A MODIFICATION OF DR. CHARLES CREIGHTON'S VIEW OF MALIGNANT GROWTHS.

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"... Fresh work must be undertaken and fresh minds enlisted in the pursuit. There is no reason why victory should not be achieved, given money, imagination and patience. The first of these essential munitions of war cannot be supplied by the soldiers themselves; and the second is a rare and often elusive gift. It is by far the most difficult to secure, yet without it no success will be won." (From the "Times," June 1st, 1922.)

"We are wondering and are the subjects of curiosity and inquisitiveness... occasionally curiosity leads to creative thought, alters and broadens our views and the views of others. Some of the greatest advances of modern science have had their origin in simple observations called into life by reflection and curiosity." (Sir Robert Firth, "Fragments," XXXIII, April, 1923, p. 274.)

Reasoned imagination based upon considered observation: that is what I think is needed to-day in the study of many diseases of whose mode of causation we are still ignorant, in which we have to deal with a new factor, as yet invisible and undemonstrable, manifest only by its effects.

The necessity for a comprehensive knowledge of the biology of tissue-cells, if the cancer problem is to be successfully attacked, is now generally recognized. By cell-biology I mean habits, mode of life and especially of nutrition. It is essential to remember that the tissue-cells are individual units—specialized homologues of unicellular animals. There is, therefore, no a priori reason to think that tissue-cells are incapable of exercising the
elemental functions of animal cells, and in particular that of the ingestion and digestion of "solid," organized material, this holozoic character being one of the principal ones which distinguish typical animals from typical plants. I have been led to consider tissue-cells from this aspect, with the result that I regard this factor as of very great importance for physiology and pathology, and one which stands in immediate relation with the question of the causation of several diseases of hitherto unknown etiology, including malignancy.

I will first outline, in a more ordered sequence than it has gradually developed, my general conception.

THE THEORY OF HEMETABOLY.

Many types of tissue-cell are accustomed normally to digest, or metabolize blood-elements, especially the red corpuscles, or erythroplastids. This function of blood-digestion is called hemetaboloy. It may be preceded by actual ingestion (hematophagy) of the corpuscles or cells (e.g., leucocytes), or it may take place extracellularly.

Unlike what obtains in single-celled animals (Protozoa), the products of hæmetaboloy in the case of the individual cell-units of tissues are not, in general, assimilated mainly for the purpose of the growth and multiplication of the cells, but are utilized—as a rule and very largely so—in the production of various substances coming in the category of "secretions" or "excretions," for the welfare of the body as a whole, of which the tissue-cells are dependent and co-ordinated members. Indeed, various occurrences or changes are met with in the cell-history of various types, which constitute such unusual and remarkable phenomena, regarding them, from the standpoint of the behaviour of a free, single-cell individual that they appear to be of the nature of specially developed adaptations, tending to limit the multiplication of such cells and prevent them from an excess of proliferation, in relation to those of other tissues, which would otherwise result from the complete assimilation, for their own use, of this organized nutriment.

In this blood-digestion, another factor, an enzyme or ferment, of specific character for specific types of hæmetaboloy, must inevitably be concerned.

In various diseases, affecting especially certain tissues, the normal hæmetabolic function of the particular type of tissue-cell becomes altered and unsuccessful, and various bodies or granules, of very different form, are produced instead, as a result of this abnormal hæmetaboloy. These characteristic inclusions are met with so constantly that they are regarded respectively as diagnostic features of the different diseases. As these diseases are all "virus-diseases," in which, so far, no indubitable micro-organism has been established as the cause, it is reasonable to consider (in view of the Twort-d'Herelle phenomenon) that the active, infective
principle of such viruses is a pathogenic enzyme, which acts by inducing the particular type of pathological hæmatoxyly associated with the disease. Among such diseases are the various exanthemata, hydrophobia, typhus fever, and other infectious blood-fevers, etc.; probably, also, from the recent work of da Fano and of Levaditi, Harvier and Nicolau, *encephalitis lethargica*. In such diseases, the ultimate breakdown of the cells particularly affected, especially those containing included and altered corpuscles (or .cells) is probably inevitable, when more bodies or granules, resulting from the karyolysis, will be produced.

In the case of malignant tumours, on the other hand, something quite different occurs. In its inception, malignancy is, rather, a biological reaction than a pathological process. The cancer-cells may be regarded as recuperated cells, which have acquired a fresh (if spurious) lease of vital activity. The disease results from the effects, both upon the body politic and on themselves, of their excessive and unrestrained multiplication and spread. And the essential factor in the causation of this malignant condition is the independent re-acquirement, by certain individual cells, of the capacity to assimilate the products of hæmatoxyly entirely for their own use, instead of performing their normal bodily function in this respect; in other words, they have reverted to the condition of free, single cells. The many variable factors, intrinsic or extrinsic (e.g., long continued or excessive functional activity, or chronic irritation or intoxication, respectively), any one of which may serve as an exciting or inducing agent, can only be held to be accessory, in the sense that they are predisposing. Because (a) other cells, of the same type and in the same situation, do not become malignant in character; and (b) any of these factors may be in operation without malignancy necessarily resulting at all, as a natural consequence. Therefore it follows that the fundamental cause — the only "constant"—is a profound change in the life of the cell itself, it may be of even a single cell or cell-line, or at most, of the cells in a minute area. This *causa causans* lies hidden in the secret of the meaning of vitality; and it may be a very long time before this can be revealed, let alone controlled. But its chief expression is manifest in the production of some enzyme which can thus completely digest, for assimilation by the cell, organized material; and this working cause is the practical feature which has to be combated.

Such is my thesis: and I ask any biologist to say whether there is anything contradicted by known facts, inherently unreasonable or even improbable about it. While I should be the first to admit that there is a long road to travel before this view can be conclusively established in its entirety, nevertheless, I have already a substantial body of evidence in various directions, in support of certain parts of it (*vide* Woodcock, [10—13]). The farther I go, the more I obtain; and the more I obtain, the more cumulative is the effect. I do not say, of course, that every point and particular will be proved exactly right! But I firmly believe the
time will come when it will be recognized that this generalization rests upon a broad basis of truth; and if further progress in the direction of finding out the nature of the diseases to which I have alluded is desired, this question of hæmataboly will have to be seriously considered, with all that it implies, and, moreover, tested along experimental lines by those who are able to do so, e.g., biochemists, in order that the foundation it provides may be built upon.

This theory of hæmataboly, in the definite shape it has now assumed, is the outcome of nearly three years' observation and thought, and in gratitude I desire to dedicate my thesis to my mother.

NORMAL HÆMatabOLY.

Here, I can only deal with the subject of normal hæmataboly in its bearing upon malignant growths.

In the first place, I regard the presence of iron as the central fact of the matter; I think the iron is a great source of danger to the cell, from the point of view of its co-ordination with its fellow members in harmonious working. Growth and multiplication cannot take place without increase (inter alia) of the nuclear material, including the chromatin. Increase of the chromatin cannot take place without an additional supply of iron. This is a truism, but one which cannot be too greatly emphasized. On the other hand, given a supply of iron in an assimilable form, the cell will use it to form additional chromatin, this in turn leading eventually to cell division, unless the metabolic activity of the cell is modified and regulated in a particular manner. The vascular tissue, including the blood, is that which above all others makes use of the iron taken in by the body; and this is the tissue, the "free" tissue, in which, above all others, active multiplication is continually taking place.

It follows, therefore, that if a cell ingests and digests iron-containing material, such as hæmoglobin or chromatin (of cell-nuclei), we have every reason to expect the end-result to be seen in an increased rate of cell-division, unless something else happens. Now, let us take first the case of the ordinary macrophages, large mononuclear cells of endothelial type. What do we find here? These cells are admittedly "phagocytes" i.e., they ingest and digest blood elements of all kinds. Digest: that is the important point. It is remarkable that no one seems ever to have paid any attention to the effect of this digestion of organized material on the hæmatophage itself. Everyone seems to have been entirely satisfied with the thought that the "phagocyted" material was destroyed and finished with! A protozoologist, accustomed to consider the holozoic mode of nutrition of animal cells, inevitably thinks of the benefit of this food to the cell. A large mononuclear cell (or so-called "transitional") which begins this hematophagic mode of behaviour and digests this food, grows in size, and its nuclear material increases greatly in quantity,
mainly, of course, because of the iron which it is able to assimilate. Eventually, it becomes a megakaryocyte, that is to say, a giant cell. The nucleus of such a cell is relatively enormous and often extremely complex in appearance, or it may be subdivided into several nuclei.

It is interesting to remember that only in certain haemopoietic organs or glands do we find these cells, where the large mononuclears are engaged in "phagocytosis." In the normal condition, we never see haematophagy in the general circulation. It looks as if there were either some influence inhibiting this behaviour on the part of the macrophages in the bloodstream, or else some influence exciting it, in the organs where it occurs. As the large mononuclears grow into giant-cells, they gradually become too large for the capillaries and are confined to the situation in which they develop.

Now, by all analogy with the Protozoa—and these cells are essentially Amoeba—we ought to find active multiplication and a great increase in number; indeed, we might expect what would really amount to a malignant condition of this particular type of blood-tissue. Instead of this, we find these cells are specialized in a particular direction. (I do not mean to say that there is no multiplication at all; there is, but it is relatively very slight in amount and among the young forms, except, of course, when there has been disturbance of the haemopoietic system.) The cells are repeatedly liberating portions of their cytoplasm only, in the form of platelet-cytoplasm, giving rise to platelets. The cells themselves, when they have attained a huge size, ultimately disintegrate completely. This view of the origin of platelets is universally accepted in America, following the work of many observers, e.g., Wright, Downey, Jordan and others: and from my own observations, I have no doubt about its truth. I consider that the great majority of the platelets are formed in this manner, though not necessarily all. The platelets are only fragile cell-remains, not living cells, and probably, at times, may be produced by the "free" lysis of the nuclei of the immature reds, or of the corpuscles themselves. But I am afraid that I cannot consider that they represent an independent, specialized cell-line: I think, and so does Jordan (loc. cit.), that they are only functionally analogous with, and not true homologues of, the thrombocytes. The characteristic platelet-granules represent the inassimilable remains of the digestion of the blood-elements—be they red corpuscles, free nuclei, or leucocytes—by these macrophages. In any protozoan, feeding in a holozoic manner, there are generally fecal remains, which are at length ejected; it is probably not often that a cell is able to assimilate in toto and completely incorporate its protoplasm, the products of digestion of organized material; though, at times, certain tissue-cells appear to be able to do so—at least no "solid" inassimilable residue appears to be produced.

There is another very interesting case of haematophagy on the part of mesoblastic cells, to which I may refer, though I have not yet myself been able to study it. This is the known occurrence of "phagocytosis" by the
endothelial Kupffer-cells, in the liver. These cells do not (at any rate, normally) become giant-cells. Why is this? These cells, unlike the macrophages of the type above considered, are known to produce pigment, as a result of this blood-digestion. And I think this pigment will contain the iron of the haemoglobin, which has thus been, as it were, excreted and not used to build up chromatin.  

I think this fact of the occurrence of haematophagy and haemataboly on the part of macrophages has a very great a priori significance in relation to my general view. Here we have mesoblastic tissue-cells, now entirely separated from the hypoblast—the essentially nutritive layer—still retaining this ancestral 'mode' of behaviour. Why, therefore, should not various types of tissue-cell arising from other embryonic layers also have retained it?  

Taking first the hypoblast (endoderm), both Reichenow and I have shown that, in the case of certain blood-sucking arthropods, the digestion of their food (which happens to be blood in their case) is intracellular; i.e., the blood-corpuscles (or cells) are first ingested and then digested by the cells of the alimentary tract. The important point, in the present connexion, is not that it is their food which is so digested, but rather that the cells are still capable of this mode of behaviour. And we have thus added to the instances already made known by Metchnikoff in the lower Metazoa.  

Again, in cells of hypoblastic origin now entirely separate from the alimentary canal, we have the important case of the hepatic epithelium. It is indubitable that red corpuscles normally occur inside the liver-cells (Browicz, and Herring and Sutherland-Simpson, and I may add that I have myself observed them in any number). These corpuscles are undergoing digestion in some specific manner, which I have not yet myself studied. But the important point is, what are the cells doing with the iron? Temporarily, at any rate, the cell appears to retain and incorporate the iron. Now there is one observation which, I think, has very great significance in this connexion. As is well known, many, often most, of the hepatic cells have two nuclei. Reinke [8] has found that these two arise from the direct (amitotic) division of one, as this increases in size (cf. the megakaryocytes). Very frequently Reinke found that one of these nuclei disintegrates and all traces of it ultimately disappear, i.e., the quantity of chromatin is again halved! And, on the contrary, he did not find cell-division following this nuclear division.  

Another endodermic instance is that of the epithelium of the thyroid gland. Here too, the cells exercise a haemataboly function, but in this case it is very largely extracellular, the enzyme being secreted into the lumen of the acinus, where it metabolizes the blood-elements, mainly the  

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1 Indeed Kupffer himself, in his original paper, stated that he had found this pigment to be iron-containing, in the stellate cells of horses.
corpuscles, into colloid. The cells themselves derive no immediate and special benefit from their exercise of this function. I may add that my account of the formation of the colloid has recently been in a measure corroborated by Parhon and Dérévici [7], working along semi-experimental lines.

Doubtless, there are many other cases among glandular epithelia of hypoblastic origin, where the "secretion" is formed, at any rate in part, as a result of hæmatoboly.

We now come to the important epiblastic (ectodermic) epithelium. There are already two cases in which it can be said with some confidence that hæmatoboly occurs. The first is that of the formation of pigment. In an interesting and suggestive article on the possibility of a pigmentary origin of cancer, Sir George Beatson recently wrote [2]: "Of the endogenous pigments not derived from hæmoglobin, the most important are the melanins." I am afraid this statement is almost certainly incorrect. I have indicated my own reasons for considering that melanin pigment is a product of normal hæmatophagy and hæmatoboly, on the part of epithelial cells (e.g., of the skin) basing them on the definite observation of red corpuscles inside the cells and on a review of the known work of various authors. And, in a paper published about the same time, J. R. Fulton, in a most useful analysis of animal chlorophyll in relation to hæmoglobin and other animal pigments [5], also concluded that there is both biological and chemical evidence in favour of this view.1

As, however, I had not then seen an interesting paper by Acton [1], on melanotic growths, some further reference to this instance is necessary. Acton concludes that the only cells concerned with the production of melanin-pigment are mesoblastic in origin; and, also, that melanin is an iron-free pigment formed by the action of the enzyme, tyrosinase. As regards the first of these much-debated points, both the weight of the evidence furnished by other workers and my own observations lead me to

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1 Fulton [5] mentions that Halliburton, in his treatise, points out that the use of hydrochloric acid in making the test tends to remove the iron. And I have myself just had an illustration of this, in dealing with the pigmentiferous excreta of the normal louse. All this pigmentiferous residue contains the iron of the great bulk (not quite all) of the hæmoglobin taken in; this is a most interesting point, showing that this huge quantity of iron is not used by the cells (cf. also the pigment-formation in the intracellular blood-digestion in the case of mites). But unless the ferrocyanide-HCl mixture is extremely weak in the latter constituent, the pigment-grains are dissolved and all the iron dissipated when the test fails. [I may just take this opportunity of adding that I have found "Rickettsia" bodies of regular occurrence, in small numbers and usually in clumps, in the excreta of normal lice. And for the most part, these are produced by a further alteration of this unused residue of the hæmoglobin, in that, most probably by the action of the auto-cytolytic ferment of desquamated cells, the pigment-grains are "broken down" further. They lose their iron constituent and then the ultimate proteid fraction left takes up the Giemsa-stain and appears as "Rickettsia" bodies, in one form or another. I hope to publish a full account of this shortly.]
think that Acton's view is undoubtedly mistaken. This author does not appear to have considered the excellent accounts given by Dyson [4a] and Jordan (6a), the conclusion of both of whom is that the manufacture of melanin-pigment is a normal function of epidermal cell-metabolism. And, as Jordan says, there is no reason to doubt that both epidermal and dermal cells can produce their own pigment-granules; both types of cells owe their pigmented condition to the same underlying cause, which is in some way related to the blood as a source of nutrition or supply.

I have recently examined sections of black patches of skin from the mammary area of a guinea-pig, and the appearances found are precisely like those shown by Jordan and by certain of the earlier workers, to whom I referred previously. Nearly all the pigment is actually in, and being formed by, the epidermal cells; in this particular case, scarcely any pigment formation is occurring in the cutis. Hæmoglobin "vacuoles," resulting from the ingestion of corpuscles, are plentiful; here and there a leucocyte also is seen inside a cell. And around these "vacuoles" are, very frequently, numerous pigment-grains, the condition being very similar indeed to that which Miss Lodge and I described in the case of the blood-eating Ciliate, Hematophagus [14].

As regards the question of the iron, I agree with Acton that the melanin of the epidermis does not contain iron; and this is in accordance with the findings of several workers. It must be pointed out, however, that this does not mean that such pigments never contain iron. Different melanins vary considerably in their constitution, and of this as shown by various chemical analyses, I think there can be little doubt. It is especially likely that pigment formed by certain types of connective-tissue cell possesses iron, and this point is of importance in connexion with melanotic sarcoma. What becomes, then, of the iron of the ingested hæmoglobin; in the case of epidermal cells? I find that, although the pigment remains unchanged in colour, the cytoplasm of the cells becomes distinctly blue; the colour is deep in the basal layers, gradually becoming paler in the more superficial ones. And there is a sharp line of demarcation shown between epidermis and dermis, which latter, except for the nuclei of scattered cells, remains quite colourless. A very interesting point is that in the stratum granulosum, although the cytoplasm of these cells is only faintly blue, nevertheless the small masses and granules which it contains are strong blue and stand out sharply.

I think, therefore, that the explanation of this condition is as follows: The iron of the hæmoglobin is not "excreted" in the pigment, in this case, but is incorporated in the cytoplasm. It is, at any rate as regards the bulk of it, not assimilated by the nucleus, with the consequent result of active general proliferation, but remains in the cytoplasm,

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1 To avoid repetition, fuller discussion of these is reserved until their occurrence in cancer-cells is considered (vide below, p. 264).
gradually becoming accumulated in characteristic little bodies occurring in the cells of the granular layer. It would seem, that, even given the presence of available iron in the cytoplasm, some factor is still necessary before it can be utilized in the formation of chromatin. Now it is generally considered (cf. Fürth, Jordan) that iron-free melanin-pigment results from the action of a nuclear ferment (tyrosinase) upon a chromogenic compound (e.g., tyrosin, or like body). This compound itself probably results as an early stage in the alteration of the globin-portion of the hæmoglobin. It may be, therefore, that such a substance, which may be of the nature of an "auxetic" (i.e., inducing "growth" and reproduction, Ross), is also essential for the elaboration of chromatin for nuclear increase; hence, to the extent that such substance is modified by the action of the tyrosinase, the cell-nucleus may be unable to utilize the iron.

Another very interesting consideration bearing on this question, has occurred to me, namely, the fact that there is far greater production of pigment in races accustomed to tropical sunlight. Hæmoglobin is known to be a compound closely related chemically to chlorophyll; and further, it has a very active absorptive capacity for ultra-violet light. It is quite likely, therefore, that sunlight has an important share in the work of metabolizing red corpuscles ingested by the ordinary epidermal cells and that there is some photo-chemical action comparable with that taking place in green plants, the part played by the erythroplastids corresponding with that performed by the chloroplastids in the latter case. It may be that, as regards the general epidermis, the assistance of light energy is now in many cases necessary, either to produce or "activate" an enzyme requisite for this normal hæmetabolic function on the part of this particular type of tissue cell.

Secondly, there is the instance which I am at present engaged in studying, namely, hæmetaboly in connexion with the mammary gland and the formation of milk. Although it will be some time before this work is ready for publication, it throws such a flood of light on the whole question that I will briefly indicate the conclusions to which my observations have already led me. The great and rapid increase in growth of the epithelium during the later stages of pregnancy is accompanied by hæmato-

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1 Samuely (Hofmeister’s Beitr. 2, 1902, p. 356) says that it is necessary to reckon with the possibility, where circumstances point strongly to pigment-formation from hæmoglobin, that not the small percentage of hæmatin is the parent-substance of iron-free pigment, but the twenty-fold amount of globin present. That globin possesses the ability, to form melanin-like pigments follows readily from the presence therein of colour-forming groups, which easily produce pigment, e.g., tyrosin, skatol [and, it may be added, from the work of Hunter and Borsook, tryptophane]. Lastly, there is the possibility that the chromogen groups of albumin [i.e., in this connexion, globin] and of hæmatin, are ultimately identical, so that according to circumstances, at one time hæmatin-pigment, at another time melanin-pigment, can be formed. I think these remarks of Samuely, which I have translated as well as I can, are extremely important.
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phag.y. And from the appearance of the large, richly chromatinic nuclei, the absence of pigment or other signs of residual products, I consider that the cells are assimilating for themselves the hemoglobin, apparently completely, using the iron to form abundant chromatin, this in turn leading to cell-division.

In the lumen of many of the young acini, hæmoglobin is present in quantity, just as I found it to be in the lumina of the thyroid acini. As to how it gets there in the earlier stages, I wish, at present, to express my view with a slight reservation, just because in dealing with isolated nuclei it is sometimes difficult to be sure that such are indeed epithelial ones, which vary very greatly. In the case of the nuclei of the thyroid-epithelium, this difficulty did not arise, because of the definite and uniform appearance they presented. There, I have found, not only in an adenoma, but also (since my paper was published) in the normal gland, that the nuclei may pass inwards and come into direct relation with a minute capillary, and then give rise by multiplication to a wall of epithelium around the latter, thus forming a new, young acinus. Now, what the epithelium of one vascular gland does, there is no reason to think that of another is incapable of doing, and I have distinct evidence that a similar process may take place in the formation of fresh acini, in the extending mammary gland. It will be noted that I have had regard to nuclei, rather than to cells. The accompaniment of a certain amount of cell-cytoplasm is, of course, implied; but, especially in this latter case, there may be so little apparent cytoplasm that the cell-nucleus itself is evidently of paramount importance in this behaviour. On this view, therefore, the lumen of a small acinus is, or has been (for it may become cut off), in direct communication with the vascular system.

At any rate, at a later stage when the gland is functioning, the blood can be forced en masse into the lumen, most probably by diapedesis, just as in the case of large thyroid acini. And, if my experience as a microscopist counts for anything, I say without hesitation that the only conclusion which can be drawn from what is to be observed is that altered hemoglobin in the lumen, which in this case has the form of "colostrum" instead of "colloid," becomes in part further transformed into milk-fat.

But this is only half of the matter. When the gland is fully developed, the character of the hæmatoboly is changed. This is a most interesting and significant point. The production of the requisite blood-digestive enzyme, for the "growth" of the epithelium was most probably incited from "outside," by some "hormone" formed in connexion with the developmental activity, which ceases to be produced after the time of birth. Hence, no

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1 As an instructive item of experimental evidence of significance in this connexion, it may be mentioned that Loeb found that the epithelial cells of regenerating mammalian skin ingest red blood-corpuscles. Now, why should they do this?

2 O'Donoghue has found that the corpus luteum produces a hormone which incites growth of the mammary gland.
longer are the cells living on the blood, assimilating it solely for their own use. Haemoglobin is still being taken in, and the cytoplasm contains iron; but the proteid of the haemoglobin is being metabolized into fat-droplets, and the nuclei are not using the iron, at any rate in the manner and to the extent they were doing before. Instead, what do we find? Portions of the cytoplasm and even of the nuclear material are cast off, along with the fat-globules, into the lumen of the acinus, where they, too, “break down” and are metabolized into milk-constituents (cf. also the similar condition met with in the case of colloid-formation). Nature wastes nothing that can be utilized!

To summarize: all the above observations in regard to normal haemataboly indicate clearly, in my opinion, that the exercise of this function is accompanied by special adaptations of one kind or another, on the part of the tissue-cells, enabling them to metabolize this iron-containing material without cell-division necessarily ensuing as a consequence. The main point to be emphasized is that normal haemataboly is not, in general, for the benefit of the cells themselves, but for the welfare of the body as a whole; its utilization for their own “growth,” or multiplication, is most stringently controlled. And normal haemataboly is, I believe, the key to the understanding of the malignant condition.

MALIGNANT TUMOURS.

I hope we are now in a position to realize that the cardinal feature in Dr. Charles Creighton’s view of malignancy is eminently reasonable and understandable. “The tissue-cells become cancer-cells by feeding on the reduced” (i.e., digested) “substance of the blood.” That is the essence of the matter, from the practical point of view. I first saw Creighton’s book “Some Conclusions on Cancer” at a time when I was studying the megakaryocytes and feeling profoundly impressed with these giant cells and the potentialities latent in them; and I immediately realized that “blood-eating” might well be a vastly more important factor in malignancy than had hitherto been thought to be the case. Most unfortunately, Creighton took the view that cells of the vascular tissue itself thus produced the cancer. But this must not be allowed to militate against a recognition of the great step forward which he took in elucidating the essential nature of this disease. The more I study his book and note its wealth of facts and observations, both by himself and by others, all pointing unmistakably to the occurrence of blood-digestion, both normally and pathologically, the more I am amazed that no one has taken the trouble to winnow the good, sound grain from the chaff. No investigator can be altogether right in his conclusions; but, surely, if no one threshed out the wheat, we should be very badly off! Adami was the first, I think, to point out the right direction in which to travel, when he ascribed malignant disease to an alteration

1 In true endotheliomata, it will be, of course, cells of this tissue which are concerned.
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in the activities of the cell whereby function, i.e., its specialized function, becomes lost and only the power of growth remains. Creighton and I have developed this thesis, by trying to show what is the character of this profound alteration in the cell-metabolism.

In the light of the occurrence of normal hæmataboly, it is seen that this blood-digestion is no entirely new development on the part of tissue-cells, something originating de novo, which bears no relation to the normal metabolism. Indeed, in the increase of the mammary gland, there is something which can be regarded as actually corresponding to neoplastic behaviour, with the all-important distinction that it is regulated, not merely from "outside" but also from within, because the cell-equilibrium is not disturbed. And probably other cell-types may on occasion behave similarly, e.g., placental tissue, as Creighton has pointed out. It by no means follows, even in these cases, that the hæmataboly is of exactly the same character as in malignancy, bearing in mind the enormous variety of different ways in which red corpuscles can be metabolized by cells.

The main difference in a cancer-cell is that this has become able to produce of itself an all-powerful digestive-enzyme, independently of outside influence or control; and this inherent capacity is transmitted to its descendants, in cell-division. It will be readily understood how the elemental vital activities can be amazingly stimulated, granted the acquisition of this power. And, in the early stages of a malignant growth, the cells are not unhealthy or feeble. They tend to eschew their normal specific function in relation to the body, as can indeed be readily understood on my view of normal hæmataboly; they are making other use of the blood. But, regarded as living individuals, they are full of vigour, as expressed by their growth and multiplication. It is only in the later stages, as the cells become cut off from the vascular supply—now more than ever essential—and surrounded by the concentrated toxic products of their own metabolism, that they degenerate and die.

The point may be raised that this view takes no account of the disruption of the "tissue-tension." Why do the cancer-cells pass inwards? I think far too much stress has been laid upon this question, as an "external" cause. Certainly from the case of the thyroid gland, and in all probability from that of the mammary gland also, my indications are against the view of a rigid delimitation between cell-layers, and a constantly fixed situation of the epithelial cells. I think the cancer-cells pass inwards because in this direction they will meet with blood-elements, to which they may now be chemotactically attracted.

Similarly as regards possible bodily factors which have been adduced in a causative sense, for instance, altered conditions of the blood, such as the presence of "auxetics," the absence of inhibitory or other agents, these are

1 Sir Clifford Albutt (Lancet, 1920, ii., p. 1), has asked, "May the dive inwards of epithelial cells in cancer be due to some inversion of chemotaxis?"
rather to be looked upon as results of the metabolic activities of the growth and not as its cause. In all such cases, we are up against the fact that only certain cells of a particular tissue, gland or organ, take on this property of malignancy. The ultimate cause must be, beyond doubt, I think, inherent in such cells themselves. One may look upon it as a biological response or reaction on the part of "weakly" cells, which have passed into some physiological state of depression or exhaustion, in which the cell-equilibrium becomes upset—a kind of "cell-madness," if I may venture to use the term. But as I said at first, this is only a cloak to hide our ignorance of the nature of life and individuality.

I do not think any special reference to the parasitic view is necessary. Neither do I consider that it is at all necessary to postulate the presence of "embryonic rests" in order to account for the origin of malignant growths (apart, of course, from teratomata).

**THE OCCURRENCE OF "BLOOD-EATING" IN MALIGNANCY.**

That cancer-cells may "phagocyte" not only corpuscles and other blood-elements (leucocytes) but also eat one another is, I understand, recognized, though, before Dr. Creighton, no one seems to have given this remarkable fact the attention it deserves. And, of course, it will have to be ascertained that such is of regular occurrence. But a word of caution is here necessary. It must not be thought that all the cancer-cells will always be engaged in feeding! Far from it. At any one time, or in any particular zone, only few may be found so doing. After a "meal" there will be a period of assimilation, nuclear increase and multiplication—for some generations—before that cell-line takes another "solid" meal. All the time, of course, the cells are also able to obtain their customary, pre-digested nutriment from the plasma. Even among the admittedly normal "phagocytes," many large mononuclears and megakaryocytes in the bone-marrow or spleen contain no ingested blood-elements, recognizable as such, at the time of examination, though they often have the inassimilable remains of such digestion, the platelet-granules, in their cytoplasm. And at periods, or in little areas where the cancer-cells most nearly present their typical tissue-characters, we may well find haematophagy in abeyance. But once the cells have acquired this capacity, it will be inherent in all their descendants, even though sometimes it may remain latent.

On the other hand, at times or in areas where this mode of behaviour is active, we shall probably find the cells least resembling in character the type from which they have originated. Most if not all the cancer-"parasites" which have been described are undoubtedly remains of haemoglobin, cell-nuclei, etc., in an early stage of digestion. But when the digestion is

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1 Murray also considers that "the malignant transformation is a positive change in cells previously healthy... and is not due to a failure of control by the body-fluids or neighbouring cells" (Medical Press, April 5th, 1922).
completed, there is nothing left visible of the digested material, unlike what obtains in "virus-diseases" of epiblastic, epithelial cells, in which the hæmetabolv is unsuccessful and incomplete, when we have Negri-bodies, Guarnieri-bodies and so on, as unmistakable witnesses of its occurrence. The results of completely successful assimilation are manifest; however, in large, irregular nuclei, rich in chromatin and great cells, sometimes multinucleate—in fact, in the typical characters of giant-cells. Creighton has rightly laid emphasis on this point. The all-important difference is that, instead of cutting off portions of cytoplasm only, as is the ordered function of megakaryocytes, cancer-cells enter upon a period of rapid, it may be, irregular, division—which, in the circumstances, is naturally to be expected!

When I came to examine malignant growths, I had no difficulty in observing the occurrence of hæmatophagy, at times on a surprising scale. Of course, I have not yet studied many cancers but as I have found it in all so far examined, I think, in view of the urgent importance of the subject, it is well worth while to give some instances now, in order that others may realize for what to look.

I desire to express my grateful thanks to Dr. D. J. Reid, for kindly taking the accompanying photomicrographs for me. They represent fields of three malignant growths, namely, a very young epithelioma of the gum, from a section kindly given me by Dr. Reid; a very early epithelioma of the lip, from a section kindly lent me by Dr. Leitch, of the Cancer Hospital; and an early (though not quite so young as in the preceding cases) carcinoma of the tongue, from preparations made by Dr. J. D. Thomson and myself.

Before considering these, however, it must be noted that there are two premisses which it is essential to bear in mind in considering hæmetabolv on the part of tissue-cells. In my paper on the formation of the colloid I dwelt upon these two points, but I think it is advisable to emphasize them again. One is that hæmoglobin, in the early stage of digestion, becomes bleached, i.e., colourless; hence an ingested corpuscle may appear as a "vacuole" or space. The other is that corpuscles undergoing digestion (or lysis) may "run together," when masses or globules of hæmoglobin (or "vacuoles") larger than the size of a single corpuscle, may result. Both these premisses are founded on known facts, viz., experimental observations made by the renowned Metchnikoff.

For my present purpose, the first of these is all-important: once this is recognized, the second presents no difficulty. I briefly alluded to it in my first paper, when dealing with "phagocytosis" on the part of the macrophages. As, however, I was there more concerned with the subsequent appearance of the granular, red-staining material (the precursor of the platelet-granules), I give here in fig. 1 two instances of a colourless hæmoglobin-"vacuole", in a macrophage. The blood-smear from which this photograph was taken was kindly lent me by Dr. Bedson; it was from a
To illustrate "A Modification of Dr. Charles Creighton's View of Malignant Growths,"
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H. M. Woodcock

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guinea-pig in which marked hæmatophagy had been induced.1 Two
macrophages are seen, each containing a recently ingested corpuscle, still
staining 'like the free ones around, and also another which has become
completely bleached and appears as a "vacuole." I may add that Dr.
Bedson entirely agrees with me upon this point.

Now, these two conditions occur very frequently in the early stage of
hæmatolysis by tissue cells (cf. my work on the colloid.) And in the two
very young growths to which I have alluded, I have no hesitation in saying
that they are presented by the cells of the down or in-growing epithelium
to a marked degree. Figs. 2 to 4 are from the epitheloma of the gum.
The central part of figs. 2 and 3 shows the epithelial cells in close relation
with connective-tissue areas (one on either side in fig. 2, one to the upper
left-hand corner in fig. 3), which the epithelium is invading. Many of
the cells show the characteristic "prickles." And many of them contain
ingested corpuscles, in some stage of digestion, either singly, or in small
masses of two or three, which have run together. These happen to
be mostly (though by no means always) in the form of pale hæmoglobin-
"vacuoles." 2

Now, it might be thought that these clear areas are merely shrinkage-
spaces, due either to contraction of the nucleus during fixation or to old
and naturally shrunken or degenerating nuclei.

I am confident that neither of these alternatives is the explanation of
this condition for the following reasons. As regards its being an artefact,
this is at once negatived by the fact that it is only shown by certain cells,
especially those in the advancing area of the growth, near the connective
tissue. At the right-hand side of fig. 3, for instance, the nuclei of similar
epithelial cells are all of the customary appearance. Borrman, in his
account of skin carcinoma [3], figures (figs. 67 and 82) identical appearances
and dismisses the idea that they are artificial for the same reason.
Borrman, however, does consider that the second alternative is the correct
explanation, but this worker had not my advantage of knowing of the
occurrence of hæmatophagy and hæmatolysis by tissue cells!

In the first place, it is not the cells which might reasonably be regarded
as old and degenerating that show these appearances. On the contrary,
they are found mainly in cells near the growing, advancing edge of the
epithelium, in which situation one is bound to conclude the cells are active
and healthy (cf. also the second case, below). It is extremely improbable
that all these nuclei, in the earliest stage of a young cancer, are going to

1 To produce this result one cubic centimetre of anti-whole blood serum had been inocu-
lated intra-peritoneally. The smear was made about seventeen hours after the inoculation.

2 Unfortunately, the section was not counterstained; if it had been counterstained with
eosin, for instance, more of the "vacuoles" would have shown faint tints of colour.
Moreover, it must be remembered that the actual contents of some of the "vacuoles," if in
a more fluid condition, at a certain stage, may have been dissipated in the course of
making the sections.
shrivel up and degenerate! The older, quiescent cells nearer the surface do not show this condition (cf., again, the right-hand side of fig. 3). On the other hand, similar appearances are shown in relation with the cell-nuclei, in the case of normal epithelial cells forming pigment (cf. above). In these malignant growths, on the contrary, there is not the least sign of pigment-formation in connexion with these haemoglobin "vacuoles"; a most significant point!

The nucleus is usually wrapped closely, in a crescentic form, around the included corpuscle, or little corpuscular mass. And the inner rim of such a nucleus, abutting on a "vacuole," can sometimes be seen, with a high magnification, to be thickened and stained more intensely, having probably been somewhat compressed; I have often observed this appearance in the case of large mononuclears and lymphocytes containing ingested corpuscles. Now and again a corpuscle has been ingested, one on either side of the nucleus, which is then indented on both sides (the arrow in fig. 2 points to such a case); an identical appearance is seen sometimes in the case of a lymphocyte which has ingested two corpuscles which it is metabolizing into Kurloff-bodies (cf. fig. 11 of my first paper). Lastly, here and there the contents of these "vacuoles" have a definite, though generally pale, staining tint, indicating unmistakably the presence of substance in them. Near the centre of fig. 3 (marked by the arrow) is such an instance, where the two included corpuscles, still separate, as shown by the division-border between them, have well retained the stain and appear as little homogeneous round bodies, quite distinct from the closely applied nucleus. In fig. 4 the same cell is seen at a higher magnification.

I have laid stress on this case, because one could hardly obtain, I think, an earlier malignant growth to examine, and I regard it as of great importance in showing that one of the earliest manifest changes in cells assuming malignancy is their tendency to hæmatophagy.

The next case, that of the epithelioma of the lip, furnishes further corroboration of the extent to which this blood-ingestion and digestion goes on. Though still very young, this growth is not quite so early as the first. It is still everywhere connected with the superficial epithelium, and there are no internal separated areas of the growth; but the proliferated

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1 Here and there in the connective-tissue, granules of bright yellowish pigment can be seen.

2 As I know it is somewhat difficult at first to realize this point, it may be worth while to give an illustration from the Protozoa. Thanks to a useful suggestion recently made to me by Colonel A. Alcock, re. hæmatophagy and hæmetaboly in Balantidium, I looked up a paper by Comes (Arch. Protistenk., xv, 1909, p. 54), on this subject. This author describes perinuclear vacuoles, markedly lobed in outline, which can only indicate the pale and partially digested haemoglobin of the ingested red cells, some of which have "run together," and including, of course, the minute quantity of the requisite ferment produced by the nucleus. The author expressly notes that no liquid is taken in with the cells, i.e., the digestive vacuole is "virtual." In this case, the nucleus retains its shape unaltered.
epithelium is thicker, i.e., it extends more deeply into the underlying connective tissue, and the cells are more changed, having largely lost their characteristic form and appearance. The most striking impression gained is that the growing cancerous epithelium is permeated and pervaded by the blood. This is seen especially well in fig. 5, which shows a tongue or zone of active, elongated cells, advancing in the direction of the connective-tissue area on the left. In many places, between the individual cells, are rows of a few pallid corpuscles in intercellular channels (a). At (b) are two cells, abutting on the connective-tissue area, each of which contains an ingested corpuscle, the one in the left-hand cell being pallid, the other still staining with the eosin. The arrow (c) points to a similar condition, and immediately to the right (and, indeed, in many other places of the field) is a cell with a pallid hæmoglobin-"vacuole" (d), perfectly similar in appearance to the condition prevalent in the case above considered, and with the nucleus partially wrapped round it.

Figs. 6 and 7 show how the advancing epithelium encloses minute capillaries, which thus become completely embedded in it. The capillary wall becomes dissolved, even the endothelial nuclei seem to be digested (cf. the upper capillary in fig. 6 (a), where the endothelial nucleus stains faintly and seems to be on the point of disappearing). Into these channels cancer-cell nuclei penetrate, alter the corpuscles, producing the same hæmoglobin "vacuoles," and absorb this nutriment. At (b) in fig. 6 there is still a faint tint of colour in this area, which appears perfectly similar to that of the pale corpuscles in the vascular channel just on the left (running up from the south-west). Ultimately, these large nuclei lie bathed in a bath of blood (cf. a, fig. 7); I cannot express the condition better. There is often extremely little cytoplasm visible in connexion with such growing nuclei; one almost obtains the impression that the nuclei are largely independent of the cytoplasm! At any rate, the initiative is clearly with the nucleus.

Nowhere are there any signs of conspicuous "bodies," granules, "Rickettsias," or the like; the only reasonable conclusion one can come to is that these epithelial cells are living on the blood themselves, for their own use.

At first, the cancer-cells appear to engulf, or surround only red corpuscles, as in the case of the normal hæmatacetic function; but later, they acquire a taste for leucocytes, especially polymorphs, which are ingested to a predominating extent. The remaining plate-figures are from sections of the early carcinoma of the tongue, which was, however, rather further advanced than either of the other two growths; and they are chiefly to show this ingestion of polymorphs. Fig. 8 shows two finger-like processes of active cells pushing into the stroma, to the north of the field: The arrow points to a cell containing in its cytoplasm both a corpuscle and a polymorph. The dark body, just to the right, is the huge nucleus of another
cancer-cell. (The nuclei in all these figures, I should add, appear denser and more uniform because these sections were stained with Giemsa.) In the finger to the left, a cell-nucleus is seen undergoing mitosis. In fig. 9 is another rapidly growing area, in which the cells are invading and replacing the connective-tissue. To the north of the field is the commencement of a large zone practically filled with polymorphs; and, actually, in the upper part of the figure, many of the polymorphs are surrounded by, and in some cases definitely included in, the cancer-cells.

Fig. 10 shows a small lacuna or channel of this nature, containing numerous polymorphs, which is surrounded by cancerous epithelium. Unfortunately, I cannot say what, exactly, these lacunae represent. They are not infrequent in my sections of this growth, and in some which were kindly shown me by Dr. Ledingham, of a young carcinoma of the ear, they are also common. They are more probably lymph-spaces rather than vascular channels. However this may be, the important point is that they contain blood-elements in any number; at times mostly polymorphs, at other times chiefly corpuscles. Into these blood-containing channels the cancer-cells readily pass. In this case, two large cells have invaded the lumen; the upper one possesses three distinct nuclei (to which the upper arrow points), and the lower one two, of which one is almost out of focus. The cytoplasm of these cells practically obliterates the lumen, and some of the polymorphs are definitely included in the cytoplasm. I think there can be little doubt that many of the compact, solid-looking little morulae of cells result in this manner, from the invasion of such a channel by a few cancer-cells, which eat the blood-elements, multiply actively, and ultimately leave no indication of the lacuna. In fig. 11 is seen such a morula; ingested polymorphs are plainly visible, and the smaller arrow-head points to an included corpuscle.

Cannibalism and Cell-Nests.

As briefly indicated, cancer-cells are known, on occasion, to eat one another, i.e., they become cannibals. This is a most interesting point, because, though they can digest other forms of cells and organized material, they appear to be unable properly to digest and assimilate protoplasm of their own specific type and character. And a valuable instance of cannibalism in an Amoeba has been recently described by Lapage [66], which affords almost a perfect parallel to this mode of behaviour. In text-figs. A and B I have reproduced, by kind permission of the author, two of his figures, which show the result of a series of such performances on the part of the various amoeba-individuals. The remarkable appearance shown in the first figure is to be thus explained: The amoeba, whose nucleus is designated by n3, has been first of all ingested by that one next enclosing it (n2), when the latter was in the free, active state. This cannibal and its victim were next engulfed by another amoeba (n1), and finally these three have all been ingested by the large, still active individual, the karyosome
of whose vesicular nucleus is designated by E. (The clear zone represents the nuclear sap and is not a shrinkage space.) In text-fig. B the large, free amoeba (N) has eaten both a cannibal and its victim (n1 and n2) and also, separately, another small amoeba (n3).

These ingested amoebae are killed and become rounded, and later, they may be partially altered or broken down. Lapage found that they were at times extruded again, in a killed or injured condition, unable to recover. This, in itself, indicates their indigestibility, and Lapage concludes that it is most probable the amoebae are unable to digest and assimilate individuals of their own species—at least if ingested in a normal and healthy condition. It is apparent, indeed, from text-fig. A, that the first victim (n3) must have been ingested some time previously, since two successive acts of cannibalism have taken place; but none of the eaten individuals shows any sign of being digested. An interesting and rather important detail of difference is to be noted in this case from what occurs when tissue-cells are digesting ingested organized material. There is no indication that the nucleus becomes applied to or tends to wrap round the included material.

In the young carcinoma of the tongue, such instances of cannibalism, or attempted cannibalism, are not infrequent. Text-fig. 1 shows a large cancer-cell containing another, smaller cancer-cell, which it has engulfed, and in this case the large, richly chromatic nucleus of the cannibal is crescentic in form and closely applied to the included material. In text-fig. 2 precisely the same condition is present as in text-fig. B. The large cancer-cell whose nucleus is indicated by N has ingested both a cannibal and its victim (n1 and n2) and also, separately, another cell (n3). It will be noticed how attenuated the cytoplasm of the outer cell (N) is where it encloses the pair of cells (n1 and n2) on the south-east side; it appears here as little more than a line. Just the same thinned-out condition is seen in the case of the amoeba-cannibals in text-fig. B, especially as regards the amoeba (n1), where it encloses the first victim (n2) on the south-west side, and also, though not to quite the same extent, as regards the large, free amoeba, at nearly the same point. In such cases it appears as though the cannibals had only just been able completely to surround their victims.

Now, in the case of cancer-cells, this process may go on to a surprising degree. But soon it becomes, rather, a case of attempted cannibalism only. After the first few instances of multiple cannibalism, as it may be termed, the cancer-cells are no longer able to surround the ever-increasing mass. Those in the immediate neighbourhood become applied as a whole closely around it, becoming greatly narrowed and extended, but forming only incomplete rings, as it were. An indication of this is seen already in fig. 2.

1 There is no question that these are ingested amoebae and not endogenous buds. This is shown conclusively by Lapage, who points out that many of these included individuals themselves contain diatoms and other food-material, a proof that they have been in the outer world.
Text-Figs. A and B: Illustrating cannibalism in *Amoeba vespertilio* (after Lapage). A, x 900; B, x 450 (approx.). (In fig. A, a portion of a large pseudopodium on the right has been omitted, to save space). 1, 2, and 3: To show cannibalism and attempted cannibalism, leading to formation of cell-nests, in carcinoma. 1 and 2 x 500; 3 x 300. (For reference-letters, see text.) (Photos 1-3 were kindly taken by Mr. A. Dennis.)
but in a better-defined manner in text-fig. 3. Thus we get the well-known concentric "cell-nests." Multiplication of the component cells may perhaps occur to a very slight extent (e.g., possibly the two applied cells just on the right in text-fig. 2 have resulted from the division of one), but I think, in the main, multiplication plays a very small part in the formation of these nests.

Alteration of the ingested cells occurs, but my indications are that proper digestion and assimilation of this material cannot take place. In text-fig. 2 the nucleus of the first ingested cell (n2) has become rather dense, and the cytoplasm has peculiar granules in it. The nucleus of the separate victim (n3) has become fragmented. But generally the ingested cells simply alter into a more or less uniform, densely staining mass (cf. text-fig. 3). I think this alteration results in the production of some chemical substance which acts as a stimulus to the surrounding cells, inducing them to continue to try and enclose the mass in ever-widening rings. But, ultimately, the whole degenerates to form a sort of keratinized mass.

**Extracellular Digestion.**

It is important to note that partial digestion, at least, of the blood may take place extracellularly, the ferment being poured out of the cells. There is nothing surprising in this behaviour. In some sections of the bone-marrow of a purpuric guinea-pig, which were kindly lent me by Dr. Ledingham for the purpose of my platelet work, a particularly vigorous "phagocytic" response on the part of the megakaryocytes is seen to be occurring. Many of these contain several included eosinophil polymorphs, in one great, comprehensive "vacuole" (cf. figs. 7 and 8 of my first paper). Here, the digestion is occurring, in reality, extracellularly. Because a huge lobe of a megakaryocyte may thus enclose eight or nine cells, and even when these are surrounded they and the included plasma remain, for all intents and purposes, part of the "outside" world, the digestive ferment being poured into this "vacuole."

Now plate-fig. 12 shows a perfectly comparable condition. A large lacuna, surrounded by cancer-cells, contains blood elements in various stages of alteration. In the upper part the corpuscles have been resolved into fragments and large granules; here also are a few dis-organized polymorphs. In the middle of the larger part of the space is a uniform, finely granular mass of altered hæmoglobin. I know, of course, it can be said that this is just "broken-down" blood and means nothing; it is being destroyed by auto-lysis and will be "absorbed." I venture to submit that it means a very great deal. I think the blood has been reduced to this condition by the action of the blood-digestive ferment secreted by the surrounding cancer-cells, and that it is being used as *pabulum* by them. Red corpuscles themselves are not living cell-individuals; they are (now) only plastids. That much is certain,
According to the generally accepted view that enzymes are only produced by living cells, these corpuscles cannot themselves, therefore, produce a ferment. I have been informed they contain catalase, but I do not think this, itself, can exert any lytic action upon them. I do not see how they can contain a lytic (digestive) ferment, because, if so, they would—being non-living—automatically undergo autolysis, in the manner that dying cells do. As I have pointed out previously, there is no evidence of such behaviour in the blood. Where masses of altered haemoglobin, etc., resulting from the lysis of corpuscles are found (naturally), this occurrence must be due, I think, to the ferment action of neighbouring cells; though it may possibly be that the catalase assists, in a manner comparable, for example, with the action of entero kinase (cf. "Poskrscrip," p. 268).

And I think, from what I have so far observed, that this extracellular hæmotabolyl operates largely in sarcoma, and that there the blood-digestion is mainly extracellular rather than intracellular. In a section of a sarcoma of a foot, also kindly lent me by Dr. Leitch, this "break-down" of the blood presents, at least to my eyes, an amazing sight. Numerous large areas of blood, in all stages of disorganization and "alteration," are present into which the advancing sarcomatous cells are penetrating. I am inclined to think that more use is made of the hæmoglobin in sarcoma, and this may be why this form of malignancy tends to travel along the route of the vascular system, while carcinoma tends to follow the lymph-channels, where there are more cells.

Sir George Beatson has recently laid stress [2] on the occurrence of unusual pigment, and in increased amount, in the cells of other tissues in the neighbourhood of a growth, and considers that cancer may have a pigmentary cause. I think this question of pigmentation is, far more probably, a concomitant of the development of the malignant state. Its occurrence points to a stimulation by the cancerous growth of the functional metabolism of other types of normal cells, along more or less usual lines. In melano tic sarcoma, on the other hand, the malignant cells themselves may produce pigment in quantity. I think this is because, owing to the action of the powerful exo-ferment, these cells are able to digest and absorb more hæmoglobin than they actually require; hence, in addition to using sufficient iron for their own rapid nuclear increase, a surplus is "excreted" in the form of melanin-pigment.

The Possibility of Infectivity in Cancer.

The radical cancerous change in hæmotabolyl is, in general, so inherent in origin that normal cells are, as a rule, in too well-balanced a state of vital equilibrium to be induced from outside to revolt. But there are one or two suggestive cases which indicate that malignant behaviour on the part of cells can be directly induced from outside. By this I mean, not merely self-inaugurated as a result of continued, artificial irritation, but on the lines of the Twort-d'Herelle phenomenon, the same digestive enzyme,
or a chemical substance probably closely akin to it, at once stimulating the production of the malignant enzyme in normal cells. Peyton Rous's transmissible fowl-sarcoma is such an instance. Rous himself said [9] that, instead of a minute parasitic organism being the infective agent, "it is conceivable that a chemical stimulant elaborated by the neoplastic cells might cause the tumour in another host, and bring about in consequence a further production of the same stimulant." A very suggestive and prophetic idea, enunciated long before the Twort-d'Herelle phenomenon was heard of! If we regard this chemical stimulant as being the blood-digestive enzyme, I think we have the right explanation of the nature of the "infective" agent in this particular type of malignant disease. Dr. Arkwright, it is interesting to note, has recently also suggested [1a] the possibility of the "virus" of fowl-sarcoma being of enzyme-nature. Now, does not this case then fall into line with my general view of the ferment-viruses? The all-important difference is that, in the latter, the abnormal hæmetyabol thus induced is incomplete and unsuccessful, whereas in malignancy it is only too successful.

Again, in Fiebiger's Spiroptera-cancer, some metabolic enzyme produced by the worm may be able to induce certain tissue-cells of the host to develop the necessary digestive enzyme which will start them on their career of unrestrained multiplication and spread.

In view of such instances, I would greatly hesitate before saying that human cancer never has, in any case, an element of infectivity about it.

It may be thought that this admission of the possible "outside" origin of the malignant enzyme conflicts rather with the sharp distinction I drew in my opening paragraphs between "virus diseases" and malignant growths. But, really, one cannot draw hard and fast distinctions in biology; lines of separation are rarely straight and unbroken. So in this case, one can only speak in general terms. The instances of "exogenous" origin of a malignant state will be very rare, compared with the generality of cases. On the other hand, I would not say that some "virus-diseases" do not, now and again, "originate." According to my view of typhus fever, for instance, I think it is quite likely that the abnormal type of hæmetyabol characterizing the disease in the louse may sometimes "arise" as a pathological condition of the digestive function.

THE DIFFERENCE BETWEEN BENIGN AND MALIGNANT TUMOURS.

I think that benign tumours and malignant growths have quite different causes of origin, and that the resemblance between them (such as it is) is largely due to the fact that increased multiplication happens to be a feature of both conditions.

It is most important to remember that, in single-celled forms of life (Protozoa), growth and reproduction are two distinct functions, which have no necessary correlation. The young (small) forms of an individual may
divide as well as the full-sized adults. On the other hand, in the Metazoa, the growth-size function, not only as regards organs and tissues, but also in very great measure as regards many types of cell, has been secondarily taken over, as it were, by the multiplicative function of the cell-individual, which has (necessarily) lost its original significance of reproduction (for the survival and spread of the species). With one or two exceptions"growth" is attained by increase in number of the cells, rather than by their increase in size. Body-size depends on the total number of cells rather than on their size individually considered (Wilson, "The Cell"). It is only very rarely that the individuals of a particular type of tissue-cell show variation in size comparable with that which is frequently found among Protozoa.

Hence, I regard benign tumours as indicating a disturbance (hyperactivity) of this growth-size function on the part of cells, either as components of tissues, or as individuals, which is expressed in this manner. But, just as in the case of the increased exercise (or other disturbance) of other cell-functions, this of itself does not mean malignancy; neither does it necessarily produce a malignant condition. The vital equilibrium of the cells, their power of responding to the co-ordinating control of the body, is not upset. They are still behaving (apart from their increased "growth"-rate) as members of the tissue of which they form a part. And they are not living on the blood-elements in the manner in which they do in malignancy (contrast in general the slow rate of increase of benign growths with the rapid rate of malignant ones). As in other cases also, however, this condition may, and often does, lead to a depressed state of the cell-vitality in certain "weakly" individuals; and then results the cell-revolt which is indicated by malignant behaviour.

If we regard the view of malignancy which I have above considered as a working hypothesis, does it afford any indication of rational lines along which attempts to find a therapeutic cure may be pursued? I think there are two: (1) in the direction of counteracting the blood-digestive enzyme; and (2) in that of substituting some other metal for the iron of the ingested organized material. I will venture to illustrate these two lines by suggestions, but whether they will be considered promising enough to try is quite another matter.

(1) This implies the application of sero-therapy; an attempt to obtain anti-bodies to the enzyme. I take it that efforts to obtain anti-bodies by inoculating extracts of growths into other animals and subsequently using their serum have often been made? Indeed, from the whole character of the disease, and from the fact that self-recovery is (so far as is known) very rare one would fear such efforts would not be very promising; cancer is such an intrinsic cell-disease. (Prevention, by the development of a degree of immunity on the part of the cells, would be more possible, I think, along such a line, than the actual cure of a growth. Indeed,
it is not unlikely that, in the natural course, the cells of similar type, apart from the growth, may become "immunized," in the sense that they can not assume the malignant condition.) But there is one exogenous, infectious disease which, it seems to me, perhaps more nearly approaches malignancy in character—I mean as regards its principal mode of expression—than any other, namely, typhus fever. Here there is a greatly stimulated degree of hemetabolism on the part of endothelial cells, which leads to an increased rate of multiplication. These macrophages are the cells which ordinarily, as a routine behaviour, exercise hemetabolism in a manner most nearly approaching, perhaps, that in which cancer-cells are doing this. To this disease subsequent immunity, involving the production of anti-bodies to the virus (the hemetabolic enzyme) can, of course, be obtained, at any rate in man. If anti-typhic serum, from immunized animals, could be procured it might, perhaps, be worth while trying this in the hope that cancer-cells might be affected thereby—at any rate, mesoblastic growths (sarcomata).1

(2) As I have emphasized, iron is necessary for the formation of chromatin. If voracious cancer-cells could be induced to take up some compound containing another metal than iron, they could not use this to build up chromatin, and in their exalted and unstable condition they might quickly be killed. I read that Professor Blair Bell, of Liverpool, is trying the effects of lead salts, apparently with a measure of success. The trouble, of course, is to obtain something which would be fairly "specific" and not toxic to the normal cells. Is it of any use suggesting an organic compound of some other metal (manganese, copper), such as is known to occur in the blood of certain invertebrates?

Finally, there is one general point to which I may just allude. I sometimes think that many people are eating too much—not merely more than they require, but more than is good for them—in these days, in which many of us lead a relatively sedentary life and are not conspicuous for muscular development. If we eat a large quantity of iron-containing

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1 Since this was written, I see that Levaditi and Nicolau, in the course of their deeply interesting studies, have made certain observations (C. R. Acad. Sci., 175, 1922, p. 1649), which are, I think, very important in this connexion. The authors find that the cells of (ectodermic) epitheliomata are no longer able to develop immunity to the vaccinia-virus. On the contrary, the tendency is for grafts inoculated therewith to gradually undergo necrosis and disappear. On my view of the enzyme-nature of these exanthematic viruses, such behaviour is quite comprehensible, and indicates that the malignant cells, by their assumption of the property of what may be regarded as basic hemetabolism, have lost all cell-regulatory power of reaction vis-a-vis such abnormal ferments. The loss of the lesser control is included in that of the greater. And the point is that the pathogenic action of such an exogenous enzyme, against which the normal cells are able to acquire protection, might afford another, related, line of attack on the cells of a malignant growth. In this case, on the other hand, sarcomatous cells are only slightly affected.
food (e.g., meat) we are certainly helping, particularly, to make more blood. And, as I pointed out, the blood is that tissue to which, apparently, no limit is set upon its multiplication. Now, it has been generally assumed that the red corpuscles (restricting myself to these, as they vastly predominate) are “dying” as fast as they are being produced, and that the “effete” ones are eliminated by the macrophages, of one kind or another. I have grave doubts about this being the case.

It is, perhaps, endeavouring to probe rather deeply into the mystery of the co-ordination of the different tissue-systems, but on my view of general hæmatoboly, as a normal occurrence, I think it is most likely that this function, in its origin, served primarily as a means of keeping the numbers of the cells of the vascular system fairly constant and thus counter-balancing the much superior capacity and facility for proliferation possessed by these elements, especially the red-cell line. (Let us always remember that the metazoan body arose as a colony of little, unicellular animals.) It follows, therefore, that if a relatively large amount of hæmoglobin is continually being produced, and an insufficient proportion safely side-tracked, as it were (e.g., into the muscles), there may be an undue degree of hæmatoboly activity among various glandular and “secretory” tissues. And excessive functional activity may at length prove too much for some weakly cell-line!

It may be noted that coloured races have, at any rate, one “avenue of relief” which is not open to the white peoples. In their case, the entire cutaneous epithelium is able to exercise its normal mode of hæmatoboly (pigment-formation) and thus “account for,” if I may so put it, a considerable quantity of hæmoglobin; whereas, in white races, this mode of utilization is very largely in abeyance. And in addition, moreover, many coloured races do not eat much meat. (Of course, this argument applies only to the above intrinsic set of predisposing factors. As regards others, e.g., special forms of chronic “external” irritation due to popular customs, etc., the tissue-cells of coloured races may be just as liable to be ultimately upset thereby as those of white races to corresponding ones. But the development of a malignant growth cannot by any means always be correlated with known “irritation.”)

There are men who work best in a team and men who prefer to work alone, and . . . there is ample room for both types.”—(From an article on “National Health and Medical Research,” by “J. C. G. L.” Nature, March 31, 1923, p. 422.)

“The endowment of research in general, rather than cancer-research in particular, may be better policy than to attempt to induce men of imagination to restrict their range.” (Brit. Med. Jour., June 17, 1922, p. 964.)

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EXPLANATION OF PLATE FIGURES.

(All are photomicrographs, kindly taken for me by Dr. D. J. Reid. All are magnified 
300 diameters, with the exception of fig. 4, which is 500 diameters. For full description, see text.)

Fig. 1.—From a blood-smear of a guinea-pig in which "phagocytosis" had been induced 
(kindly given me by Dr. Bedson). Two large mononuclears, each containing a recently ingested 
red corpuscle and a pale hemoglobin "vacuole," are shown. Polychrome methylene-blue.

Figs. 2-4.—From a very early epithelioma of the gum (section kindly given by Dr. Reid). 
Cancer cells in down-growing epithelium, containing ingested corpuscles in early stages of 
digestion. Dilute Delafield’s hematoxylin, not counterstained; the staining is, unfortunately, 
not very precise.

In fig. 2 the arrow points to a cell containing two separate, included corpuscles, one on either 
side of the nucleus. In figs. 3 and 4 the arrow indicates a cell containing two corpuscles, side 
by side, but still separate, which have well retained the stain.

Figs. 5-7.—From a very early epithelioma of the lip (section kindly lent by Dr. Leitch). To 
show the extent to which hematophagy and hematoboly are taking place in the actively growing 
and extended areas. Hematoxylin and eosin.

Fig. 5.—(a) Points to pale corpuscles, in intercellular channels. (b) Two cells, each of which 
contains an ingested corpuscle, the one to the left being pale, the other tinted with the eosin. 
(c) Another cell, similar to that last mentioned; note the crescentic nucleus, partially wrapping 
round the corpuscle. (d) Another cell containing a pale hemoglobin " vacuole."

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A Modification of Dr. Creighton's View of Malignancy

Fig. 6.—(a) Points to a capillary, the endothelial nucleus of which is very faint and appears to be disappearing. (b) A capillary into which a large cancer-cell nucleus has penetrated and caused the corpuscles to "run together" into a pale hemoglobin mass.

Fig. 7.—(a) Cancer-cell nuclei "bathed in" hemoglobin. (b) Large nucleus, with a hemoglobin "vacuole" on either side, that on the right being formed of a single corpuscle. (The black mass at the right-hand side is a piece of debris which is, unfortunately, lying on the section.)

Figs. 8-12.—From a young carcinoma of the tongue (sections made by Dr. J. D. Thomson and myself). To show the predilection of the cancer-cells for polymorphs, after the earliest stages of the growth. Sublimate alcohol acetic; Giemsa. The section from which fig. 10 was taken was, unfortunately, somewhat over-differentiated.

Fig. 8.—Two finger-like processes of active cancer cells pushing into the stroma (to the north of the field). The arrow indicates a cell containing in its cytoplasm both a polymorph and a red corpuscle. The dark body to the right is the huge nucleus of another cell. In the finger on the left a nucleus is seen in mitosis.

Fig. 9.—Rapidly growing cancer cells invading an area occupied by numerous polymorphs (to the north). These are becoming surrounded and ingested by the cancer cells. The arrows point, respectively, to a minute capillary, a large, multi-lobed nucleus, and to another in the act of mitosis.

Fig. 10.—Lacuna, surrounded by cancer-cells, which contains several polymorphs. Two cancer-cells have invaded the lumen, which is largely filled up by their cytoplasm, and some of the polymorphs are definitely included therein.

Fig. 11.—Morula of large cancer-cells, occupying what has probably been a lacuna containing blood-elements. The arrow points to an ingested polymorph and red corpuscle.

Fig. 12.—Large lacuna, surrounded by cancer-cells, containing blood elements in various stages of alteration (digestion).

POSTSCRIPT.

I should like to add, even as this goes to press, that only a few days ago I came across a reference to a paper by Leupold (Zieglers Beitr., 59) on the important question of the auto-lysibility of the red corpuscles. This worker kept blood in a sterile condition for three or four weeks. He found that, while some corpuscles suffered changes due to osmosis (crinkling, slight shrinkage, and so on), many remained unaltered the whole time, and there was absolutely no pigment formed. If, however, a minute fragment of tissue was added, containing an autolytic ferment—e.g., kidney—a granular brown pigment quickly developed, which gave the iron reaction. The author concludes that red corpuscles contain no autolytic ferment and are durable ("dauerhaft"). This is most important from my point of view.