but to be allowed to resume his work. I have mentioned it before (*Clinical Journal*, July 23rd, 1924), but should like to do so briefly again.

G. H., a railway carter, aged 55, was wheeling a hand truck carrying 7 cwt. of goods in October, 1922, when he felt a sharp pain behind the sternum and over the heart but not down the arms. For half an hour he felt short of breath and had to sit down, and attempts to breathe "punished him like a knife." After this he felt practically normal, but reported the incident, according to instructions. He went to work next day, feeling sore before the heart and in the chest, and with a sharp pain now and again when he was lifting heavy weights. He was sent, against his wish, as he wanted to work, to see the company's surgeon, who found nothing wrong, but thinking of the possibility of heart strain advised that the man be sent on to see me. I found systolic blood pressure 150. There was no albumin or sugar, and no arterio-sclerosis; the heart was practically normal, rate 90 standing, no sign of aneurysm. An electro-cardiograph record was taken, but it showed nothing abnormal.

The seat of the pain and its nature and mode of onset certainly suggested the likelihood of strain of the heart from sudden overexertion, but I thought it might be due to strain of a skeletal muscle and of the triangularis sterni. As the man was very anxious to get back to work we accepted this view, but put him back on a lighter job, and he kept perfectly well until he had an attack of encephalitis in February, 1924; from this he recovered.

DIFFICULTY IN PROVING HEART STRAIN.

Heart strain is not easy to establish in a court of law because of the difficulty in proving accident. I will briefly relate an instance of this.

A railway porter claimed compensation for strained heart, caused when carrying full milk-cans weighing up to 300 lb. up the station steps with the assistance of another porter, each porter taking hold of one handle of the can. Whilst doing this one morning the projecting flange which strengthens the bottom of the can caught under the overhanging edge of the stairs and pulled the porters up suddenly; this caused a pain over the heart of the claimant and subsequent shortness of breath, which persisted for several months on slight exertion, and kept him in bed most of the time until I saw him on his own behalf. I found that he had some slight enlargement of the heart and symptoms which could have been caused by heart-muscle strain. He was a healthy youth of about 24, though not of robust type; there was no history of venereal disease, but there was some neurasthenic element in the case. I told his lawyer, from past experience, that it would be very difficult to prove "accident"; but I agreed to say what I could on the strain, neurasthenia, and debility theory. It then transpired that the man had been first treated for a feverish cold or influenza, and as his doctor found unexpected cardiac weakness four or five days after the commencement of the illness or influenza he asked the porter if he could have strained his heart in any way. The man then thought of the accident, but had never mentioned it to his fellow porter working with him, or to anyone in the station at the time it occurred, nor did he do so until a week after the doctor had asked if there had been a strain. The railway company's doctor put the condition down to influenza, and on the above evidence produced in court, and heard for the first time, the judge held that an accident had not been proved and that the heart condition was due to influenza, which I think was a proper decision on the evidence.

I really did think that the man, who was not robust, could have strained his heart in the way claimed.

Another case was that of a collier, aged 38, who said that one day in the pit he had lifted a crane weighing $4\frac{1}{2}$ cwt. which had become displaced. He felt short of breath but complained of no pain at the time. A couple of weeks afterwards he had some pains in the joints. He worked for four weeks after lifting the crane and then had to give up because of shortness of breath. I examined him nine weeks after the supposed strain. There was little to be found, only some slight dilatation of the heart with weak and doubled sounds. There was no albumin in the urine and no increase of blood pressure. The man was very short of breath. He was sent to bed for two weeks, and then got up again, feeling no better. He dropped down dead, presumably from heart failure, five weeks after I saw him. No *post-mortem* examination was held, unfortunately, but the predisposing cause of death was very likely atheromatous coronary arteries.

Here I had no doubt that the man strained his heart in some way lifting the heavy weight, but the court found against him, holding that strain was not proved, and that even if it had taken place could not so badly affect a sound heart, and that there must have been pre-existing heart disease. The case was tried in 1907, before the House of Lords decision on the aneurysm and the spanner claim, which influenced so greatly the meaning of an accident. I am sorry that I was unable to get a Wassermann test here, for very probably, in one so young, we should have found it positive.

An Address

ON

A NEW OUTLOOK ON CANCER:

IRRITATION AND INFECTION.*

BY

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MORE than three years ago I¹ published an account of an organism obtained from carcinoma, and since then I² have described in increasingly more complete detail the morphological characters of this parasite. I have claimed, on the basis of a study of more than sixty cases, to show that this microbe can be obtained almost constantly from cancer. My conclusions have in some quarters met with opposition on two grounds. In the first place, it has been urged that to account for the cancer phenomena it is unnecessary to predicate the existence of a parasite. In the second place, it has been stated that my views are opposed to the established science of bacterial morphology. Within the limits of this paper I propose to deal with these two objections.

Of all the diseases of man cancer has probably the most unique features; it has little direct contact at any point with other morbid processes, and, for that reason, analogy is of small positive help in a search for the cause. The essential fact which marks it off is that, beginning in the proliferation of a small group of cells, it ends, when running its ordinary course, as a myriad host of anarchic cells destroying by direct inroad the healthy surroundings and burrowing often into the springs of life itself. Any class of cells in the body may be seized with this tragic impetus, and, according to their site of origin, so will the cancer differ in structure and, it may be, in deadliness; but in all, no matter what the origin, the same unique features dominate the process, in all we have a plague of riotous cells spreading as a blight without control or cessation.

It is important to stress the essential unity of the cancerous process, especially at the present time, for some observers are so immersed in detail that they have allowed themselves to lose sight of this unity and have accordingly, I believe, fallen into serious error. The differences in detail are seen when malignancy involves structures of different kinds. For example, when originating in squamous epithelium, squamous epithelioma is produced; when in gland acini, glandular cancer; but that these structural differences, which may be considerable in detail, are non-essential in regard to the ultimate nature of cancer is shown by the fact that, in an organ possessing both types of epithelium—for example, the uterus—we may find both types of cancer side by side. So, in the same way, carcinoma and sarcoma may occur together, and the essential similarity between these two such divergent types of "cancer" is further proved by the experimental finding that transplantable cancer may end as transplantable sarcoma, the cancerogenic factor in this case having been transmitted from one class of cell to the other. Considerations of this sort indicate that, where the malignant change is occurring in widely different tissues, the diversity in structure, and it may be in other points as well, cannot be held to justify any diversity in the ultimate nature and cause. The differences are rather local and environmental, and therefore non-essential.

The unique phenomenon of malignancy is not limited to man; it is found throughout the lower animals, and a process of an analogous kind is found also in the vegetable kingdom.

CHRONIC IRRITATION.

One of the most important positive facts in regard to the etiology of cancer acquired within recent years concerns the role played by chronic irritation. The experimental production of cancer in animals by the exposure of the skin to chemical irritants, of which there are now several, has lifted a long-established clinical observation into the realm of proved laboratory fact. It can now be claimed with

* Delivered in opening a discussion on cancer at the Liverpool Medical Institution, December 11th, 1924.

certainly that cancer can be induced by factors which vary as greatly in their nature as do tar, soot, arsenic, α rays, heat, etc. By some these isolated and distinct irritant influences have been adduced as necessarily so many direct "causes" of this unique process. To many who have followed the specious arguments which have sometimes been advanced in support of this extraordinary claim it must come as a surprise that even distinguished observers may be negligent of the warning lessons of medical history. Sixty years ago to claim that the specific disease, phthisis of the lungs, had a multiplicity of direct causes was in keeping with the knowledge of the period. Thus it was believed that the inflammation of a bronchitis, the irritation of the inhaled fragments of stone with which the mason worked, etc., were each one a direct "cause" of pulmonary phthisis, and that there were many other causes as well—for example, heredity, unhealthy environment, etc. Time has shown that the greatly differing direct irritants and the other indirect agencies operate in one common way—by increasing cell and tissue susceptibility to the one common factor, the *tubercle bacillus*. In many other cases the history of medical progress has shown that, where several causes have been advanced to account for a disease, these have proved to be nothing more than factors preceding, and predisposing to, the single common agent.

NATURE OF THE CANCEROGENIC FACTORS.

There are two facts which stand out distinctly in those cases where chronic irritation plays an antecedent part. (1) The regions so affected are typically covered by an adult resting epithelium—for example, lip, cheek, bowel, cervix uteri, etc. (2) The irritant influence typically has to operate for a long period, it may be months or even years, before the appearance of the cancerous change.

However we attempt to assess the influence of irritation we must admit that the special cellular alteration culminating in cancer must be a common effect of all the different materials and influences concerned—for example, tar, soot, arsenic, heat, α rays, etc. Cancer implies such a unique reversal of cellular activity that it is impossible to escape this conclusion. As I have pointed out, it must also be evident that the differences in structure in the tumours produced when irritants act on different classes of cells must be due to the original structural difference in the tissue involved and not to any difference in cause. It must be clear that the same irritant operating on the skin will tend to produce squamous epithelioma, whilst on a gland surface it will tend to produce a cancer derived from the gland cells, and so on. It would seem unnecessary to stress such an obvious fact were it not that some observers have inferred that in cancer we have a jumbled congeries of morbid conditions. Read aright, the confusing array of "causes" comprise so many different ways in which the common cellular upheaval is induced.

Even a superficial study of this cell upheaval proves that it consists of an alteration of the affected tissue in such a manner that cells which were previously well behaved and orderly and stable have acquired the power of ready and continuous proliferation. In a healthy epithelium there are always cells which can proliferate to repair damage, but under normal conditions such dividing cells constantly tend to differentiate into stable resting elements. Where the damage is long-standing there is gradually acquired an increasing impetus to reproduction and a diminishing impetus to differentiate. The one property is exaggerated at the expense of the other.

By some observers it is believed that the cancerous tendency is the direct outcome of the irritative process without the operation of any other factor. This view implies that where the tissue is damaged for a sufficiently long time in a certain way the cells eventually gather such a momentum of proliferation that this goes on in an unending and destructive sequence. Opposed to this view is that of those workers who, while agreeing that irritation probably operates by unlocking the reproductive faculties of the cell, suggest that the real immediate stimulus to a cancerous proliferation consists of a new and different stimulus added to the susceptible cell. So long as the epithelium consists of healthy stable cells the immediate

cancerogenic factor is inoperative. Let this stability be undermined in any one of a variety of ways and the addition of the immediate factor launches the cells on their disastrous career.

That there are two such factors, each the complement of the other and each equally essential—namely, an antecedent cell susceptibility and an immediate agent—is indicated by a study of those cases of cancer where chronic irritation does not play the part that is so obvious where an adult epithelium is concerned. In chorion-epithelioma the cancerous change typically overtakes the chorionic cells within a short time of their being stranded in the uterus; there is not the delay which characterizes a cancer, for example, of the cervix uteri, where the antecedent chronic irritative change may be in operation for years.

This distinctive difference in the time onset of the chorionic cancer is clearly to be correlated with the fact that in the chorion we are dealing from the beginning with susceptible cells—cells, in other words, already naturally endowed with marked reproductive powers. This state is natural to the cells, but obviously cannot of itself drive them to cancer without the existence of some other factor. Loose thinking is responsible for an attitude which sees an ample explanation in looking upon chorion-epithelioma as dependent upon a cell which has become excessively embryonic. This attitude, which, I believe, has done more than any other single error to obscure the real issue, fails to recognize that between the embryonic cell and the cancer cell there are differences not of degree but of kind. These differences are fundamental, and it is impossible to evade the conclusion that chorionic cancer is due to the addition of some drastically new factor to a cell already by nature able to respond. In somewhat the same way the ovum is an embryonic cell, and it becomes launched on its career of segmentation because its "proliferability" allows of a very special response when the new and necessary extrinsic factor is added to it.

There are other considerations which suggest that in chronic irritation there is only one of the factors concerned in the cancer process. For example, it is well known that not all surfaces exposed to chronic irritation become cancerous; and, moreover, the cancer when it does appear develops as a wholly new phenomenon, often many months or years after the damaging process has been in full swing. The conditions suggest that the chronic irritation is one thing, the cancer another thing, and the abrupt leap from one to the other implies the accession of some new factor.

Factors a and b.—The essential problem revealed by the study of cancer as it develops, on the one hand, in an adult epithelium rendered primitive by irritation, and, on the other hand, in an epithelium primitive by nature, may be depicted in the following formula, where the two cancerogenic factors are represented by *a* and *b*:

Adult epithelium + *a* + *b* = cancer.

Primitive epithelium + *b* = cancer.

A conception of this sort at once removes the confusion with which the irritation factor has been surrounded. It relegates it to its proper place, and it moreover disposes at the same time of much of the loose argument which has been advanced against the parasitic hypothesis.

TWO FACTORS IN PARASITIC PLANT TUMOURS.

In plant tumours we find an interesting analogy with the dual factors operating in cancer. In the plant this dual phenomenon—cell susceptibility and immediate cause (parasite)—is very clearly represented. The immediate and necessary agent is the parasite, but this is potent only when it operates on a cell capable of, or in the act of, continued proliferation. It thus happens that the tumours develop in areas where the cells are young and primitive—for example, in warty disease in potatoes, where the tumour begins at the "eye." So in crown gall, a plant neoplasm caused by the *Bacillus tumefaciens*, the tumour growth originates in tissue which is primitive and capable of further growth, and not in resting adult tissue. Erwin Smith's² investigations have shown the many and intimate ways in which crown gall resembles cancer in animals. The growth can be grafted on to other plants of the same species. It can be cut out, but it will recur if all the

tumour has not been removed. It destroys both by compression and by infiltration, and the latter process may spread into healthy tissues for a considerable distance from the original focus. Ordinarily the growth consists, as in cancer, of actively dividing cells with little tendency to differentiate. On the other hand, where multipotent cells are affected a true differentiation from tumour issue into leafy organs may take place, culminating in a malignant plant embryoma in essentials comparable to the malign embryomata of animals. As Erwin Smith reminds us, Jensen was so much impressed by these striking resemblances between crown-gall tumours and his mouse cancer that he considered them of much service in throwing light on the etiology of neoplasms, especially as, like cancer, they could not be considered as due to the operation of micro-organisms! A final and significant fact with regard to crown gall is that, as Erwin Smith points out, it tends to develop on irritated places. The irritation must clearly operate either by producing an abrasion in the tougher tissue by which the parasite can gain access to the primitive cells or by driving the mature resting elements back to the primitive state.

The conditions obtaining in these plant neoplasms bring out in a very clear light that, whilst the *a* factor of cell susceptibility is a necessary antecedent, the *b* factor (parasite) alone can stir the cells into a malignant overgrowth.

HEREDITY IN CANCER.

Amongst some of the other facts on the general etiology of cancer which have been accumulated during recent years are those bearing on the hereditary basis of malignant disease. By an extensive series of experiments Maud Slye⁴ has shown, apparently conclusively, that in the mouse there exist characters of individual resistance to and of susceptibility to the development of spontaneous cancer. These factors of resistance or susceptibility have an hereditary value, and, by selection, this observer has been able, on the one hand, to breed a race of mice insusceptible to cancer, whilst, on the other hand, she has bred a race every individual of which over a number of generations develops cancer, sarcoma, or pseudo-leukaemia. The latter condition Slye considers to be a form of malignant disease.

These findings are striking, and have been advanced by Slye as an argument against the infective nature of malignant disease. Such an argument would be logical only if it can be shown that susceptibility to infection, which exhibits great individual variation in man and animals, were a phenomenon with no dependence on heredity. So far is this from being established that some writers actually profess to have demonstrated that resistance to and susceptibility to infection are transmissible factors. Webster⁵ has shown this recently in mice with regard to resistance to infection with organisms of the typhoidal group.

Plant pathology provides again a suggestive analogy along these lines, for in the case of some of the parasitic tumours the heredity element may be prominent. In warty disease in potatoes, for example, it is common knowledge that the tendency to infection with the tumour-producing parasite varies greatly in different strains of potato. The recognition of this fact has led to the almost complete stamping out of what threatened to be a severe scourge by the success which has attended the efforts of horticulturists to breed immune stocks.

A general consideration of the phenomena underlying the factor *a*, the antecedent susceptibility of the cell to neoplasia, thus suggests that, as in other diseases, it is a compound of several factors, amongst which the operations of both heredity and irritation may be apparent.

An analysis of the data carried out along the lines which I have indicated leads to conclusions in no way opposed to an organismal conception of cancer. If the argument be sound which impels us to predicate the necessary existence of another and a more immediate factor in those cases where chronic irritation plays an obvious antecedent role, it is clear that a strong presumptive claim for a cancer parasite is established.

Another consideration in this connexion is that underlying the immediate cancer-producing agent there are two

mutually dependent facts. First, it must be clear that, however we interpret this factor, any indirect agency can only operate by adding to the cell something by virtue of which it is lashed into its undue reproductive activity. Secondly, it is clear that this new factor, once within the cell, is perpetuated and multiplied without ceasing, for only by its continued presence can the unending cell divisions and destructive growth be explained. It cannot be supposed that there are two separate factors, for this implies that the factor which stirred the first cells to a cancerous proliferation is different from that by which the later divisions are induced. The factor added from without and the factor which is then multiplied from within must be one and the same. Unless we can conceive of a motive power received *de novo* by the cell and then perpetuated by the cell, we are driven back to a living parasite as the sole possible explanation.

Despite the suggestive evidence supplied by the existence of so-called cancer houses and cancer cages, cancer has no obvious infective characters. This of itself is, of course, no proof of its non-organismal origin, as some diseases of definite micro-organismal nature may lack infectiveness in the ordinary sense. Just as there are all degrees in this character of infectiveness amongst diseases which owe their immediate production to a parasite, so cancer has some links with diseases whose general clinical and pathological associations presuppose an infective basis. I have said that cancer has unique features and that analogy is of little help in a search for the cause. If, however, we include within the scope of the cancerous process all the conditions with the same manifestations of a malignant cell proliferation—for example, chicken sarcoma, infective sarcoma of dogs, and the leukaemias—we find very definite support for the parasitic view. In all these conditions there is strong evidence of an infective basis, and the "leukaemic" state is especially interesting and suggestive, because in it are embraced all grades between lesions with obvious infective traits and lesions which are indistinguishable from malignant growths (lymphosarcoma).

THE CANCER PARASITE.

This I have described fully elsewhere, and in this place I can refer only to the general features of the organism and to the extensive support which my views on these characters obtain from bacteriological literature. I have shown that the microbe has a complex morphology, appearing in a variety of forms, each of familiar type and each capable of leading an independent life: hypha, yeast, coccus, and bacillus. In addition I have described an amorphous phase or "plasm." I have urged that the failure to recognize this varying morphology has vitiated the problem from the outset, and I have claimed to show that an understanding of the alternative forms assumed by the organism under different conditions of life serves to unlock the secret of cancer, for the phase living symbiotically within the cell is wholly different from that found growing ordinarily in the test tube.

In support of these views I now have a mass of evidence so great that it is almost impossible to handle. Added to this, the literature proves that a large and increasing number of bacteriologists entertain views on general bacterial morphology similar to those for which I stand. Any close student of this literature cannot fail to be impressed with the tendency amongst practically all investigators on morphology to identify the bacteria with the fungi, and to look upon each form (coccus, bacillus, etc.) as merely one of several shapes in which the same organism can appear and in each of which it can grow true to type. The evidence, indeed, is so great that it must have been apparent to many that the very foundations of bacterial classification are tottering.

Many investigators have described coccal, bacillary, blastomycete, and hyphal phases as occurring in the life story of the same organism, and, within recent years, work based upon the employment of single-celled cultures has removed the last shred of criticism that the innumerable instances of variability can be discarded summarily as "contamination" (Mellon,⁶ Hort,⁷ de Negri,⁸ etc.). The fact, established by many workers, that each such variant

can propagate itself true to type in a vigorous normal fashion disposes also of the objection comprised under the term "involution," which in such circumstances is robbed of all meaning.

The present position is rendered all the more confusing by the demonstration that not only is bacterial form unreliable for purposes of classification, but that the very factors which, in the past, have been considered as belonging to the most delicate of the means of distinction (for example, Gram's stain and the serological reactions) may in the same organism differ within as large a range as the morphology. These variations may imply nothing more than an index of the physico-chemical alterations which an organism exhibits during its changing morphology.

THE AMORPHOUS PHASE.

From the beginning of my research I have urged that it is to this amorphous and often unstainable substance that we have to look for the secret of the cancerous process. Elsewhere I have given evidence that, in this phase, the organism lives in symbiosis with the cancer cell, and the flora which quickly appears in a piece of incubating cancer tissue is derived from the rapid increase and the organization of this material under conditions of laboratory environment, which differ wholly from those obtaining in the living body. From this "plasm" any or all of the various forms can be derived. It is thus totipotent. On occasions I have seen it becoming organized simultaneously into yeast, coccus, bacillus, and filament. The details of this phenomenon I have described fully elsewhere.

This amorphous alternation in the mode of life of bacteria has been described by many workers under a variety of names. It has been noted in practically all known bacteria. Some investigators have dismissed it as an inert matter formed by a crumbling of living cells. By many others, however, it has been recognized as a homogeneous, often hyaline and highly refractile living substance, in which the organizing vegetative forms are laid down as granules, which subsequently enlarge into the mature elements. As Löhnis⁹ has pointed out in his exhaustive summary of the literature, it has been described as such from early days down to the present time (Ray Lankester, Klebs, Koch, Haberkorn, Malassez and Vignal, Pernet, Rosenbach, Maher, Herzog, Almquist, Kellermann and Scales, Mellon, Löhnis and Smith, de Negri, etc.). The extent and unanimity of the findings of such a large body of independent workers leave no doubt of the reality of this alternative mode of bacterial life. Whilst this is so, the indefiniteness of its appearance and, in some stages, its complete absence of structure have made it a phenomenon of extreme elusiveness. For these reasons, apparently, the early investigators were deterred from devoting to it the attention which more recent research shows it to warrant. For it must be clear that the recognition of this class of structure brings into the science of bacteriology a fact of very great practical importance, as well as one of considerable academic interest. A most comprehensive study of this form has, within recent years, been carried out by Löhnis, who rightly insists that in it is to be found the means of co-ordinating much in morphology that is at present in a state of chaos.

In justice to my own work, and incidentally as an argument in support of the general facts surrounding this plasm phase, I must state that during the first period of my research I was in ignorance of the work of my predecessors, and my recognition of this phase came independently as the result of a search for the source of bacterial forms, which, during the early stages of incubation of a cancerous growth, could always be seen to appear first as very minute elements, which were often gathered into bundles scattered throughout the tissue. In my most recent paper I have shown by means of photomicrographs that the forerunner of these organized elements consists of an amorphous slime which exudes from the cancer cells and appears first as globules or as filaments, which ordinarily are very unstable and persist for only a few hours. [By means of lantern slides Dr. Young showed the plasm emerging from the cells as pale rods, filaments, or globules of greatly differing size. The alternative ways in which the plasm became organized were shown.]

As I have pointed out, the essential link in the chain of bacterial morphology is the amorphous phase. Without it an understanding of the phenomena is impossible, for, after organization, the different individual forms which arise from this phase may each pursue an independent morphological career, growing true to type as yeast, coccus, bacillus, etc., when the common origins are quickly lost. It is sometimes urged that this conception of morphology is unlikely on biological grounds. The multipotential property of the bacterial plasm is, however, surely no more extravagant a conception than the multipotency of the germ plasm of higher organisms. In both instances, with development, an unfolding into differentiated cells is found, and in both the individual cells tend to grow true to type. In the higher organisms, as recent research has shown, the true to type growth may, like that of bacterial cells, even continue when the cells are separated from the body and placed in the test tube in a suitable medium. The analogy, it is true, must not be overstrained, for in the case of the higher organisms the unfolding of cell types is by a ladder-like sequence, whilst the bacterial plasm may differentiate directly and, as it were, on a flat plane into the variegated forms. Moreover, with the bacteria, although differentiation may apparently be complete—so complete indeed as to have given rise to the whole superstructure of monomorphic bacteriology—the careful studies of many observers have shown that, with a suitable environment, even the most stable elements can quickly retrace the whole morphological compass of the race. Each element has, as it were, the totipotency of a germ plasm. Again it may be urged, however, that amongst the more primitive of higher organisms a similar totipotency may be present, and that we are on safe biological grounds in insisting that any differences in these respects are of degree and not of kind, and are satisfactorily accounted for by the evolutionary simplicity of the bacteria.

To those with imagination and courage the fresh fields opened out by these new data furnish an unbounded opportunity for research. I cannot do more than touch on one or two topics that invite a vigorous attack. An amorphous phase of the tubercle bacillus, for example, was described by Klebs,¹⁰ Malassez and Vignal,¹¹ and others many years ago. Such findings have naturally been submerged during the era of monomorphic bacteriology. They must, however, soon be revived by the discovery of several recent writers—for example, Valtis,¹² Vannucci,¹³ and others—that the filtrates of tuberculous tissue are capable of producing on injection typical tuberculous lesions in animals, although from such filtrates no tubercle bacilli can be grown. So, also, to those who are conscious of the drift of recent bacteriological discovery, it must seem not unlikely that the chaos of morphological forms associated with influenza will find its solution in the new and broadened outlook.

It is apparent that with a substantiation of the views which are rapidly gaining ground in bacteriology must come a strong confirmation of my conception of the cancer parasite. It must also be equally apparent that some at least of the organismal forms previously obtained from cancer by different workers are in reality isolated alternative phases in the same cancer organism. This view I have urged from the beginning of my research since I discovered that within the morphological range of my organism were elements not to be distinguished from the yeasts of Plimmer, San Felice, etc., the coccus of Doyen, the filtrable micrococcus of Nuzum, etc. The nearest anticipation of my own work I believe to be that of Monsarrat,¹⁴ who in 1903 described several bacterial forms obtained from cancer which correspond to some of the phases included in the life story of the organism described by me. Monsarrat, at the stage which his investigation reached, did not claim any definite significance for his organism. These previous observations all suffered, I believe, from the failure to discover the key to the problem, which is to be found in the "plasm" phase—the phase, as we have seen, that constitutes the essential link in the cycle of the organism, and is at the same time the secret of its parasitic mode of life.

I have pointed out that many recent observations prove that the methods usually employed for the differentiation of species are ill adapted for the purpose for which they are devised. This applies not only to morphological appear-

ances and staining characters, but also to serological and sugar fermentation reactions. In previous papers I have shown that different phases of my organism differ from one another widely, not only in morphology, but also in staining and sugar reactions. This aspect of the question, however, is in the meantime relatively unimportant, and is of little help so long as morphology is in its present unsatisfactory state. It cannot do more than multiply distinctions which are non-essential if the new lines of research are well founded.

CONCLUSIONS.

1. There are two completely independent factors underlying the change of a normal cell into a cancer cell. The first is an antecedent cell susceptibility. The other is the immediate cancerogenic factor. Analysis shows the antecedent cell susceptibility to be the capacity for continued proliferation in the body, and, when possessed naturally by the cells ("embryonic"), allows of a development of cancer when the immediate cancerogenic factor is added. In the case of a mature epithelium this cell susceptibility is acquired often as the result of chronic irritation. When the cancerogenic factor is now added cancer is possible.

2. In plant tumours this dual phenomenon—cell susceptibility and immediate agent (parasite)—is well seen. It explains why in warty disease of potatoes, crown gall, etc., infection by the parasite produces neoplasia in the healthy plant only when cells of a primitive kind are affected. Irritation of a mature surface of the plant may, however, make it susceptible to neoplasia after infection.

3. An organism with a complex life story has been obtained almost constantly from cancer. It possesses yeast, coccal, bacillary, and amorphous phases, and each of these can grow true to type and live a wholly independent life. Evidence has been given that the parasite lives in symbiosis with the cancer cell in the amorphous phase, and it is from this that all the other phases are derived during incubation of a cancerous growth. The discovery of this phase, it is claimed, provides the key to the cancer phenomena, as also the key to the morphological variants.

4. The morphological features of this parasite resemble the life story described by many writers for other classes of pathogenic organisms. There is now strong evidence to support the view that a similar morphological variability is common to all bacteria and that bacterial classification is in need of revision.

5. The parasite belongs to familiar bacteria which are widespread in nature, and the ease with which cancer can be induced experimentally in animals by chronic irritation suggests that tissue susceptibility wherever found implies the immediate risk of infection by a ubiquitous organism.

The free and universal exposure of man and animals to infection, combined with the (relatively) small proportion of the total which develop cancer, suggests the all-importance of cell susceptibility, and corresponds to the laboratory difficulties attendant on an attempt to produce cancer experimentally by the injection of the organism. In previous papers I have shown that a marked proliferation of primitive tissues can sometimes be induced in animals by the experimental injection of the cancer organism. This proliferation may resemble an ordinary infective process, whilst in an advanced case it simulates a progressive lymphoma or pseudo-leukaemia.

The investigations described in this paper were carried out at the Royal College of Physicians Laboratory, Edinburgh.

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DIAGNOSIS AND PROGNOSIS IN CHRONIC RENAL DISEASE:

THE RANGE OF UREA CONCENTRATION OR RANGE OF FUNCTION TEST.

BY

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THE purpose of this paper is to describe the above test, and also briefly to comment on other methods of investigating chronic renal disease. During a study covering three years extensive trial has been made of: (1) The urea concentration test (Maclean). (2) Estimation of urea or non-protein nitrogen in the blood; the uric acid, creatinine, inorganic phosphorus, and diastase contents of the blood have also been determined in many instances. (3) Diastase value of the urine. (4) The various dye tests. (5) Water and salt excretion tests. (6) The variations in reaction of the urine.

Like others, I have not infrequently been surprised by the degree of destruction of kidney tissue found *post mortem* in some cases in which the tests failed to indicate inefficiency, or by the disparity between the amount of damage and the calculated impairment of function. Actually, certain workers have shown by experiment that as much as three-quarters of the total kidney substance may be removed before any abnormal accumulation of urea occurs in the blood. Apparently positive results are only obtained when the reserve power of the kidneys is reduced to a certain low level or when failure of compensation sets in. More sensitive methods are required, and it is in hope of stimulating, however slightly, further research that I venture to record the following notes.

The Urea Concentration Test (Maclean¹).

In carrying out this test in "normal" individuals one is impressed by the wide range of results. Thus, in one series the maximum concentration varied from 1.8 to 5 per cent.—usually found in the second, sometimes in the third, and occasionally in the fourth hour-period. Inquiry proved that, as a rule, the low figures were obtained in persons whose twenty-four hour urine was considerably greater than the average in volume (and incidentally less in concentration) and the high figures in those whose volume of urine was less than the average, the same amount of fluid having been taken in each instance. The above findings, therefore, are not altogether extraordinary, and seem merely to reiterate the fact that marked variations occur in the response of normal people to other diuretics, such as water, tea, and prolonged exposure to cold.

When the "resting level" of urea in the urine (that is, the percentage prior to the test) is taken into account we gain a better idea of the value of Maclean's figure. For example, a result of 3 per cent. which is derived from a resting level of 0.9 per cent. indicates a greater degree of renal (perhaps better termed cardio-vascular-renal) efficiency than the same concentration derived from a level of 2.3 per cent.; or again, 1.8/1.0 per cent. means better function than 1.8/1.5 per cent.

Quite a number of seemingly normal cases have been encountered in which the test results did not exceed 1.6 or 1.7 per cent.; in all of these, however, the volumes of four-hourly specimens somewhat exceeded (by 10 to 30 c.cm.) the prescribed limit, the urea having had prolonged diuretic effects. But when the test was applied over the hours most conducive to concentration—the period of sleep—percentages of 2.2 to 2.8 were obtained; the "resting levels" (7 to 9 a.m.) stood at 0.9 per cent. approximately. It is now clear that the lower the latter value the more does the maximum concentration indicate efficiency, and also that in employing tests of this nature the fullest attention must be paid to the ability of the kidneys to excrete water.

The Water Secretion Test.

This test takes note of the proportion of water passed over the day and night hours, and also of the variation in the rate of secretion during the former. In the normal