growth of connective tissue, has been lost. Such a loss of itself would not explain the progressive growth of the sarcoma after disappearance of the carcinoma, e. g. on transplantation.

A mere loss of power to induce hindrance to their own growth on the part of a small group of cells in the circumscribed area within which a cancer arises would not explain the origin of the disease, because the influence of all the remainder of the normal tissue of the same and different sorts must remain dominant, otherwise the abnormal growth would be diffuse in the tissue in which cancer arises. The loss of power to induce hindrance to their own growth, combined with an insusceptibility to the hindrances produced elsewhere in the body, is an hypothesis having more to commend it. It is conceivable that a circumscribed group of cells may become insusceptible to the constitutional forces correlating growth, because of some modification analogous to that by which tumour-cells lose their power of inducing resistance, and although susceptible to it in strange hosts are indifferent to it in their hosts of origin. The fact may be recalled that young animals are more suitable for inoculation [1] than are old animals, although cancer arises during senescence when there is general

[1] Old animals have not been found to favour the experimental development of sarcoma more than young animals. The greater suitability of young animals for inoculation is probably to be found in the greater rapidity of the reactions of the connective tissues and blood-vessels.

decline in cell-growth; these are facts which must be taken account of in any hypothesis of the nature of cancer.

The delicate reactions thus far revealed are all of a new order, and are probably closely interrelated. They have admitted of a little penetration into what a few years ago was quite unexplored territory. At present their study appears to show that the etiology of cancer is complex and compounded of both local and constitutional conditions. Although it is not yet possible to be sure of the interpretation of the few new facts and their relation to one another, any day may bring some other fresh fact or facts to light, permitting of a harmonious explanation.

Further speculation may be avoided, for there is need for more investigation in the new field of experimental biology which the study of cancer has opened up.

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