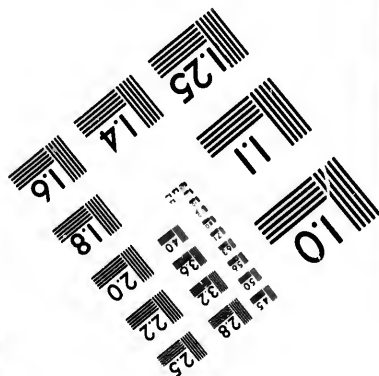
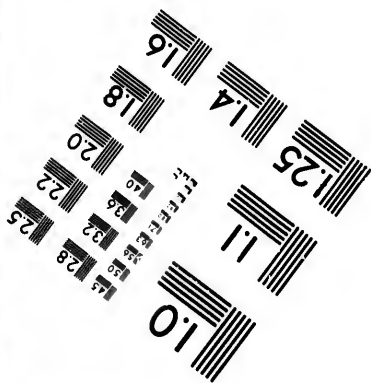
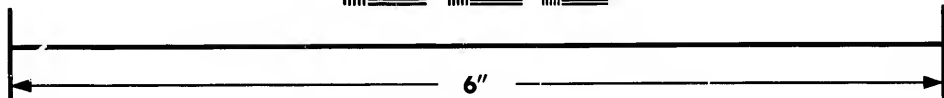
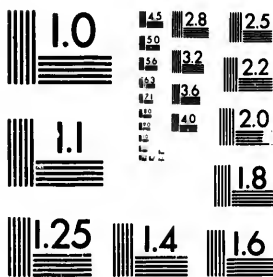


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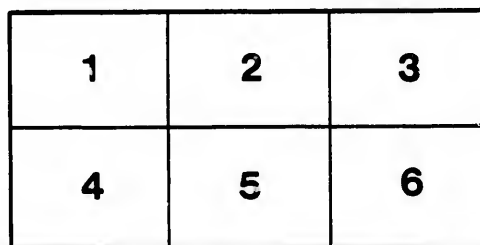
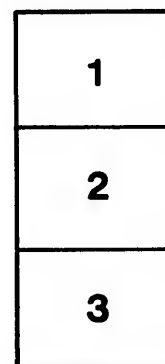
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DISCUSSION ON CARCINOMA.

NOTES ON THE PARASITIC THEORY OF CANCER

By C. F. MARTIN, B.A., M.D.

Demonstrator of Pathology Gill University : Assistant Physician, Royal Victoria
Hospital.

So much has been written within recent years on the parasitic nature of cancerous tumours, and the results of investigations have in some respects been so plausible that I thought I could best contribute to the evening's discussion by briefly considering the possibilities of this theory and observe on what grounds we may be induced to place malignant tumours in the category of parasitic affections. While not presuming to champion the advocates of this theory, inasmuch as my experience is so limited, I will nevertheless endeavour to lay stress on its most favourable features, many of which render the parasitic nature of cancer something even more than a probability. We cannot at all events repudiate the theory without a careful consideration, for among its adherents are numbered two scientists whose names stand foremost in bacteriology and pathology. Metchnikoff after examining the specimens prepared by English and European investigators emphatically pronounced in favour of the presence of parasites in cancerous tumours, while Virchow is so strongly imbued with the same idea that he is withholding his final volume on tumours, trusting that the near future may bring increased light on the etiology of malignant growths. It must, however, be confessed that while perhaps many observers are willing to acknowledge the presence of parasites in cancer masses, they are less readily satisfied that their presence is directly associated with the cause of the malady.

Though it be true that the parasitic theory of cancer formations is at present incapable of scientific proof, yet it should not be forgotten that in many, indeed in the majority of our infectious diseases, we are unable to carry out the postulates laid down by Koch to prove their parasitic nature. The epidemic nature of some of course renders this character probable, but in others even this feature is wanting. The amoeba of dysentery is generally accepted as being the causative factor of the tropical malady, yet the absolute proof is entirely wanting. Few scientists to-day will deny the relation between typhoid fever and Eberth's bacillus, or of the plasmodium malarie to the disease with which it is associated, yet in neither instance are we positively enabled to fulfil the requirements necessary to establish

satisfactorily the etiological relationship. As in these diseases, so too in carcinoma, where our knowledge is likewise very limited so far as the true cause is concerned, we are scarcely justified in discarding the theory of a parasitic origin till definite proofs to the contrary are established.

The customary classification of tumours, in so far as it does not consider their etiology, has been formed entirely on a basis of convenience in their nomenclature. The histological structures alone are taken as a means of differentiation between all the different types of neoplasms quite regardless of the cause inducing their growth. The distinction likewise between benign and malignant tumours is as much a clinical as a pathological differentiation and conveys no idea of their respective etiology, and one of the reasons is apparent. At the time when Virchow's classical work on cellular pathology appeared, parasites played absolutely no role in the study of pathological processes, and as the nature of tumours was then even more in doubt than now his desire was to formulate merely some convenient plan of nomenclature.

It is here that the first difficulty arises, for the merest superficial study of benign and malignant tumours suggests at once a difference so great as to render it more than likely that their respective causes are equally distinct. There are few pathologists to-day who ascribe the formation of malignant tumours to an overgrowth of embryonic cell remains, as suggested by Cohnheim for the origin of benign tumours, and the reason is obvious. When a tissue in its overgrowth ceases to remain local, ceases to retain its simple structure and regularity of outline, but tends to be distributed throughout distant portions of the body, there is at once suggested some special kind of stimulus, some unusual cause for such an irregular mode of procedure and extension of cells. The cause can hardly be identical with that for other more benign tumours, else one would surely get at some time or other an extension by metastases of lipomata, fibromata, etc. This, however, never does occur with the same invasive propensities, and there is at no time a paramount tendency to extension even locally. Some would explain this by the greater regenerative and proliferative power of epithelial cells over any other kind of tissue. While, however, such is the case, it is but a poor explanation of the atypical character of the growths in malignant tumours. Rapidity of growth alone can certainly not explain it, for whenever the epithelial growths extend rapidly it is because they find paths of small resistance, *i. e.*, the looser tissues and the surfaces, forming thus cauliflower excrescences, and so forth. It is rather where their growth is slow

that they invade denser tissues and infiltrate. Fibromata and other benign tumours may remain untreated for years and their tendency to invasion of other tissues is never manifest. They remain nearly always localized, encapsulated, and cause injury only by mechanical pressure.

The question is reasonably asked as to why in the one case we get metastases and not in the other, if a mere overgrowth of cells from irritation or other non-parasitic causes will account for the origin of both forms of tumours. The explanation cannot be offered that the nature of the individual cells of benign growths unfits them for transmission by vessels, for when the varied nature and sizes of cancer and sarcoma cells be considered it is not to be supposed that cells of other tumours find greater difficulty in passing through the vessels. Again, the mere fact that emboli of fat globules can be distributed over the body after fractures, etc., and be found in the smallest capillaries of the lungs would show that in one kind of tumour at least there is no mechanical obstruction to the passage of its elements by vessels.

There is further in malignant tumours not only a great activity, but this activity is directed in a special way. It is a true invasion of tissues—and invasion of vessel walls of all forms of tissues and by all possible channels. Wherever a distant part is infected with cells from the original growth the process begins anew.

So far as I am aware there is no other pathological process apart from parasitic affections possessing this same tendency of invasion and extension.

A further point of interest as illustrating the insufficiency of Cohnheim's theory as applied to malignant growths is obtained from a comparative study of tumours. Metchnikoff has pointed out that in the invertebrates cancer does not exist, while on the other hand it is very probable that cell remnants of epiblastic origin frequently occur in this order of life, so that reasoning by analogy we are scarcely justified in attributing to such remnants the cause of cell proliferation in malignant growths so far as vertebrates are concerned.

To examine into the nature of malignant neoplasms it is in the first degree necessary that we should see if in other parasitic diseases we have any evidence of new growths—if, in other words, parasites can induce cell proliferations in any way analogous to cancers. Of this I think we have abundant proof, and it will be of interest to institute a few comparisons between cancerous disease and those maladies where multiple new growths occur from the invasion of the parasite. Prof. Coats and others have asserted that an essential difference exists between the lesions found in parasitic diseases and those occurring in cancer,

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that in the former the results are always irritative, inflammatory and destructive, in the latter purely proliferative. To these views, however, can be opposed the authority of equally capable pathologists, who insist on the neoplastic nature of such maladies even as tuberculosis. The bacilli once having found a resting place manifest their presence at once by a new growth of cells, the tubercle, and only subsequently do we get degenerative changes. It is practically the same in many other diseases, such as leprosy, where the earliest evidence of the presence of bacilli in the vessels is manifested not by an inflammation, but by a hyperplasia of the neighbouring tissues. As a result of the hyperplasia true tumours form chiefly in connection with nerve endings, while degenerative processes may be quite absent. But a yet more striking analogy between cancer and infective processes is seen in actinomycosis. It is true that here an irritation is set up by the advent of the fungus, but on the other hand so great is the proliferation of cells and bone formation in the jaw that before its parasitic nature was understood, its structure was looked on as being that of an osteo-sarcoma. From the primary seat metastases can spread to any part of the body, the first evidence of their presence in the newly-infected region being a multiplication of cells in the vicinity. But whereas it may be argued that in these instances the inflammatory conditions are primary, there are tumours formed by parasites where no sign of irritation exists. Such is the case in typhoid fever. The lymphomata sometimes found on the serous coats of the intestines, in the liver and elsewhere, are essentially neoplasms induced by the action of the typhoid germ.

In passing I would refer also to Hodgkin's disease, now classed by most pathologists among the infective maladies, for there, too, non-inflammatory neoplasms likewise occur.

But there are examples approaching still nearer to our subject, inasmuch as it is evident that in some instances an animal parasite (*i. e.*, one more nearly allied to the supposed parasite of cancer) can induce a hyperplasia of cells, a true tumour not running the ordinary course of inflammation. In chronic malaria the almost constant result of the parasitic infection is to produce in the spleen an enormous overgrowth in its essential cells and the fibrous stroma surrounding them.

It would seem, then, from what has been said, that parasites are quite capable of inducing overgrowths of tissue purely hyperplastic in character.

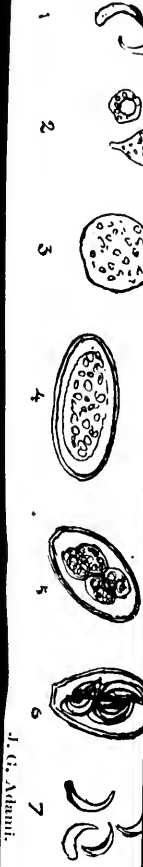
And further, it is known, that in some at least of the infectious diseases the parasites select chiefly certain cells for their habitat during a part at least of their life history. In malaria the blood cells

are selected, in leprosy the large multinuclear leprosy cells, in tuberculosis the bacilli are nearly always found in giant cells, in the last instances an active growth being apparent from the multiple nuclei. It may, then, be asked with reason, if cancer be parasitic why the epithelium cannot equally well be selected as a cellular habitat by parasites just as the blood cells, etc., in other diseases. Advocates of the parasitic theory of cancer find their organism constantly within the epithelial cells and it is here that the proliferation occurs.

Hitherto the instances given of hyperplasia have concerned cells other than those of epithelial structure, but we do not by any means lack an example where true epithelial overgrowths are induced by parasitic invasions; this is found in a disease of rabbits known as coccidiosis. Since the researches of Malassez, Delepine and others it has been recognized that certain parasites (whose form and general character bear a striking resemblance to the supposed organism of cancer) often infest the alimentary tract of rabbits and make their way thence to the liver, where they invade the epithelial cells in the bile ducts. As a direct result, an extensive proliferation of the epithelial cells takes place and also of the fibrous stroma about them, so much so that a luxuriant overgrowth occurs resembling very much a malignant adenoma of the rectum. (v. fig. F and Nos. 1 to 7.)

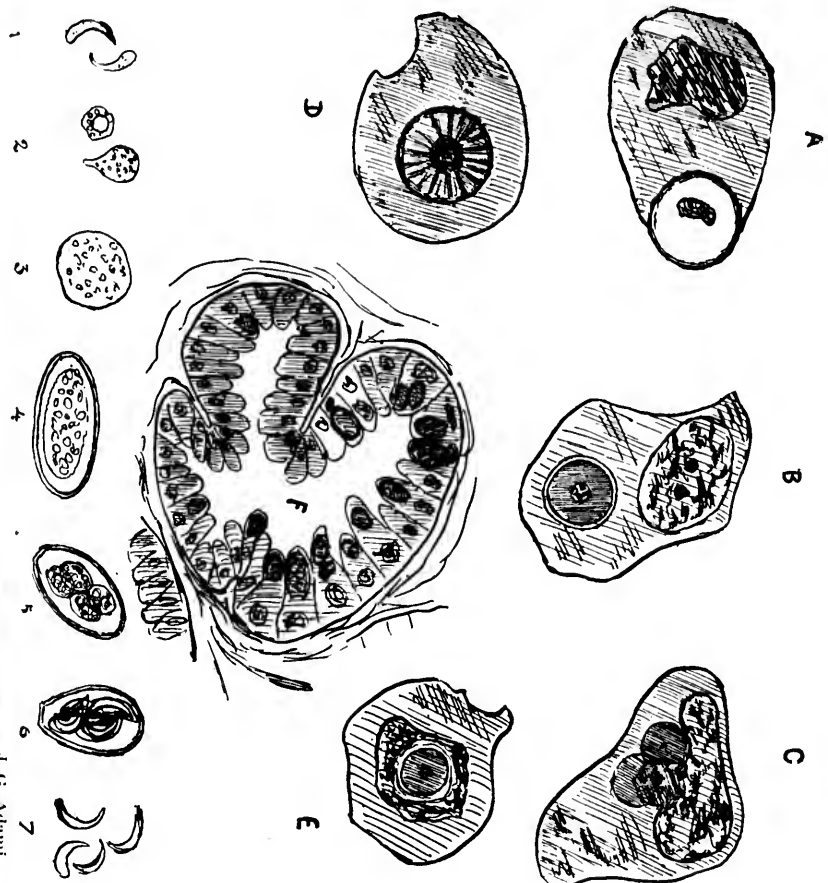
From what has been said, then, it seems clear that, firstly, parasites are quite capable of producing cell proliferation independent of inflammatory conditions, *i. e.*, a proliferation analogous in general features to cancer; that, secondly, they produce metastases, as does cancer; that, in the third place, it is not uncommon to find parasites selecting special cell structures for their habitat; and that, finally, we can find in the lower animals an epithelial overgrowth and the formation of a fibrous stroma, all being induced by the invasion of a parasite.

Before considering further the general reasons upon which the parasitic theory of cancer may be based, I will briefly describe the main characters of the organism supposed to be concerned in the formation of cancer tumours, though the diagram kindly prepared by Dr. Adami will perhaps better give an idea of their nature. In attempting such a description one is beset with difficulties, owing to the various opinions among investigators as to what is and what is not to be regarded as the true parasite. This confusion arises from the supposed resemblance which certain other structures have to these parasites; among these may be mentioned forms of cell degeneration, morbid karyokinesis of cancer cell nuclei, invaginated cancer cells, enclosed leucocytes, and endogenous cell formations.



J. G. Adami.

Figures A to
Figure F. Pro
Figures 1 to 7



Figures A to E. Supposed parasites within cancer cells (after Ruffer).

Figure F. Proliferated epithelium of bile duct, containing coccidia (after Delepine and others).

Figures 1 to 7. Coccidia in various stages.

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The main opinions, however seem to be that the parasite is usually spherical or oval, with a more or less rounded nucleus, this latter occupying a relatively small area of the parasites' protoplasm. The cell body is homogeneous or mottled, sometimes radially striated. These striæ were supposed by some to be evidences of reproduction, such as is observed in malarial parasites. A capsule of double contour surrounds the organism and seems to be intimately associated with the protoplasm of the cancer cell, as though secreted by the latter. Sometimes the organism seems to lie in a kind of cyst or vacuole, in this way resembling the bacilli of leprosy, where the same condition often occurs. The parasite may be single or multiple within the cell, and invades sometimes the nucleus, sometimes the protoplasm. It is largely from the staining reactions that these are differentiated from the various other structures above mentioned. Where, however, so much strife is at present going on among the various English investigators I will not attempt further details in this matter, inasmuch as there seems but little possibility of rendering it more lucid from our present knowledge.

A point of interest, however, in regard to these bodies lies in the fact that they are invariably found in greater numbers at the growing edge of the tumour, and inasmuch as the cells in these areas are the youngest they are also least likely to be degenerated. Where, too, the greatest degeneration is seen in the tumours one finds a distinct paucity of parasites. An examination of the individual cells invaded by the parasite shows, further, that while little or no mitosis is seen in them, there is active proliferation in adjacent cells, the parasite thus acting as a stimulator of cell growth.

These facts in themselves though suggestive of the possibility that these organisms produce the cell proliferation, are of course far from proving it. In attempting to establish the proof serious difficulties arise, inasmuch as hitherto no one has succeeded in isolating the parasite and obtaining it in cultures. But the same is practically true of other diseases—hydrophobia, scarlatina and many others. Furthermore, however, we cannot be satisfied that transmission by inoculation from man to man is possible. A few isolated cases have been recorded where some of the lower animals have successfully been inoculated and the transmitted portions have given rise to new growths with metastases. This, it may be argued, is a mere grafting from one animal to another, but inasmuch as the same organisms will be found in the metastases of the inoculated animals, it remains yet to be proven that there is not something else besides the simple transplantation of cells. It is quite as possible that the experimenters,

without being aware of it, overcame in some way the obstacles that ordinarily prevent successful inoculations. Within the last few months a melanotic sarcoma was readily transmitted to a rabbit and in a few weeks had given rise to metastases throughout the body.

At all events we are too little familiar as yet with all the conditions necessary to produce successful inoculations. How many people have already ingested myriads of cholera vibrios by way of experiment and have subsequently felt no ill effects? Our methods at the present day are in many respects imperfect, and failures do not necessarily render the general underlying principles fallible.

On much that has been written on the contagiousness of cancer and its frequent occurrence in people who live much together I cannot touch, nor of the plausibility of the so-called "cancer-houses," which are marked as being contaminated. I would merely conclude by suggesting that until some other reasonable explanation is afforded we are not in a position to despise the parasitic theory of cancer formations.

It has been so often urged, and with apparently great emphasis, that in the majority of cancerous growths there is associated some chronic irritation, it may be a slight and persistent one, that I cannot close without referring for one moment to this theory. Whereas it is true that in a great number of cases some irritant is associated with the development of carcinomata, yet in the vast majority of instances the self-same irritant may be at work in just the same mild chronic and intermittent way and yet never induce a cancer. Of the number of men who use clay pipes there is surely but a small minority in whom cancer develops on the lip, while in the cases of cholelithiasis how rarely do we find cancerous conditions of the gall-bladder. It is true that with almost every case of cancer of that organ gall-stones are associated, but the mere presence of the cancer, implying as it does some destruction of the epithelium, etc., will supply a most ready nucleus around which concretions can form. Considering, then, how common are gall-stones and how rare is malignant disease of the gall-bladder, the latter would seem to be the primary condition and the cholelithiasis a secondary result. The same holds true to a more marked extent perhaps in calculi of the urinary bladder, which, in themselves so frequent, yet only under the rarest conditions are associated with epithelioma of that organ.

If it be true that chronic mild irritation can stimulate epithelial cells to overgrowths of a malignant type, we have yet to explain why this condition does not more often result from such a pressure. The persistent irritation which produces a *clavus* never, or scarcely ever,

results in an epithelioma; there occurs merely a superficial growth of epithelium, layer upon layer, never tending to become malignant, never forming metastases.

Where chronic inflammation exists there ensues frequently an extensive downward growth of the epithelial structures, but always more or less regular in its distribution. There are, however, occasions where scar tissue can develop into an atypical growth of epithelium, and this, it must be admitted, is difficult to explain. Here again, however, chronic irritation alone will fail to give an explanation, else the condition should be far more frequent than actually occurs.

It would seem that irritation alone, then, cannot explain the formation of cancerous tumours, that to the mere activity of epithelial cells alone cannot be accredited the formation of cancers, and it would seem that our only resource is to examine for some deeper cause, to search for the original stimulus which brings to the cells the power to proliferate. It has been shown how characteristic are new growths as the result of parasitic invasion and how scarce are evidences of similar growths in diseases that are proven to be non-parasitic. So that placing together all our facts we feel that, for the present at least, there still remains a hope that in the near future something more may be discovered to account for the similarity of malignant processes to those in the infective diseases.

