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THE GENERAL PATHOLOGICAL CONCEPTION OF CANCER*

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THE conception that cancer is not a single disease but a generic term covering a broad department of biology and a universal property of tissue cells has become widely accepted only in recent decades. Yet Virchow, many years ago, divided biological processes into three grand classes: (*a*) normal growth and functional changes, (*b*) inflammation, (*c*) neoplasia. He thus made neoplasia correlative with inflammation. While some pathologists still limit inflammation to exudative processes, and discuss cancer as they do tuberculosis, the great majority have adopted the broader point of view. However, current literature reveals that many physicians and biological investigators who are not trained in general pathology assume the attitude that the problems of cancer are as simple as those of syphilis, and very much like them. This attitude invariably influences the conceptions of those who adopt it and often misdirects their activities. It might, therefore, prove a substantial service to combat this misconception and to encourage the broader viewpoint which the facts about cancer abundantly warrant.

If cancer is a single disease then one is justified in assuming a single cause and welcoming the recurring announcements of its discovery. A single cure is also a reasonable expectation, and thus we find a warm reception for a great number of remedies devised by all manner of persons, often under the patronage of men of large means, who fall victims to the fervid tales of would-be discoverers. The public mind, misconceiving the true nature of the problem, is ready to provide abundant social, financial and even governmental support, to secure for suffering humanity the great boon of a cancer cure, which the intolerant medical profession rejects. It seems possible to secure entrance into almost any scientific organization for one who makes a suitable appeal with a program of direct approach to the cause and cure of cancer. Foundations and institutes are not uninfluenced in making grants by a lingering hope that after all a quick solution of the cancer problem is within reach. It is not difficult to discern even in high places a tendency to subsidize research in one direction, preconceived as likely to solve the cancer mystery.

Local and national governments will not make special provision for cancer service and control when they regard the problem as similar to that of venereal disease. University medical schools devote the departments of anatomy, physiology and embryology to normal growth and functional changes; they segregate by necessity the infectious diseases; they build special hospitals for tuberculosis, ophthalmology, pædiatrics, orthopædics, etc.; but neoplastic diseases enjoy neither compact organization nor efficient direction and take their chance with the interest or neglect of the heads of clinical departments. Thus the student gathers a miscellaneous collection of facts about cancer from numerous sources, and struggles with conflicting opinions about the nature, scope, diagnosis and treatment of a group of diseases which form the most impor-

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tant problem of medicine and biology, and the major cause of death.

In the practical laboratory field one of the favourite pursuits is the search for a universal serum test for cancer. Although one type of these tests rapidly succeeds another, each new announcement meets a hearty response from those who think of cancer as a single disease. Yet cancer, in its earlier stages, when a serum test might be valuable, is a local overgrowth homogeneous with the surrounding tissues, and nothing that we know about it justifies the hope that it stamps the blood with any peculiarity detectable by physics, physical chemistry, serology or immunology. Only in the terminal stages is such change admissible, and then the test is of little use.

A general predisposition is perhaps consistent with the expression of a universal cell property such as malignant overgrowth, and Reding and Slosse, Waterman and others find it in alkalosis of the blood, by methods which most physical chemists regard as unreliable, and by overestimating differences which are inconstant and within the limits of error. This theory replaces the popular belief of thirty years ago, when the predisposition was attributed to defective sugar metabolism. The whole theory is inconsistent with many facts known about many different forms of cancer.

Geneticists generally take a broad view of the scope of the cancer process, and yet they emphasize the occurrence of a slight but definite excess of cancer in the families of cancer patients, thus suggesting the existence of a single dominating hereditary influence. Yet the results of Slye who produced inbred strains of animals most of whom died of cancer of the liver, breast or thyroid, strongly emphasize the specific character and individuality of these different diseases.

Chemists have made many efforts to demonstrate some single specific feature of the constitution or metabolism of cancer tissue which might explain the mystery of the process, but without success. Warburg's discovery of aerobic glycolysis and lowered respiration finds its importance as a contribution to general cell physiology, but these properties are not constant in malignant tumours; they are shared by embryonal and some normal adult tissues, and their removal may not affect the malignant capacities of the cells. The long pursuit of the parasitic theory has been dominated by the hope of reducing the cancer problem to simple terms. There have been some interesting by-products of this work, but the failure to accomplish its main objective indicates that the theory that cancer is a single parasitic disease is erroneous. Thus throughout many ramifications of the cancer problem it is clear that progress has been obstructed by an unsound point of view. When, after a long trial, a theory does not work, should it not be abandoned?

CANCER AS A UNIVERSAL CELL PROPERTY

The view that unrestrained and malignant proliferation is a universal cell property is supported by a vast body of knowledge accumulated through many centuries, and especially during recent decades. While the data are familiar to most, it may be helpful to review them again.

If cancer is a universal cell property then one would expect it to manifest itself in all classes of animals. So we find malignant tumours in all vertebrate species, and even in the insects. Plant tissue also shows local overgrowths with some of the features of malignancy. When the limiting influence of age can be excluded the incidence of cancer in some lower animals approaches that in man, and in old dogs it is said to be greater than in man. The same variety of predisposing, contributing, and exciting factors, and the same general biological properties, are revealed in the lower animals as in man.

A universal cell property should affect every cell in the animal body. There seems to be no cell, at least in the human body, which is incapable of excessive proliferation, and descriptive oncology provides records of malignant growth of every cell type, but nearly always under specific conditions. So far as we know, these conditions favour the growth of cell groups rather than single cells, so that the process usually has an organoid quality. Even bone cells and cerebral ganglion cells may be released from long quiescence and become malignant.

A universal property of growth would be expected especially in embryonal cells. Cohnheim's doctrine of the embryonal origin of a large group of tumours was probably the most important single contribution to the knowledge of cancer. Today there are still many efforts to introduce the embryonal theory in places where it does not belong. Oncology is not a department of embryology. Most tumours arise from adult cells which never become young again. Atavistic tendencies have been detected by some in the resemblance of tumours of man to the organs of lower animals. Release of suppressed growth seems to determine the high incidence of certain tumours in atrophic and vestigial organs.

The course of normal growth is controlled mainly by heredity, and if tumour growth is the expression of a universal cell property it should be notably influenced by heredity. In man, neurofibromatosis, glioma of the retina, and multiple tumours of bone show pronounced hereditary influence, and many others reveal occasional hereditary connections. Cancer families I am inclined to refer mostly to environment. In the lower animals heredity attains great prominence and may become the

determining factor in the outbreak of many forms of cancer. So obvious are these relations that some geneticists would resolve the whole cancer problem into one of genetics. They have pursued the hereditary factor to extreme detail and with great refinement, pointing out the complete dependence of cancer incidence, transplantability, and the clinical behaviour of many tumours upon inherited characters of the hosts. No experimental study of tumours of the lower animals ventures to proceed without full attention to the hereditary history of the strains employed. Among 38 cases of homologous twins reported in the literature in 26 tumours appeared in both individuals, of the same general character, in the same organ, and at about the same time.

A process dependent on intrinsic cell properties should be homogeneous with the tissues of the host. No specific chemical substance has been found in tumour tissues. The peculiar metabolism of some tumour cells is shared by some normal tissues. The ferments of tumours differ from those of normal tissues only in degree. New growth apparently excites no true immunity. The human body may be extensively invaded with cancer and yet the patient may assert that he is in good health.

Excessive growth of homogeneous tissue should not be incompatible with function. Many tumours function normally, and some, excessively. Metastatic thyroid tumours may be necessary to life after extirpation of the parent gland. Pancreatic island tumours produce insulin; adrenal tumours yield cortin; and melanomas, when highly malignant, may flood the body with pigment. Erythroblastomas manufacture hæmoglobin on a large scale. All these functions draw on the body's sources of material by the usual channels. Organoid tumours provide their own blood and nerve supply. On the other hand, many malignant tumours of all classess lose function and devote all their energies to growth. On the whole, the display of function, normal, excessive, or perverted, or its total absence, furnishes impressive evidence that the tumour process is the expression of intrinsic powers of the cells.

Nature seems to protect the fertilized ovum from the outbreak of neoplasia, most of the growth anomalies of the early embryo taking the form of twinning or multiplication of members and organs, but in the sex glands the sex cells mimic much of the normal embryological history. The teratomas of the testis yield abortive embryos, or mixtures of deformed organs, or single predominant tissues, and every grade of adenomatous, carcinomatous or sarcomatous neoplasia. The congenital epignathi and the complex tumours of the caudal extremity reproduce mainly the organs of those regions, by a process analogous to budding, but always with some neoplastic overgrowth, either benign or malignant. There seems to be every transition between the normal benign neoplastic and the malignant processes frequently commingled in these remarkable tumours.

Teratology gives a marvelous display of the eccentricities of cell growth in the extrauterine sex cell and its derivatives, including benign and malignant tumours, and points unmistakably to the origin of all these processes in original cell potencies. In this field one can construct an unbroken series from cancer to twins.

Atypical growth, if dependent on intrinsic properties, ought occasionally to exhaust its momentum, and tumours should sometimes regress spontaneously or be recontrolled by growth restraints. Many benign tumours enjoy only a limited period of advance, not often realized in these days of aggressive therapy. Moles and neurofibromas become sclerosed, myomas calcify, chondromas ossify. Very few cancer cells may be found in the bodies of subjects dead of scirrhous carcinoma; gastric cancer may end in linitis plastica; and lymphosarcoma is sometimes fatal without leaving demonstrable tumour tissue in the body. Partial removal may prove such an insult to the momentum of growth that ovarian cancer, chorio-adenoma, lymphosarcoma, and some adenomatous tumours may regress after such an experience.

Normal growth receives restraint or stimulus through the distribution of nutriment, demands for function, and the altruistic relations of the organs which we now know are maintained through the glands of internal secretion, interlocked by the sympathetic system. Neoplastic growth, if of the same order, must show signs that it responds to the same forces. There is abundant evidence to this effect, much of it recent, and all tending to confirm the old doctrine of cell autonomy. Simple pressure restrains growth, even completely, and ruptured capsules of many tumours allow fungation and increase in malignancy. Cancer increases with overweight and diminishes with exercise. Charlatans temporarily restrain growth by starving their patients, with regression of some tumour nodules. Mammary cancer can be produced in male mice by implantation of ovarian tissue. Bagg[2] produced mammary cancer in mice by inducing stagnation, but chiefly in predisposed strains and in periods of reproductive activity. Little found this method successful only in strains predisposed to cancer. Michalowsky and Bagg produced carcinoma of the testis of the cock by injections of chloride of zinc, but only in the Spring. Giant-cell tumours of bone appear with hyperplasia or neoplasia of the parathyroid glands, and extirpation of the parathyroids permits the spontaneous disappearance of the giant-cell tumours. Adrenal hyperplasia and tumours are observed with a variety of disturbances of the sex glands and the hypophysis. Various grades of atypical hyperplasia of the endometrium and prostate are produced by injections of folliculin. Vitamins are beginning to enter into the class of agents upon which the growth of tumours is dependent.

In subjects of mental deficiency and various organic abnormalities of growth tumours of peculiar types are to be expected. Certain racial peculiarities in the incidence of cancer must be referred chiefly to inherited tendencies. In Java, where there are two distinct native races, Bonne[4] reports that cancer of the stomach is the chief cause of death in one, but practically unknown in the other, although the dietary habits of both seem to be identical.

The variety of external influences now known to act as exciting agents of cancer is very great and covers almost every class of natural forces. Many act rather directly, and others more indirectly. They include:—(*a*) mechanical trauma, especially when repeated; (*b*) physical agents, x-rays, radium and sunlight; (*c*) chemicals, inorganic and organic, such as arsenic, chloride of zinc, coal tar products, anilin, dibenzanthracene, phenanthrene, Sudan III, and other dye-stuffs; (*d*) organic cell products, hormones, folliculin, œstrin, decomposition derivatives of bile acids (Cook); (*e*) bacteria, especially the tubercle bacillus, *B. caviæ* (Lacassagne), the virus of infectious epitheliosis (Shope); (*f*) animal parasites; *Spiroptera neoplastica* (Fibiger); *Tænia crassicollis* (Borrel), distomiasis. All these exciting causes of cancer have been reviewed many times, and most recently by Maisin (Madrid Congress, 1933).

It thus appears that the scope of cancerigenic agents is coextensive and nearly identical with the excitants of inflammation. This fact compels the conclusion that both processes, inflammation and neoplasia, are the expression of universal cell properties, and are correlative. Inflammatory agents produce degeneration, necrosis, exudation, growth of new tissue, regeneration, and are usually self-limited, but sometimes run into neoplasia. Cancerigenic agents also produce some degeneration, often exudation, but mainly overgrowth of tissue with various grades of anaplasia, and they are usually, but not always, progressive. The manifestations of inflammation vary greatly, but within certain limits. Inflammatory neoplasia passes by insensible gradations into neoplastic. The morphology and clinical features of neoplasia are

extremely diverse, and reveal many peculiar and even bizarre properties of cell growth, never observed in inflammation. Thus one may venture the suggestion that there are more clinical and pathological entities in the field of neoplasia than exist outside of that domain.

The foregoing review, covering some of the many departments of established knowledge, forms an overwhelming body of evidence in the minds of those familiar with it that cancer includes a great group of diseases, varying widely in conditions of origin, clinical course, physiology, morphology, and is the expression of a universal cell property. On the other hand, on many physicians, experimentalists, and biologists, who are not very familiar with the facts about cancer, but who devote attention to peculiar tumours and other departments of biology, this knowledge does not make the same impression. These observers are more inclined to regard the old knowledge as old-fashioned, obsolete, and unworthy of much serious consideration. It is, therefore, difficult to get the two groups to speak the same language.

The chief difficulty lies in the persistent feeling that cancer is a single disease, with a universal parasitic cause. Although almost every type of microorganism, as its existence became established, has been found in cancer and regarded as its cause, often by distinguished scientists, yet all these efforts proved futile, and the pursuit of the parasitic theory practically ended with the 19th century, with the discovery of the transplantability of lower animal tumours and the occurrence of x-ray cancer. The discovery that a group of chicken sarcomas may be transmitted by a filterable agent revived and intensified interest in the parasitic theory, and this group of tumours has been investigated on an elaborate scale. Foulds[12] has recently given a very comprehensive and judicial review of the accumulated knowledge of these diseases. Andrewes,[1] in an authoritative communication, reviews present data, definitely endorses the virus theory for the chicken tumours as well as for other infectious tumours of lower animals, and leaves the reader to infer that all cancers are probably caused by viruses. He definitely states that the theoretical objections to the parasitic theory are no longer tenable, in view of the facts of filterable fowl tumours. Rous,[28] also, after a study of the infectious papillomatous tumour of the rabbit, concludes that present knowledge makes the parasitic theory a reasonable basis for further work.

These communications, coming from distinguished investigators, cannot fail to have an important influence on medical opinion and on research activities. An examination of the new evidence bearing on the virus theory may, therefore, be timely, in order to determine whether the new evidence really does call for reopening the whole subject of the parasitic theory, or whether the new facts belong mainly or exclusively to those diseases in which they have been observed.

The Borrel formula: small-pox to cancer.— About 1903 Borrel[5] devised his well-known formula connecting small-pox with cancer through a series of diseases supposedly related and marked by the presence of peculiar intracellular bodies. The formula was long since rejected as unsound. The flaws in it are numerous and fundamental. Why exclude rabies, with its Negri bodies, yellow fever with its liver cell globules, and diphtheria necroses from the list? The vaccine bodies were supposed to represent virus nests, but the natural history of the vaccine body ends in a globule of mucus, at which stage it is not suggestive of a virus nest. No one has succeeded in demonstrating in these bodies any parasitic structures. The exact location of Paschen's elementary bodies, whether within or between the cells, is undetermined. Molluscum contagiosum is a curious process which resembles a sebaceous cyst more than a tumour. Since the passing of Feinberg's famous bird's-eye inclusion the intracellular bodies in cancer cells have been finally assigned to secretory and degenerative products. Moreover, many cancers, especially the very malignant, do not show any inclusions.

Some authors emphasize the tendency of vaccinia of the cornea to induce mitoses, yet this tendency is often equalled or exceeded by streptococcus lesions, and is a very transient phase. Mitosis of itself is no indication of a neoplasm. Recently Masson[22] has pointed out its significance as a forerunner of necrosis. Variola virus is an exquisite necrotizing agent, and human variola is remarkably free from cell proliferation. The pulmonary lesions of sheep-pox are said to resemble a neoplastic process,

and so also do the pulmonary lesions in some cases of human influenza.

Between the known virus diseases and rodent ulcer there is the wide chasm of the secret of malignancy, and it may not be bridged by the impulse of a fertile imagination. This is the whole point at issue. The passage from smallpox to cancer requires a series of unwarranted assumptions, but why stop at cancer? As pointed out many years ago by Lubarsch, the steps from cancer, through the benign tumours, the mixed tumours, the teratomas, up to twins, is simple, logical and inevitable, if the argument is to be frank and accept all the facts. If one wishes to revive the parasitic theory of cancer reference to the Borrel formula is hardly a fortunate introduction. The attempt to construct a similar formula for the connective-tissue series fails for lack of material. The infectious myxoma of rabbits (Sanarelli) begins as a violent exudative and necrotic process, and terminates in a peculiar myxomatoid tissue. The virus disseminates through the body, but the cells apparently do not. The position of the infectious fibroma of Shope[29] is undetermined.

Properties of the fowl sarcomas.—Since the discovery by Rous in 1910 of the filterability of the chicken sarcomas the characters of these tumours have been very thoroughly investigated, but the nature of the transmissible agent has not been finally determined. The tumours are undoubtedly malignant neoplasms of peculiar types. More than a dozen varieties have been identified, each of which is filterable, and each produces exactly the type from which the agent has been derived. The tumours grow from surviving cells in the grafts, and there is little evidence of any passage of the agent from tumour to normal host cells in the initial transplants. In cell-free transmission the tumours seem to be induced chiefly at points of injury or other tissue alteration. Metastasis occurs chiefly by cell emboli, but the agent circulates in the blood and in the testis and ovary may apparently induce new tumours. The exact type of cell originally attacked by the filter-passing agent is not determined, but the resulting tumours follow the original morphology. The agent resists glycerination for some days, but at 37° it disappears rapidly, probably by oxidation. It is very resistant to irradiation, but is destroyed by heating to 55°, by many dyes, bile, saponin, and certain chemicals. It is far more resistant to ultraviolet light than most bacteria and viruses (Murphy[25, 26]). About 2½ per cent of normal fowls are resistant to active filtrates, some to the agent, and some to cells. All the agents have been found to yield antisera, which, while generally specific, show the usual group relations of bacterial antisera. Yet the observations in this field are extremely complicated and somewhat conflicting. No two antisera have been serologically identical. The agent may be separated from the cells by precipitation by ammonium sulphate or aluminum hydroxide, and comes down with the globulin fraction. Inhibitory substances have been demonstrated under several conditions. Filtrates inactivated by heat reduce the potency of active filtrates. When filtrates are precipitated by acidification the supernatant fluid is strongly inhibitory, and the precipitum is more active than the original fluid. The serum of fowls bearing slowly growing tumours generally inhibits active filtrates. Filterable fowl tumours have been produced by dibenzanthracene.

From the above comprehensive but very complex data two opposing views have developed; one, that the active agent is an extrinsic living virus, and the other, that it is a cell product developed in demonstrable quantity by actively growing tumour cells. It is the belief of the writer that the evidence has steadily strengthened in favour of the latter view.

1. The evidence regarding multiplication indicates that the agent increases only in the presence of actively growing cells. This property is characteristic of viruses. Yet crystalline enzymes multiply rapidly in suitable substrates.

2. The sudden disappearance of the agent, at least in demonstrable form, seems inconsistent with the theory of an extrinsic virus.

3. There is a definite quantitative relation between the success of inoculation and the amount of material inoculated.

4. The agents are remarkably resistant to drastic chemical treatments. While some viruses are also notably resistant to certain chemicals, it does not appear that any typical animal virus has survived equally vigorous exposures.

5. While antisera may be produced by the various agents, this fact does not necessarily mean that the agents are living viruses. On the contrary, it may safely be said that all the immune reactions demonstrated for the sarcoma agents may be duplicated by simple chemical agents and by some hormones. Kirk and Sumner[15] have produced neutralizing sera against crystalline urease. If one unites any protein with a chemical

its antigenic properties are specifically altered (Boycott[6]). There is an unfortunate lack of agreement concerning the interpretation of the serological experiments (Foulds[12]), but there is no doubt that the sharp and pronounced immunity reactions of the infectious viruses are not satisfactorily reflected in the chicken sarcomas. The normal tissues of the animal appear to be insusceptible to the "virus". Gye and Purdy[13] produced neutralizing serum dependent on the presence of complement by injections of embryo fowl tissue in goats. These authors resort to various hypotheses and subsidiary hypotheses in order to support the theory of an extrinsic virus and a specific factor. Murphy[25] points out that Gye and Purdy and Andrewes continue to use crude extracts in their serological studies, although he has shown that even the partially purified agent is without antigenic properties. des Ligneris[10] found that antisera prepared in alien species react solely against the proteins of the tumour-bearing animal and furnish no evidence of any extrinsic agent. It is at least evident that present serological data do not strongly support the virus theory. There are now about 14 different fowl sarcomas, each yielding a specific neutralizing serum. It is, therefore, necessary to assume the existence of as many different viruses. To escape this dilemma, various hypotheses have to be introduced, none of which is satisfactory. The best of them is that the virus is ubiquitous, which is also the most damaging to the virus theory. "If one postulates a normal virus occurring in normal cells, one had better call it something other than a virus" (Boycott). Here the argument transcends science and passes into the realm of humour.

That the active agent in chicken sarcomas is a chemical substance resembling the class of enzymes is strongly indicated, if not definitely proven, by the investigations of Murphy and his associates. They first showed that from extracts of chicken sarcoma I a protein fraction can be separated out which contains all the active agent, and which can be dissolved and reprecipitated several times without loss of activity. From the extract nearly all the protein can be removed by adsorption with aluminum hydroxide, leaving the fluid still fully active, but nearly protein-free. The active agent is associated with an inhibitor, which may be adsorbed by aluminum hydroxide. The inhibitor is capable of neutralizing the tumour-producing agent in its most active form (*Science*, 1933, **78**: 521), and also inhibits the growth of some mammalian sarcomas, but is without effect on carcinoma. The active agent is absorbed by emulsions of mesoblastic tissues of susceptible animals, but not by those of non-susceptible animals. It is much more resistant to ultra-violet light than are most of the filterable viruses. The most effective neutralizing sera were those prepared against the purified agent, and these sera contained no precipitin or complement-fixing antibodies. Contrary to the rule with viruses, neutralizing sera are readily obtained in non-susceptible species.

MacFadyen[20] finds that aqueous extracts of chicken sarcoma I contain two enzymes, polynucleotidase and phosphatase, the former being in proportion to the tumour-producing activity of the extract. Further steps in the purification of the agent have been carried out by Claude.[8] By adsorption and dialysis he removed from the watery extract 95 per cent of the original solids, leaving a fraction containing a protein and a phospholipid. Adopting the hypothesis that the inhibitory factor in chicken sarcomas is a product of cell growth, Murphy and Sturm[26] have demonstrated in extracts of dessicated rat embryo skin and placenta, and rabbit placenta, during the middle period of gestation, an inhibiting agent which markedly suppresses the growth of mouse carcinoma but has no effect on mouse sarcoma.

Throughout these systematic investigations all the phenomena observed may be explained as the result of the action of intrinsic cell products, and at no time is it necessary to introduce the idea of an extrinsic virus. This series of studies, therefore, constitutes a notable confirmation and expansion of the doctrine of cell autonomy.

Significance of the Fowl Sarcomas for the Cancer Problem

It would really make little difference for the cancer problem as a whole if it should be proved that the fowl sarcomas are initiated by living viruses. They would then take their place as a special group of neoplastic diseases caused by viruses, and another group of agents would be added to the already comprehensive list of exciting causes of malignant growth. It would still remain an interesting and difficult problem, how the viruses initiate, and maintain, if they do, the malignant process. Such an outcome would not prove the existence of a universal cancer parasite, which appears to be the real ambition of the adherents of the parasitic theory. To some it might appear a relatively simple problem to explain malignant growth on the basis of an intracellular parasite, but to others, as has often been pointed out, it would remain as great a mystery as ever. If, however, it should transpire that the filterable agents in fowl sarcomas are cell products, then the results might be of very great importance for the whole cancer problem, especially if similar agents can eventually be demonstrated in other and mammalian tumours. One would then be justified

in assuming that these separable cell products at least maintain and possibly excite malignant growth, and by a vicious cycle increase in quantity and activity and determine the inevitably fatal issue of most cancers. There are possibly other vicious cycles which may contribute to the maintenance of the cancer process, such as aerobic glycolysis, the cumulative influence of mitogenic rays, if we can still believe in their existence, and even other minor physical and chemical factors, such as heat, electric phenomena, and the interactions of hormones. The idea that a natural cell product should excite a process highly detrimental to the host should not be rejected, since, according to Weigert's law, the reaction to irritation is generally in excess of the need and often injurious to the body. Ehrlich called this "horror autotoxicus". There are many maladjustments in Nature with a lethal outcome.

The presence in tumour tissue and blood of substances capable of exciting malignant growth in other homologous tissues might throw light on the peculiarities of tumour extension and metastases. The mode of extension and the metastases of lymphosarcoma, the myelomas, and neurogenic sarcoma are far from clear. Such substances might explain the curious selection of certain organs by cancerous metastases, which we now set aside under the caption "genius loci"! The presence of substances inhibitory to the active agents, if confirmed for human tumours, might prove of great value in explaining the anomalous behaviour of certain tumours at certain periods of growth, and might also lay the foundation of fruitful immunological studies. The interaction of excitant and inhibitor might form the basis of an adequate theory of malignant growth, and commensurate with modern knowledge. Based on the new data regarding active agents and inhibitors in tumour cells and influenced by the doctrine of embryogenic inducers, Murphy[25] has formulated a logical theory of malignant growth and pursued it with practical results.

It is doubtless premature to speculate too freely about the possible significance of the new facts elicited from the fowl sarcomas, but if the filterable agents should prove to be cell products instead of extrinsic viruses then the adherents of the parasitic theory, in the ambition to prove a theory, have overlooked the real importance of results to which they have contributed much.

The experimental production of fowl sarcoma by dibenzanthracene is an observation of much importance. Yet it does not contribute any new principle in the cancer field. Here the dibenzanthracene, after exciting some change in normal tissues, disappears from the scene, and the tumour cells produce some new agent, which is certainly not dibenzanthracene, but which maintains the growth of the tumour and in chickens may even of itself excite the growth of a new tumour. Similar events are well known in human oncology. Lymphosarcoma sometimes follows tuberculosis, but the tubercle bacillus has disappeared from the scene. The oldest known cancerigenic agent, anilin, produces cancer of the bladder many years after exposure to anilin. Soft x-rays lead to cancer after 10 to 20 years. Arsenic users fall victims to skin cancer long after stopping the drug. The idea that an extrinsic virus gains access to the injured tissues seems to have been adopted by virus experts, but to most persons it will appear as a desperate resort. At what point in these long stories does the parasite enter? The production of the filterable dibenzanthracene tumours was the *coup de grace* to the virus theory of the fowl sarcomas.

It has long been realized that the problem of the initiation of a tumour is entirely different from the problem of its continued growth. The virus exponents in pursuing the filterable agents of fowl sarcoma have not been dealing with the cause of cancer at all. They have been investigating the nature of the process after its establishment. The question arises— What originated the spontaneous chicken sarcoma which was propagated with so much difficulty? Certainly it was not the inoculation of chicken tumour cells, and probably not the entrance of the feebly active filterable agent. It must have been excited by some entirely different method, of which nothing is known, but which we may safely assign to the numerous traumas, infections, worms, scurvy, and other hazards of the modern chicken farm. So it is with the major forms of human cancer, for many of which we know, with considerable accuracy or complete certainty, that they arise from the action of a great variety of physical, chemical and biological agents, which have nothing to do with viruses. Accordingly,

we must conclude that the great field of cancerigenic agents, operative in Nature, is not touched by the filterable substances in the fowl sarcomas. When a tumour or tumour-like process is really initiated by a virus, as seems to be the case with human warts and the papillomas and fibromas of rabbits, that fact seems to be easily demonstrable, but these diseases are infectious and contagious, and they are not cancer.

Since the spontaneous chicken sarcoma is a comparatively benign process and not filterable, it is even conceivable that transplantation released cell potencies, previously inactive, with the formation of a new product not ordinarily present in chicken sarcoma, separable from the cells and capable of initiating a new tumour. In that case the highly malignant course and the filterable agent would stand as entirely new phenomena, never before experienced in the natural course of chicken sarcoma, and not observed in other spontaneous tumours of any species of animal. Thus the experimentalist would have unintentionally created a new and artificial problem, which it devolved upon him to solve. All cultures of staphylococcus do not possess bacteriophage, which develops only under circumstances. Since mammalian tumours are not filterable even after frequent transplantation and increase in activity, it would appear that the fowl stands apart from other animal species by virtue of a peculiar physiology.

The experimentalists state that the fowl sarcomas are identical with human "sarcoma"! To those who have wrestled with the obscurities of human lymphosarcoma, thymoma, Hodgkin's sarcoma, myeloma, granulation-tissue sarcoma, Kaposi's sarcoma, Hannsmann's syphilitic sarcoma, and the group of sarcoids, this statement is surprisingly naive. All these diseases are strikingly peculiar and specific. Kaposi's sarcoma is quite unlike any other known malady. The fowl sarcomas also stand apart as specific diseases, with the essential feature of clinical malignancy, but revealing features not shared by other sarcomatous processes. If the fowl sarcomas resemble any human disease, it is the group of sarcomas which follow specific infections, such as granulation tissue sarcoma, Hodgkin's sarcoma, and myeloma, all of which are believed to be sequels of infection. The histogenesis of sarcomas may not be ignored. Carrel and others believe that the fowl virus affects first the so-called monocyte, or an indifferent mesoblastic cell, and induces it to assume the form of a fibroblast. McIntosh[23] conceives that the virus, like tar, gets a hold of young mesoblastic cells and initiates continuous proliferation, resulting in leukæmia or sarcoma or endothelioma. All these speculations relate to an indifferent cell type widely distributed in all organs. But the important types of human sarcomas do not arise from such cells. Osteo-, neuro-, lipo-, myo-sarcomas arise from adult cells of specialized organs, and have no relation to infections. They stand quite apart from the post-infectious processes with which the fowl sarcomas may possibly be related. Yet one may not blame the experimentalists for not understanding diseases which the pathologists have barely succeeded in cataloguing.

Summarizing the data on fowl sarcomas, the following conclusions seem to be established.

The demonstration of a filterable agent capable of initiating a new tumour in a new host reveals a hitherto unsuspected property of certain malignant tumour cells. Since this property is not demonstrable in primary tumours, and appears only after transplantation and accelerated growth under artificial conditions, it is not certain that the property ever expresses itself in any effective degree during the natural course of chicken sarcomas. The dissociation of the agent from the cells, or the capacity of the agent in suitable concentration to produce a new tumour, or both, appear to belong exclusively to the fowl. The agent is probably not the exciting factor in the natural occurrence of fowl sarcoma, but it is probably essentially connected with the assumption and continuance of malignant growth. The exciting cause of fowl sarcomas in Nature is unknown.

While no such agents have been demonstrated in other tumours in higher species, it is a reasonable assumption that identical or similar processes occur in some other malignant tumours. The idea that the property is universal in all malignant tumours comes in conflict with too many inconsistencies to be acceptable. The statement that fowl sarcomas are identical with human "sarcoma", must be rejected, since it ignores the question of histogenesis. In natural incidence, clinical course, filterability, and histogenesis, the fowl sarcomas stand as dis-

eases *sui generis,* peculiar to this species. That the filterable agents of fowl sarcomas are living viruses is unproven, and the evidence in favour of their chemical nature is at present preponderant and increasing in scope and refinement. The new data on fowl sarcomas do not affect in any degree the significance of the great body of information about malignant tumours in the animal kingdom, which stands against the parasitic theory. The statement that the objections to the theory of a universal cancer parasite have been removed must be rejected. On the contrary, all the facts elicited about fowl sarcomas are most consistent with the view that these phenomena are the expression of intrinsic cell properties.

INFECTIOUS PAPILLOMATOSIS

The occurrence of infectious papillomas in man and several lower animals has long been known. In 1899 Lanz[18] transferred a wart from his own to the back of his gardener's hand by needle pricks. In 1920 Magalhaes[21] stated that he had produced generalized papillomatosis in a steer by intravenous injection of a filtrate from a spontaneous case, but he did not follow up this observation. Ullmann[31] reported the transplantation of a laryngeal papilloma from a boy to a volunteer, producing a rapidly growing lesion which had to be excised. Infectious papillomas of the tongue in dogs have been described by Borst and by DeMonbreun and Goodpasture.[9]

Recently Shope[29] has studied a papilloma of wild rabbits which he found easily transferable by a filtrate both to wild and to domestic rabbits. In the wild rabbit it usually regresses spontaneously and never becomes malignant, unless complicated by infection or trauma. The agent resists heat up to 70° C. Sera of infected rabbits neutralize the virus. It is not related to the virus of rabbit fibroma or myxoma.

Rous and Beard[28] have studied the behaviour of the induced papilloma in the domestic rabbit. They readily produced bulky papillomas on the tattooed skin, which remained polypoid for several months and then often became fissured, infected and ulcerated, especially when gnawed by the animal. A somewhat limited but definitely infiltrative growth then appears in the base of the papilloma. In one instance a discontinuous secondary tumour appeared beneath the skin of the affected region, and in one case, a lymphatic metastasis was observed. Fragments implanted in muscle exhibited certain infiltrative tendencies and remained infected, while in liver and kidney the autoplants became free from infection, but also exhibited certain infiltrative powers. I am informed that Shope has succeeded in recovering the virus from the domestic rabbit, but not in all cases. In the wild rabbit the disease does not appear to be malignant but a fatal result may sometimes be expected from infection. Transplants in series by tissue implants in the domestic rabbit have not yet been made. The sera of infected domestic rabbits neutralize the virus. Rous and Beard hesitate to assert that the virus has produced a malignant carcinoma, but they are inclined to that view. They think that the fissuring, infection and ulceration are the result and not the cause of the carcinoma. They detect indications of potential malignancy in the early stages of the papillomas.

Through the courtesy of Dr. Rous I have had opportunity to examine many sections of the tumours in the domestic rabbit, and can confirm the fact that the ulcerated tumours and the organ implants exhibit definite infiltrative and malignant features. Especially in the lymphatic metastasis the cells were atypical and were breaking up into small groups. Yet as a whole, the features of this disease impress me as quite peculiar. There is a remarkable persistence of the tendency to produce horny cysts. The cells never become very atypical, or hyperchromatic, and they cling in sheets, without losing polarity. The grade of anaplasia is very far removed from the average infiltrating squamous carcinoma in man. The malignant potentialities in the early papillomas I do not detect. The evidence seems to show rather clearly that the malignant change is coincident with the fissuring. The tumours are always heavily infected. The entire process recalls the course of events in syphilitic condylomas, syphilitic glossitis, and sebaceous cysts, which are becoming malignant. Whether the process will prove progressive or fatal or spontaneously subside can be determined only by experience. The persistence of the virus in infected rabbits is to be expected, regardless of any possible relation to the malignant change. One has to con-

clude, therefore, that the virus produces the papilloma, but that the carcinomatous change is the result of mechanical trauma, fissuring, infection and ulceration, acting on intrinsic cell potencies.

The missing evidence in this matter consists in the demonstration that the virus persists in serial transplants of the tumour cells and is responsible for maintaining a progressive malignant process. In the event of that demonstration it would still be necessary to show that similar factors exist in similar diseases in man, before transferring the observations to such diseases. In the chicken sarcomas the filterable agent appears to be essentially connected with maintaining the malignant process, but is not the original cause of the disease, while in the rabbit papilloma the virus originates the papilloma but is not concerned with the malignant process. The present thesis, that neoplasia is correlative with inflammation, would permit one to welcome the addition of a virus to the long list of exciting causes of cancer.

EMBRYOGENIC ORGANIZERS AND INDUCERS

The specific quality of the different agents found in fowl sarcomas, each determining growth of a peculiar type unchanging in many generations, is an outstanding feature.

Yet there are other substances in Nature with which it may be compared. The work of Spemann[30] and his school has shown that in the larvæ of frogs and salamanders the cells predestined to form medullary plates (or other organs) will still form medullary plates when transplanted to distant parts of the embryo. He then went on to show that watery extracts of these predestined cells would retain the property of inducing cells of other parts of the embryo to form medullary plates. These phenomena were observed only in rather early stages of the embryo. Mangold implanted a piece of blastopore lip under the indifferent ectoderm of another species and saw the development of a second medullary plate in the new host. This medullary plate then went on to induce the formation of eyeball and lens from the surrounding tissues. Similar results were obtained in widely different species. On these experiments Spemann based his doctrine of primary and secondary organizers. In 1923 Holtfreter found that embryo parts killed at 100° C. would still induce. He also showed that epidermis grown in salt solution induced epidermis, but grown in abdominal fluid induced nervous system.

Inducers are still active after treatment with alcohol, ether, acetone, and acetic acid. Most notable was the discovery that parts not normally capable of inducing induced after drying or treatment with alcohol or acetone, probably by the removal of some inhibiting substance. It was thus apparent that the inducing property resided in a chemical agent, which was sometimes kept inactive by the presence of an inhibitor. These agents are thermostable, soluble in 20 per cent ammonium acetate, but are readily destroyed by autolysis.

In recent years the study of organizers and inducers has been pursued on an extensive scale, and many remarkable features of their behaviour have been revealed. Extracts of pig liver, thymus, nucleinic acid, and muscle adenyl acid are inducers, and implants of living sarcoma and carcinoma are active inducers. It is reported that dibenzanthracene and phenanthrene act as inducers. The exact chemical nature of the active substance is as yet undetermined. Needham,[27] finding ether extract of Triton active, believes that the agent is a lipoid, and Barth[3] is inclined to identify it with cephalin.

Thus the embryogenic inducers have many properties in common with the filterable agents in fowl sarcoma. They sharply change the growth tendencies of tissue cells; are separable from the cells; are readily destroyed by autolysis; resist drying; are very resistant to heat; are unchanged by severe chemical treatment; and the active agent is associated with an inhibitor. They do not induce atypical growth. The existence of fowl sarcoma excitants and embryogenic inducers reveals hitherto unsuspected intrinsic properties of tissue cells.

THE TREND OF CANCER RESEARCH

During the past thirty-five years, cancer research has been focussing steadily upon the intrinsic properties of the cells and the forces that control them. The first impulse in this direction came from the final establishment of the fact that lower animal tumours are transplantable and that the cells survive. Substantial support of the exclusive importance of tissue cells came from the observation that the invisible rays of radium can destroy some tumours. Progress in genetics added impressive evidence that the essential phenomena of cancer may be referred to the potencies of cells and the factors resident in the host. Studies in the physiology of certain tumours had long revealed them as functioning organs, arising in response to functional demands, and not as vagrant cells or lawless unphysiological overgrowths. In aerobic glycolysis and diminished respiration chemistry has revealed hitherto unsuspected and more or less distinguishing properties of cancer cells. Even the filterable agents in fowl sarcomas seem likely to take their place as sporadic but significant expressions of cell potencies in this species. The behaviour of embryogenic organizers and inducers, separable from the cells, opens up a new field in cell physiology which may be of much interest for cancer. Recent studies of the relation of hormones to tumours and the experimental demonstration that œstrin, androtin, and prolan produce excessive, and even atypical, overgrowths in appropriate organs, which readily run into cancer, furnish convincing evidence that these processes when occurring spontaneously must also be assigned

to the action of internal agents acting upon the intrinsic properties of the cells. The chemical relationship between the cancerigenic coal tar products and hormones and vitamin D supports this view, and makes it easier to accept other external chemical substances as the actual agents exciting cancer. The great variety of agents producing cancer, as with inflammation, indicates that their mode of action is not always the same, and the resulting process not always identical.

The missing knowledge in this field concerns the mode of action of the cancerigenic agents. Androsterone, prolan A, produce enormous overgrowth of testes and comb in the cock, but no tumours. Ovarian implants lead to marked overgrowth of mammary tissue in the mouse, but close analysis reveals that cancer does not develop until stagnation occurs. Vitamin C deficiency in scurvy leads to remarkable changes in the skeletal muscles, suggesting a sarcomatous tendency, but never to sarcoma. The exact mode of action of the highly cancerigenic coal tar products has not been traced but is probably indirect. All these agents act upon the tissue cells to produce cancer, and their effects must be referred exclusively to intrinsic cell potencies, but how they induce the malignant change is unrevealed. The secret of malignancy seems still to remain enshrouded in the obscurities of intracellular life, where it will probably long remain.

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SEA-SICKNESS.—After describing the symptoms and previous theories of sea-sickness P. Cazamian gives his own views. Sea-sickness results from the effect of a multiplicity of afferent impulses, arising in the viscera as well as in the external sensory organs. These stimuli produce excessive secretion of adrenaline with a resultant sympathetic "storm". This is followed by compensatory over-stimulation of the vagus. According to the response to the oculo-cardiac reflex, in which the pulse rate is altered after pressure on the eyeballs, three types of individuals are distinguished: one, the vagotonic, in which the pulse rate is markedly slower; another, the sympatheticotonic, in which the pulse rate is increased; and a third, the amphotonic, in which it is only slightly reduced. The sympatheticotonics are the most likely to develop sea-sickness. Prophylaxis depends on breaking the reflex arc, ideally by paralyzing the sympathetic trunk. In 1917, when the author began his experiments, no drug acting directly on the sympathetic was known, so he used atropine sulphate, which inhibits the vagus, and hoped to obtain compensatory inhibition of the sympathetic. The results were satisfactory. Since then the neutral tartrate of ergotamine, a substance which acts directly on the sympathetic, has been prepared under the trade name of "gynergene", and thus gives still better results in the sympatheticotonics. The vagotonics respond best to atropine sulphate, while the amphotonics may require either or both. Treatment should never be necessary, but, if prophylaxis has been neglected, it follows the same lines in the early stages of sea-sickness. Later on the excretion of alrenalin fails, the sympathetic becomes fatigued and fails to transmit stimuli. This is followed by diminished vagus tone, though not to such an extent that symptoms of vagal stimulation predominate. To paralyze the sympathetic now is obviously useless, and treatment consists in giving stimulants to the sympathetic or vagus, or both, as may be required.—*J. de Méd. de Bordeaux*, Feb. 28, 1935, p. 143.