A British Medical Association Lecture ON THE NEW OUTLOOK ON CANCER.

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THE PROBLEM.

If we wish to explain a problem we must begin by formulating it. That seems a trite and commonplace observation to make. But it is a step which has been omitted frequently by those who have put forward "cancer theories." To many people cancer seems to be an abstract conception rather than a concrete, well defined, pathological phenomenon. How often have we not read in the past, even in the quite recent past, some article or book on cancer beginning with the lament that we know nothing about cancer. Having thus ingeniously disposed of everything concerning cancer that requires explanation, the author lifts his bonnet and his pet bee begins its flight. Of such writers it can truly be said that "they darken counsel by words without knowledge." I have always admired the courage with which a writer of that type advertised his ignorance. For as a matter of fact we know a good deal about cancer. As a result of the experimental investigation of cancer which began only twenty-five years ago a large number of facts were discovered. The difficulty was to find an explanation which would account for all the essential features of cancer, especially as some of the phenomena appeared to be contradictory. I propose, therefore, to begin by defining cancer as a pathological problem, and to state as briefly as I can the fundamentals, so far as they are known, of the pathology of cancer which must be accounted for by any satisfactory explanation of cancer.

We may begin with the fact on which the whole treatment of cancer by surgery is based: the local origin of cancer. At its inception cancer is localized. It is for this reason that we are entitled to say that cancer is a curable disease if it is diagnosed and removed in its early stage.

If we examine an early carcinoma of the skin or the tongue, where an early diagnosis is relatively easy, we find in a sharply circumscribed area a proliferation of the epithelial cells which grow down into the underlying tissue—muscle in the tongue, connective tissue in the skin. The cells which take part in this cancerous proliferation retain their special biological character. Thus, if the cancer cells are derived from the skin they continue to keratinize. Even in the metastases the cells continue to grow as the same type as that in which they originated. In the mouse most tumours are derived from the mamma, and one might expect, therefore, that on repeated transplantation they would converge to a common type of mammary tumour. But this is not so. Some mammary tumours showed from the beginning a very rapid growth and have maintained this rapid growth through twenty years of transplantation. Others, again, began as slowly growing tumours and still show the same slow rate of growth. There are also strains which at one time grow rapidly, then pass into a phase of depression with slow growth, from which quite spontaneously they recover to repeat the cycle in fairly regular intervals. In each propagated strain of mammary tumours the cells retain also their characteristic arrangement through twenty or more years of propagation, so that it is possible to identify a particular strain by merely looking at the histological preparation. One carcinoma of the mamma was characterized by cells containing glycogen. To-day, after fifteen years of transplantation, the cells of this tumour still continue to form glycogen, showing that we are still dealing with the descendants of the original tumour cells. There is an apparent exception to this statement. In a few

strains of transplantable mouse carcinomata it has been observed¹ that a sarcoma developed from the carcinoma. But this exception is, as stated, only an apparent one; for a careful study of this process, first by Haaland² and later by Russell,³ has shown that the sarcoma cells are not derived from the carcinoma cells, but from the connective tissue cells of the stroma which is supplied by the new host every time a tumour is transplanted. As the result of the more rapid proliferation of the sarcoma cells the carcinoma is gradually replaced by a sarcoma. In these cases, therefore, there is a transformation of normal tissue into malignant tissue by a neoplasm. But the cells which acquire malignancy as the result of this transformation again retain their specific biological character.

All these facts point to the same conclusion—namely, that a neoplasm is made up of the descendants of a few cells which have acquired the power to grow in an aimless, lawless manner. The problem which we have to explain is not merely that the cancer cell has acquired the power of growth. It is a growth which does not subserve the physiological needs of the body and is not controlled; it is a lawless, aimless growth. The cancer cells seem to be possessed of an irresistible impulse to grow, and by doing so they destroy the tissues and organs and eventually the organism in which they grow. There is no evidence of additional factors, such as specific cancer toxins or ferments, having a deleterious influence on the organism. Another striking fact is that the growth of a neoplasm is independent of the nutrition of the organism in which it grows.^{4,5} Thus conditions of nutrition which will bring about a progressive marasmus and eventually the death of the animal in a state of inanition—such as partial or complete starvation, a deficiency in specific amino-acids, such as tryptophane, or of vitamins—do not arrest the growth of cancer cells in the starved animal. This indicates that the impulse to grow resides within the cancer cells.

This aimless, lawless, irresistible growth, then, is one of the central problems of cancer. It would have been feasible to explain cell growth by postulating a specific organism if the disease were limited to only a few zoological species and could be transferred, like other microbial diseases, from one species in which it occurs to another. But cancer is characterized by this apparent paradox: while the disease is very widely distributed throughout the whole vertebrate kingdom, it cannot be transferred even from one closely related species to another by the inoculation of cancerous material. It is not so very long ago—only twenty-five years—that the belief was firmly held that cancer was a disease peculiar to man. As one of the few survivors of the early days of experimental cancer research I remember how the attempt to study cancer in animals was received with derision by many who claimed to be authorities on the subject. We owe it to the work of Bashford and Murray,^{6,7} and to the support which they received from the Executive Committee of the Imperial Cancer Research Fund, under the chairmanship of Sir William Church, that the investigation of cancer was placed on an experimental basis by demonstrating the essential similarity of the disease in man and in animals. Now we know that the disease may develop spontaneously in fishes, amphibians, reptiles, birds, and mammals. In all these classes of animals the disease exhibits the same fundamental features: a lawless, infiltrating destructive growth, having a local origin. But while the cells of probably all vertebrates are capable of undergoing the cancerous change, we cannot transmit the disease from one species to another by taking, for example, the cancer cells of a mouse and inoculating them into a rabbit, or the more closely allied rat. Attempts have frequently been made to transmit the disease from man to animals by inoculating human cancer material into mice, rats, rabbits, guinea-pigs, dogs, and monkeys. All such experiments have been uniformly negative.

This paradox—the wide zoological distribution on the one hand, the narrow limitation to one species of the transmission of the disease on the other hand—distinguishes cancer from other microbial diseases, and, as we shall see presently, has until recently been the insurmountable obstacle to the parasitic theory of cancer.

EXPERIMENTAL PRODUCTION OF CANCER.

There is another feature in the experimental pathology of cancer which distinguishes it sharply from the ordinary microbic diseases. If in a disease of undoubted microbic origin we take a piece of infected tissue and inoculate it into another animal, we reproduce the disease *ab initio* in the second animal. Thus, if we inject tuberculous human material into a guinea-pig we reproduce the disease *ab initio* in the guinea-pig. If we take an infective granuloma—a mass of connective tissue which has been formed in response to an infective agent—and inoculate it into another animal, the inoculated connective tissue cells die and the infective agent stimulates the connective tissue of the new host to form a new granuloma. Again, we have reproduced the disease *ab initio*. But if we transplant a carcinoma or a sarcoma, the transplanted cells themselves continue to grow. The tumour which grows is composed, not of the cells of the host, but of the cells of the animal in which the tumour originated. The cells of many of the mouse tumours which are now being propagated in the various laboratories belong to animals which may have died fifteen or twenty years ago. One might say that the cancer cell has gained immortality. This experimental method enables us to study the growth of a cancer once it has developed, and to submit the growth of cancer cells to various conditions. But, as has already been pointed out, it does not reproduce the disease *ab initio*.

In order to elicit cancer *de novo* a different experimental method must be applied. It is based on the experimental demonstration, first by Fibiger⁸ and later by Yamagiwa and Ishikawa,⁹ that cancer is produced by chronic irritation of a special kind. If a small area of the skin of the mouse is subjected to chronic irritation by painting it with tar twice or three times weekly over many months, a typical epithelioma develops in 60 to 80 per cent. of the treated animals. During the first three or four months no macroscopic changes are visible in the painted area, although microscopically hyperplasia of the epithelial cells of the epidermis and of the hair follicles has been demonstrated. Later, in the fifth month, a small wart may appear in some animals. There may be several warts. If painting is then discontinued—it may even be discontinued, as Dr. Leitch¹⁰ has shown, before any warts have appeared—the warts grow; if there were several they coalesce, and may develop eventually into a typical carcinoma with a hard infiltrating margin. If the animal lives sufficiently long, metastases may be found in the lymph glands and lungs. In some cases the tumour is of the benign papillomatous type. The length of time necessary to produce this effect differs greatly in different individual mice: it varies from five months to nine months. Some mice appear to be completely resistant to the effect of tarring and never produce either a wart, a papilloma, or a carcinoma.

It is known that tar workers frequently develop multiple warts of which one may become cancerous. Shale oil workers are subject to the same risk,¹¹ and, as Dr. Leitch¹² has shown, shale oil on prolonged application to mice will also produce cancer. It is surely a significant fact, demonstrating the identity of the disease in man and animals, that the same agents which produce cancer in man will also produce cancer in certain species of animals. The similarity goes even further: in mice it requires on the average six months from the onset of chronic irritation until cancer begins to develop. As the span of life of a mouse is about three years, this latent period amounts to one-sixth of the span of life. In man, with a span of life of seventy years, the period of induction is correspondingly long—ten to twenty years. There are exceptions. A few human cases are on record in which only a few weeks or months have elapsed. In one particularly striking case¹³ a spurt of boiling tar lodged in a man's nostril; a fortnight later he developed a carcinoma at that site. Chorion-epithelioma is a rare type of tumour that obviously requires a short period of induction.

THE LONG PERIOD OF INDUCTION.

Such cases, however, are exceptional. On the whole the process by which an area becomes cancerous as the result of chronic irritation is a very slow one. This long period

of induction throws an altogether new light on one very characteristic feature of cancer—namely, its peculiar age incidence. Cancer is a disease of middle and old age; it is rare in the young, but becomes more and more frequent as age advances. Formerly this was attributed to the onset of senility in the tissues and the cells. But it explains itself much more simply as the result of the long period of induction. The carcinoma in the stomach of a man of 50 probably had its origin in a chronic irritation which affected the stomach ten or even twenty years earlier. There are other forms of chronic irritation which may lead to cancer. I can only mention them in passing: in man x rays, heat (the kangri cancer), cancer of the bladder in aniline workers, cancer resulting from parasites such as bilharzia and *Trichina spiralis*. It is perhaps not sufficiently well known that a number of cases are on record¹⁴ in which an infection with *Trichina spiralis* was followed after many years by the development of a cancer. The sites affected were mamma, lip, and pleura. In every case the neoplasm was a carcinoma, and in several of the cases living trichinae were found in the tumour. The period of induction was again very long—a minimum of seven years and a maximum of twenty-five years. In animals, Fibiger was the first to induce experimentally cancer in the stomach of rats by means of a nematode—*Spiroptera neoplastica*. Bullock and Curtis¹⁵ subsequently produced sarcoma of the liver in rats by feeding them with the eggs of *Taenia crassicolis*. The sarcomata arise in the wall of the cyst enclosing the cysticercus.

SYSTEMIC FACTORS.

One of the most important and significant observations made as a result of the work on experimental tar cancer we owe to Dr. J. A. Murray.¹⁶ One would think that an animal which has readily responded to tar painting by the development of a cancer would be at least equally susceptible to the effects of a second tarring, or perhaps even more susceptible. This was put to the experimental test by removing by operation the tar cancer which had developed in a number of mice and then subjecting these animals to a second course of tarring. To his surprise Dr. Murray found that these animals did not develop cancer at all, the skin at the painted area becoming merely atrophic. He then took a number of mice in which a mammary carcinoma had developed spontaneously, removed the growth by operation, and subjected the mice to tarring. The same result was obtained: the mice were so resistant to tarring that no tumour developed during the period of survival. This shows clearly that once the body has developed a malignant new growth in one organ, it has become resistant against the subsequent development of a second neoplasm in any other part of the body, though it has not become resistant to the growth of the first tumour in other parts of the body. This accounts for the rarity of multiple tumours in different organs. Thus cancer of the breast alone and cancer of the uterus alone are frequent in women. But cancer of the breast and uterus in the same woman is rare. It is curious that this fact seems to have escaped clinicians and statisticians. Multiple tumours, when they do occur, affect almost always the same organ and tissue, and are then due to the tissue being subjected to chronic irritation at different sites simultaneously. Experimentally there is no difficulty in producing multiple cancer of the skin by painting simultaneously different areas of the skin. The resistance to cancer of which I have spoken manifests itself only if chronic irritation is applied successively. This observation indicates that it is possible to induce a resistance or immunity against the development of cancer. From this point of view it would be interesting to follow the history of patients who have been operated on successfully for, say, a carcinoma of the tongue or of the breast, so as to find out whether they have developed subsequently a cancer in some other organ.

These observations give evidence that the genesis of cancer may be determined by systemic factors, although in its inception the disease is, as we have seen, localized. I have recently obtained further evidence of the existence of such systemic factors in normal animals, in which it has been possible to induce experimentally the reverse condition of

diminished resistance to the genesis of cancer. The conclusion that the development of cancer in one organ induces a resistance to the subsequent development of cancer in another organ would also explain another very curious fact which seems to have been overlooked by statisticians. There is a curious discrepancy between Holland and England in regard to the mortality from cancer of the breast and uterus: it is nearly twice as high for English women as for Dutch women. An international committee of distinguished statisticians working under the auspices of the League of Nations¹⁷ has undertaken to collect detailed statistics with the object of finding the reason for this remarkable difference. The report has just been published,* and is a mine of valuable statistical information concerning cancer of the breast and uterus in these countries. But the committee has been unable to solve the problem.

Now though there is this great difference in the mortality from cancer of the breast and uterus between the two countries, there is no such difference in the total mortality from cancer. The mortality from cancer of all organs is, in fact, nearly the same in both countries, and if we investigate this point further we find that there is among Dutch women a much higher mortality from cancer of the stomach and intestine than among English women. The more frequent development of cancer in the intestinal tract among Dutch women protects them against the development of cancer in the breast. It might be equally or even more pertinent to inquire why Dutch women have a higher mortality from cancer of the stomach and intestine than why they have a lower mortality from cancer of the breast and uterus.

THE PARASITIC CONCEPTION.

An account of the essential features of the disease makes a very complex picture. The problem is to formulate a conception which will correlate, explain, and fit in with all the known facts and the truth of which can be demonstrated experimentally. All the numerous attempts to give an explanation of cancer can be conveniently divided into two groups: the parasitic conception and the biological conception. The parasitic conception explains cancer as being due to an extrinsic factor, the biological conception seeks to explain it by intrinsic factors—variations in the normal mechanism of cell life.

The attraction of the parasitic etiology of cancer is its simplicity. All we have to do is to find a micro-organism which is always associated with malignant new growth, and which, when introduced into the body, will by itself produce cancer as its specific disease, just as the *Spirochaeta pallida* produces syphilis and the tubercle bacillus tuberculosis. The experimental investigation of cancer has shown very clearly that the very simplicity of this conception makes it inadequate as a solution of the problem. I have already pointed out that the wide zoological distribution of the disease and its essential similarity in the different classes of animals would argue for one specific micro-organism as the cause. But if that were so, cancer should be transmissible from one species to another, which it is not. The strict limitation of the transmissibility of cancer, therefore, would argue for one specific micro-organism for each species, each micro-organism producing the same disease in each species. That seems highly improbable. But when we have conceded that, we are up against the difficulty mentioned before: we find that in transplanting a neoplasm from one animal to another of the same species we are not initiating the disease as we do in other diseases of known microbic origin, but we are merely keeping the cancer cells alive. That seems definitely to exclude the presence in a neoplasm of a micro-organism capable by itself of producing cancer. Nor can we explain in this way why a neoplasm grows out of its own resources and does not transform the surrounding tissues, why a carcinoma remains an epithelial growth and a sarcoma remains a connective tissue growth. From what I have said I think it is clear that the assumption of a specific micro-organism or even of an enormous group of specific micro-organisms which by themselves, when introduced into the body, produce cancer does not afford an explanation. It is for this reason that cancer researchers with rare

unanimity have in the past turned their back on the parasitic conception of cancer.

Now it may be argued that all these *a priori* considerations would fall to the ground as soon as one observer isolated a micro-organism specific for cancer in the sense that it is always present in malignant new growths and is capable by itself of producing malignant new growths experimentally in a sufficiently large number of experiments. The answer to that is that none of the claims put forward has withstood critical examination.

THE BIOLOGICAL CONCEPTION.

The second group of cancer theories are based on biological conceptions. We have here such theories as Cohnheim's view that cancer arises from embryonic rests, or Ribbert's hypothesis that dislocation of epithelium from its normal association with surrounding epithelium and connective tissue elicits latent powers of unlimited proliferation. These theories and a few others were elaborated before cancer could be investigated experimentally and before the technique of tissue culture *in vitro* had been developed. A detailed criticism of these various theories has been given in the second scientific report of the Imperial Cancer Research Fund. It is sufficient to say here that they do not explain all the features of cancer, and that when put to the experimental test they have failed.

Other biological conceptions have sought the solution of the cancer problem in a disturbance of the inner mechanism of the cell, especially that which presides over cell division. A vast amount of work on the cytology of the cancer cell has, however, failed to demonstrate any essential difference from the normal cell. The whole subject has been admirably summarized in a recent article by Dr. R. J. Ludford¹⁸ in the *Journal of the Royal Microscopical Society*. The biochemistry of the cancer cell has also been subjected to an exhaustive investigation and has been made the basis of many speculations.

So far I have tried to give you in rapid sketch an idea of the state of the cancer problem as it was six months ago. If it appears to you confused, that is exactly the impression which I wished to give you. The experimental investigation of cancer had brought to our knowledge a large number of facts concerning the disease. But many of these facts appeared to be so contradictory that it seemed impossible to correlate them by reference to a simple cause. As our knowledge increased the problem became more and more complex until we began to wonder whether what we call cancer was really a single disease and not perhaps a whole group of diseases each with a separate etiology.

THE WORK OF GYE AND BARNARD.

And now we come to "the last scene of this strange eventful history"—the work of Gye¹⁹ and Barnard.²⁰ Gye's conception of the etiology of cancer is that it is due to an ultramicroscopic virus common to different classes of animal. This virus when it enters into the cell stimulates it to the characteristic independent growth. But the mere presence of the virus in the body does not produce cancer, because by itself the virus is unable to attack a normal cell. In order to do this it requires the presence of an accessory factor or factors, which are furnished by the biological condition of the cell. This conception is a brilliant and ingenious compromise between the biological and the parasitic theories of cancer, and is in harmony with most of the essential features of the pathology of cancer.

But Dr. Gye did not develop his conception as the result of armchair speculation. It arose naturally from the results of a prolonged and technically very difficult experimental investigation on the peculiar fowl sarcomata discovered by Rous in 1911.²¹ These tumours, called "Rous tumours" for short, formed a particularly fascinating and puzzling chapter of cancer research. In a series of brilliant papers Rous disclosed the peculiar nature of these tumours. Little has been added to our knowledge concerning these tumours since. In fact, up to six months ago they had been neglected by cancer researchers as a disease which mimics cancer but is essentially different

* See BRITISH MEDICAL JOURNAL, January 23rd, p. 160.

from it. Now it appears that these tumours have in the hands of Dr. Gye furnished us with the key for the solution of the cancer problem.

These tumours have been observed only in fowls, and are rare even there. Histologically they are typical sarcomata, each possessing a very characteristic individual appearance. Rous described three such tumours: one was a spindle-celled sarcoma, the second was an osteochondrosarcoma, the third was a sarcoma having peculiar elongated rift-like blood spaces. Clinically they are highly malignant, growing with great rapidity and spreading very quickly throughout the body by metastases. On transplantation they retained their characteristic structure. Transplantation is limited not only to the same species but actually to one particular breed—the Plymouth Rock breed. In all these respects they behave, therefore, in the same way as typical malignant new growths. But they differ in one important feature: all other tumours, even other fowl tumours, could be transmitted only by using living tumour cells; when the cells were killed by any agency whatever the transplanted dead tissue failed to grow. This fact was always regarded as a strong argument against the parasitic theory of cancer. Now the Rous tumours can be transmitted by a saline extract which had been rendered completely free from cells by filtration through a Berkefeld filter. If the clear cell-free filtrate is injected, a new tumour forms rapidly. And the most astonishing thing is that the tumour formed by the cell-free filtrate retains its original structure. The filtrate from the osteochondrosarcoma forms an osteochondrosarcoma, the filtrate from the rifted sarcoma forms a rifted sarcoma.

Whatever the solution of this puzzling problem might be, one thing is clear—that these tumours can be transmitted by means of a "filterable agent," as Rous called it. *A priori* this might be either a chemical substance or a living filterable virus.

One of the first stages in Dr. Gye's work on these tumours was to determine which of these two alternatives was the correct one. He argued that if it was a virus it must be particulate, so that it can be brought down by spinning over a long time at a very high speed. He had found that when he incubated a piece of tumour anaerobically in broth of a certain composition the fluid in which the tumour had been circulated was capable of producing a tumour. By subjecting this fluid to spinning and injecting afterwards samples of the fluid separately from the top and from the bottom, where a slight deposit of the virus had been formed, he found that the top layer had become inactive, while the bottom layer rapidly produced a large tumour. The next stage was to decant after spinning the whole fluid from the deposit of virus, and after washing the deposit of the virus with saline to inject it into chicken. He expected it to produce a tumour. What he found was—nothing! Nor did the top layer of the supernatant fluid produce a tumour. But when the washed virus was injected together with the supernatant fluid a rapidly growing tumour developed within two weeks, having the typical structure of the original sarcoma. Now an experiment of this kind shows very clearly that two factors are involved in the transmission of this particular tumour under experimental conditions: one is particulate—a virus; the other non-particulate—a chemical substance furnished by the tumour cells. The virus by itself is non-pathogenic. The second chemical factor enables it to enter the cells and then to stimulate them to the unrestricted, lawless growth characteristic of cancer cells. The chemical factor has a very specific action in so far as it renders only the same type of cell susceptible to the virus as that which composed the original tumour. Gye, therefore, calls this second agent "the specific factor." If we formulate this conclusion in a more general manner by speaking of the virus as the "extrinsic" factor (extrinsic to the cells), and of the chemical substance as the "intrinsic" factor, we see at once that this conception represents a compromise between the parasitic and the biological conceptions of cancer which have hitherto held the field as irreconcilable antagonists.

This conception is confirmed by a number of other experiments which I have no time to discuss. I may perhaps mention that the living nature of the virus has

been demonstrated both by the ultramicroscopic observations of Barnard and by experiments of repeated subculturing which demonstrated a multiplication of the virus.

So far as these experiments go they allow us to apply these conclusions only to these particular types of Rous tumours in the fowl. Can they be transferred to the tumours of mammals and of man? It is important to understand the fundamental difference between the transmission of these peculiar Rous sarcomata by a cell-free fluid and the transplantation of the majority of animal neoplasms by living cells. As I explained above, in transplanting a neoplasm by living cell we do not reproduce the disease in the new host *de novo*. The transplanted cells themselves continue to grow; the new host supplies the stroma and the food which enables the transplanted cells to live and grow. The tumour which forms is composed, not of the cells of the new host, but of the cells of the animal in which the neoplasm originated—possibly ten or twenty years ago. But when a Rous sarcoma is transmitted by a cell-free filtrate the connective tissue cells of the new host become malignant at the site of the inoculation, and we do reproduce the disease *de novo*.

What is the significance of this important difference? Does it mean that these Rous tumours are a disease *sui generis*, having an entirely different etiology from true sarcomata and only resembling them so closely as to mislead the unwary investigator? That was the view generally adopted, and the Rous tumours were considered to be not true sarcomata but infective granulomata. There had always been a difficulty in making a clear-cut distinction on histological grounds between these two groups of connective tissue tumours. The experimental transmission of these tumours seemed to furnish a definite criterion: tumours which could only be transmitted by living cells were true sarcomata, those which could be transmitted by a cell-free extract were infective granulomata.

But Gye refused to accept these definitions and decrees and for a decision appealed to further experimental evidence. And it is through taking this step that he has been able with his new technique to disclose the relationship between these Rous tumours of doubtful pedigree and the tumours of unquestioned cancerous origin, and thus to change completely our whole outlook on cancer. We have seen that the cells of the Rous tumours, but for the one exception, exhibit all the characters of a malignant cell: they invade the surrounding tissue, they form metastases, they retain their biological individuality both in the metastases and after transmission, they even show the narrow limitation of transmission within a species. Gye had found that in the Rous tumours these characters of malignancy are conferred upon normal cells of the new host when a virus is made to enter it by the presence of the specific factor. Now, he asked himself, if that is so, why should not the malignant character of the tumours of mammals and of men be due also to the presence of a virus in the tumour cells. How can this proposition be put to the experimental test? His answer was: By seeing whether the virus of the Rous tumour can be substituted by a virus from mammalian tumours, so that by adding the specific chemical factor from the Rous tumour to a virus from a mammalian tumour a sarcoma can again be produced in the chick. In practice the experiment is as follows: a piece of tumour from an animal or from man, as the case may be, is taken and incubated anaerobically under such conditions as would allow a virus to multiply if it were present. This fluid when injected into a chick produces no result. To provide the second factor a cell-free extract from a Rous tumour is treated in such a way as to remove or inactivate the virus, so that this fluid when injected into a chick also produces no result. Then both fluids are mixed and injected into a chick. If now a sarcoma arises the culture fluid from the mammalian tumour must have contained a virus.

In this way Dr. Gye has been able to demonstrate experimentally the presence of a virus in various sarcomata and carcinomata of the mouse and rat, and, so far as his published results go, in one human carcinoma. His conclusions based on such experiments have been confirmed by Mr. Barnard by the examination of Dr. Gye's cultures

by means of a new ultramicroscopic technique. By means of this technique Mr. Barnard has succeeded in studying the virus cultured by Dr. Gye, and he has been able to confirm its presence in those conditions in which experimentally a positive result was obtained.

VIRUS AND BIOLOGICAL FACTOR.

Dr. Gye's work, then, leads to the conclusion that the entrance into a normal cell of a specific virus confers upon the cells those characteristics which are the essential features of malignancy. The virus appears to be the same for a great many different classes of animal. The virus alone is, however, unable to effect an entrance into a normal cell. To do so it requires an accessory biological factor or factors. What these accessory biological factors are we do not as yet know: it may be a special functional condition of the cell, or the absence of oxygen, or an abnormal cell metabolite. Only in the case of the Rous tumours do we know for certain that the accessory biological factor is a chemical substance furnished by the tumour cells. But it does not seem to me to be an essential part of Gye's conception that the cells of every neoplasm must always produce such a substance. Once the virus has been enabled to enter into a few cells the trick is done and the cells are now impelled to grow. I wish to emphasize this point because some writers have quite arbitrarily made the demonstration of a specific factor in every neoplasm the touchstone of Gye's theory. The cells of the Rous sarcomata are exceptional in forming an abundance of such a substance, and it is this exceptional property which explains why the Rous sarcomata can be transmitted with a cell-free filtrate and why they have such a high degree of malignancy. If all sarcomata contained an abundance of this specific factor they could all be transmitted by a cell-free filtrate and they would all have the same highly malignant character. We know that this is not so. Further work will have to show whether different sarcomata vary in the amount or the stability of the specific factor formed by them. So far only one tumour—a mouse sarcoma—has been shown by Gye to be transmissible by a cell-free fluid, and in this case he found that the specific factor of this tumour was so sensitive to oxidation that its presence could be demonstrated only under very strict anaerobic conditions.

MICROBIC INFECTIONS AND ACCESSORY FACTORS— DEFENCE RUPTURE.

The conception that the virus of cancer by itself is non-pathogenic and can only elicit the disease if an accessory factor is present may at first appear too novel and unique to be readily acceptable. The orthodox teaching of bacteriology has, indeed, accustomed us to regard a disease of microbic origin as being the immediate result of the entrance of the microbe into the organism. That is so for many infections, but by no means for all. During the war it was generally recognized that though most wounds were infected with the bacteria of gas gangrene only a small percentage of the infected wounds developed gas gangrene. Dr. Gye and I were working on gas gangrene at the time, and being very much impressed by this fact we investigated the cause of this phenomenon. We found²² that if the bacteria of gas gangrene, or their spores, had by repeated washing been made completely free from all toxin they had become non-pathogenic and could be injected into animals in large doses without producing any effect whatever. But if a small amount of a soluble calcium salt was injected, not necessarily together with the bacteria but even when it was given several days afterwards and at a different site, gas gangrene developed at once and killed the animal. Dr. Gye informs me that on repeating the experiments a few years later with the washed spores of *Vibrio septique* he succeeded in producing gas gangrene by the injection of calcium salts six months after the injection of the spores. When the calcium salts were injected at a different site, the focus of infection was not where the bacteria had been injected but where the calcium salt had been injected. Further investigation showed that the calcium salt produced in the tissue a specific visible lesion of such a nature that

the normal defences of the subcutaneous tissues against the bacteria of gas gangrene were broken down and the bacteria could proliferate at the site of the lesion. We therefore called this phenomenon "kataphylaxis," or "defence rupture." We showed that the same holds true for tetanus and even for streptococcal infections. Other substances, strontium salts, some colloids, such as colloidal iron or colloidal silicic acid, have a similar effect. Gye and Kettle²³ showed that tuberculous infections could be induced in animals usually resistant to it by the injection of colloidal silicic acid. Orthodox bacteriology has taken no notice of this striking phenomenon; it is not even mentioned in the chapter on gas gangrene in the official medical history of the war.

These are infections occurring through the broken skin, and the onset of the disease is here determined by substances carried into the wound with the earth. Most ordinary infections take place mainly in the mucous membranes—namely, in the respiratory and the digestive tracts. These membranes are always in contact with bacteria, but are not ordinarily infected by them, because the secretion of mucus keeps the bacteria from coming into close contact with the tissues. Now one of the effects of a diet deficient in vitamin A is to produce an atrophy of the mucus-secreting cells.^{24 25} When this occurs the bacteria of the intestinal and respiratory tracts beginning in the mucous glands gain entrance into the blood stream. It is frequently stated that such a diet produces in the animal a general diminution in the resistance against infection. That, however, is not the case. These animals are no more susceptible to infection by bacteria injected subcutaneously than normal animals, nor do the usual serological tests show any deviation from the normal: it is a local diminution of resistance in specific tissues. Excessive radiation with radium produces a similar effect.²⁶ Here, then, we have two entirely different agencies—radiation and vitamin deficiency—eliciting accessory biological factors necessary for the bacterial infection of mucous membranes.

A very striking experiment bearing on this point has been recorded recently by Webster²⁷ of the Rockefeller Institute. He introduced mouse typhoid bacilli in equal doses into the stomach of mice. The mice were of the same strain; but were kept on two different diets. Both diets were adequate to keep the animals in good health and to enable them to breed, but one diet was so constructed as to be especially rich in vitamins. Of the animals kept on the vitamin-rich diet only 15 per cent. developed the disease and died. The mortality in the other group was 100 per cent.

All this goes to show that many microbic infections result not merely from the presence of the specific microbe but require accessory factors which vary with the different micro-organisms and the different tissues. To prevent a misunderstanding it may be stated that it is not suggested that the accessory factors just mentioned play any part in the production of cancer. There we have the various forms of chronic irritation which probably take their part in the etiology of cancer in this way. Directly or indirectly they render cells susceptible to the entrance of the virus.

CONCLUSION.

It goes without saying that Gye's conception, in so far as it is based on experimental work, has to stand the test of experimental confirmation. What I have been trying to show is that his conception has given us a new outlook on cancer. Let us see now what his conception explains. The aimless, lawless, irresistible growth is the result of a virus entering into a few cells and impelling them to grow, freed from the control and inhibition which regulate the growth of the normal cell. The cell with the virus nevertheless retains its biological character as a cell of the species, of the tissue, and of the individual to which it belongs; hence the limitation in transmission and the fact that the cells of a neoplasm breed true. The virus is common to the tumours of different species and classes of animals; hence the wide zoological distribution of the disease. The virus by itself is non-pathogenic; that explains why the disease is not contagious. The virus can only enter a cell if some accessory biological factor is present: such a condition can be induced by very different forms of chronic irritation;

hence the local origin of the disease. We can also understand why agencies so different as tar, x rays, and animal parasites are capable of inducing cancer. Under exceptional conditions the parenchyma of a carcinoma may have such an effect on the cells of its stroma that the virus is able to infect the connective tissue cells and a sarcoma arises from a carcinoma. The cells of some very rapidly growing and highly malignant tumours produce in abundance a substance which will act as an accessory biological factor, but only for the same type of cell as the one of which the tumour is composed. Such a tumour can therefore be transmitted by a cell-free filtrate containing both virus and the specific factor. Other tumours contain less of this specific factor or it is more labile; they can therefore only be transmitted by living cells. There is therefore no fundamental distinction between these two types of neoplasms, as was hitherto supposed; they differ only in degree.

These differences in the amount of specific factor present in different tumours affords an explanation of the variations in the clinical behaviour of different neoplasms as regards rate of growth and malignancy. A tumour forming an abundance of the specific factor will grow rapidly and metastasize rapidly, because in such an extreme case the tumour will grow, not only by cell division, but also by a transformation of the normal cell of the same type. This would explain the fulminating growth of some types of cancer in the human subject. Tumours containing less of this specific factor or forming a less stable specific factor will grow more slowly and metastasize less rapidly. The striking fact that the growth of a neoplasm is independent of the nutrition of the animal in which it grows calls, as we have seen, for an explanation which places the impulse to grow within the cancer cell. This is obviously in accord with the conception that the growth of a cancer cell is due to an intracellular virus assisted by a chemical factor elaborated by the tumour cells.

Gye's work raises many new problems into which I cannot now enter, but it has solved our old and fundamental difficulties. Its particular merit is that it is not in conflict with any of the previously established facts, but, on the contrary, it confirms them. Taking them as his starting point, he has just gone one step further, and in doing so he has hit upon a conception which links together all our knowledge concerning cancer, which removes all the apparent contradictions, and which, so far as I am able to judge, explains all the essential features of the disease. It is the first adequate explanation of the causation and growth of cancer, and it points the way to further progress.

REFERENCES.

- 1 P. Ehrlich and H. Apolant: *Berl. Klin. Woch.*, 1905, No. 28.
- 2 M. Haaland: Third Scientific Report Imperial Cancer Research Fund, 1908, (B).
- 3 B. R. G. Russell: *Jour. of Path. and Bact.*, vol. 14, 1910.
- 4 J. C. Drummond: *Biochem. Journ.*, 1917, vol. 11.
- 5 W. Cramer: Eighth Scientific Report Imperial Cancer Research Fund, 1923.
- 6 E. F. Bashford and J. A. Murray: First and Second Reports Imperial Cancer Research Fund, 1904.
- 7 E. F. Bashford, J. A. Murray, and W. Cramer: Second Scientific Report Imperial Cancer Research Fund, 1905.
- 8 J. Fibiger: *Berl. klin. Woch.*, 1913, vol. 50; *Zeit. f. Krebsforsch.*, 1920, vol. 17.
- 9 K. Yamagiwa and K. Ishikawa: *Mit. Med. Fakultät. Tokyo Univ.*, 1916, vol. 15; 1917, vol. 17; 1918, vol. 19.
- 10 A. Leitch: *BRITISH MEDICAL JOURNAL*, 1922, ii, p. 1101.
- 11 A. Scott: Eighth Scientific Report Imperial Cancer Research Fund, 1923.
- 12 A. Leitch: *BRITISH MEDICAL JOURNAL*, 1922, ii, p. 1104.
- 13 F. Bang: *Bull. du Cancer*, 1923, vol. 12.
- 14 See J. Fibiger: *Zeit. f. Krebsforsch.*, 1920, vol. 17.
- 15 F. D. Bullock and M. R. Curtis: *Proc. New York Path. Soc.*, 1920, vol. 20.
- 16 J. A. Murray: Eighth Scientific Report Imperial Cancer Research Fund, 1923.
- 17 Report on the Results of Certain Clinical Inquiries relating to Differences of Cancer Mortality in Certain Selected Countries. League of Nations Health Organization, Subcommittee on Cancer.
- 18 R. J. Ludford: *Journ. Roy. Microscop. Soc.*, 1925, p. 249.
- 19 W. E. Gye: *Lancet*, July 18th, 1925, p. 109.
- 20 J. E. Barnard: *Ibid.*, p. 117.
- 21 P. Rous: *Journ. Exper. Med.*, 1911, vol. 13; 1913, vol. 18; 1914, vol. 19.
- 22 W. E. Bullock (Gye) and W. Cramer: Sixth Scientific Report Imperial Cancer Research Fund, 1919.
- 23 W. E. Gye and E. H. Kettle: *Brit. Journ. Exper. Path.*, 1922, vol. 3.
- 24 W. Cramer: *Lancet*, 1924, i, p. 633; *Proc. Roy. Soc. Med.*, 1925 (Discussion on vitamin deficiencies).
- 25 W. Cramer and A. N. Kingsbury: *Brit. Journ. Exper. Path.*, 1924, vol. 5.
- 26 J. C. Mottram and A. N. Kingsbury: *Brit. Journ. Exper. Path.*, 1924, vol. 5.
- 27 L. T. Webster and T. W. Pritchett: *Journ. Exper. Med.*, 1924, vol. 40.

THE SURGICAL TREATMENT OF ANGINA PECTORIS.

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IN a previous article (*BRITISH MEDICAL JOURNAL*, 1924, ii, p. 553) I described my conception of the pathogenesis of angina pectoris, and of the mode of action of the sensory cardio-aortic nerve fibres in producing the attacks. I concluded that the best surgical operation applicable to this disease was the intercepting of the maximum number of the sensory cardio-aortic fibres without interference with the important groups of the cardiac accelerators. Jonnesco's operation, in which the stellate ganglion is removed, does

FIG. 1.—Course of the sensory cardio-aortic and of the cardiac accelerator fibres. The sensory cardio-aortic fibres originate in the heart and aorta and form two groups. The first group passes through the stellate ganglion and divides into: (1) a dorsal bundle, for the second, third, and fourth dorsal pairs; (2) a cervico-dorsal bundle, for the sixth, seventh, and eighth cervical, and first dorsal pairs; (3) a vertebral bundle, entering the fifth, sixth, and seventh cervical pairs through the vertebral nerve; (4) the cervical sympathetic bundle, which follows the cervical trunk and joins fibres reaching the trunk through the superior and middle cardiac nerves and the anastomoses which unite the cervical trunk, the vagus, and its branches. The cervical sympathetic bundle is divided between the first five cervical pairs, the medulla, and cranial nerves, and the Gasserian ganglion, reached through the carotid and cavernous plexuses. The second group follows the cardiac branches of the cervical sympathetic and cervical portion of the vagus without reaching the stellate ganglion. It divides into: (1) a bundle entering the cervical trunk through the superior and middle cardiac nerves, and joining fibres in this bundle which originated from the first group; (2) a bundle following the superior cardiac fibres, the depressor nerve being included here, middle cardiac fibres from the recurrent nerve, and inferior fibres from the thoracic supply of the vagus. This bundle enters the vagus trunk and travels towards the medulla, a part of it traversing the anastomoses in the cervical bundle.

not fulfil these conditions, and should be abandoned for the following reasons.

1. The Jonnesco method intercepts important groups of the cardiac accelerator fibres, and the coronary and pulmonary vasomotor nerves. Physiologists have shown experimentally that animals deprived of their extracardiac nerves lose the power of resistance, and it has also been proved that removal of the stellate ganglion weakens the heart beat. By repeating such tests in dogs I have found that excision of the first thoracic ganglia seriously affects the fundamental physiology of the myocardium. The alterations are rendered still more grave if this operation is preceded by ligation of certain branches of the left coronary artery.