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E. F. BASHFORD, M.D. EDIN.

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Past Neglect to Investigate how Cancer Grows.

Mr. President and Gentlemen,—I propose to refer more especially to the growth of cancer. The study of the mere processes of growth as distinct from the genesis of cancer has received serious attention from the outset of our investigations,* and it will be entirely advantageous if others can be persuaded that an attack on this difficult subject can no longer be avoided, as it has been in the past. The undefined amount of the growth of cancer—which term I take to be synonymous with "malignant new growth"—has forced it to the forefront in the course of the experimental investigations of the Imperial Cancer Research Fund. The biological problem presented by the amount of growth has not hitherto been properly appreciated, even by those investigators who, like Jensen, Borrel, and Michaelis, have successfully propagated carcinomata. In the study of cancer in man, the other clinical and pathological features mask those of mere growth. By means of artificial propagation we have produced such enormous masses of tissue that the ceaseless cell proliferation has become the most impressive feature, and as the work has progressed the local nature, the infiltrative character, the absence of constitutional disturbance, the relative independence, and the formation of metastases have assumed a different perspective. That the amount of

* *Vide* "The Problems of Cancer," 'British Medical Journal,' July 18th, 1903.

growth which suffices to kill a patient is infinitesimal as compared with the indeterminate total of growth as revealed by experimental propagation, is a side issue, however important it may be. The problem which demands solution is, Why is the growth of cancer limitless? This concrete and hitherto unknown problem is thrust upon us by artificial propagation, which also provides us with a means for experimentally solving it.

It can hardly be claimed that the necessity for comprehending the nature of this undefined growth has been elevated to prime importance in the past; for it has not been made the starting point of any one of the hypotheses which have been advanced from time to time to explain cancer. Examination of the hypotheses which merit serious attention shows that they have all taken their beginning in conjecturing a nature and an origin, and the ceaseless growth has been relegated to the position of a phenomenon the explanation of which naturally followed from the nature and origin postulated. The cells of a malignant new growth have been supposed to proliferate because, *e.g.*, they were asserted to be freed from the restraint of connective tissue or liberated from the control of the other members of the cell community by "solution of organic continuity," or because they were derived from "embryonic rests," or were modified reproductive "gametoid" (reduced) tissue, or because a parasite made them multiply. I do not wish to ridicule any one of these hypotheses. I desire, however, to make clear the nature of the assumptions which have been supposed to explain the growth of cancer, and to emphasise that all these explanations have one shortcoming in common: they postulate a mode of origin and a nature for cancer, and fail to show how the actual continued cell multiplication is maintained. The mere processes of growth have not been deemed worthy of higher consideration in formulating any of the above-mentioned hypotheses. Von Leyden, a most distinguished clinician, in a recent paper upholding the parasitic hypothesis, quotes von Hansemann, a distinguished pathologist and a critic of the grounds on which the belief in a parasitic etiology is based, and taunts him for confessing his ignorance of how and why cancer cells possess their unlimited powers of growth, and for excusing himself both from attacking this problem and from attempting to explain the origin and the nature of cancer. It cannot, therefore, be asserted that the importance of the subject is denied.

It seems strange that if the power of continued proliferation is so prominent a characteristic, so little attention should have been given to it by Thiersch, Waldeyer, and Cohnheim, who so materially advanced our knowledge of malignant new growths. The explanation is the simple one, that the processes of cell division were little understood by the older investigators, who had also little information on fertilisation and on the development and differentiation of organisms to guide them in studying the normal growth of the human body, and far less still to help them to comprehend growth in the aberrant form presented by cancer.

Even in recent times pathologists have continued to concern themselves with the mode of origin and the nature rather than with the growth of cancer. This has been partly due to the continued discussion of the evidence for and against the views already enumerated, and the legacy of restricted outlook which has been transmitted to all investigations carried out under their influence. It has also been due to endeavours to find better substitutes for the old hypotheses, but always on the basis of experience limited to cancer in man; for the only important contributions to the discussions on the nature of cancer have been provided by medical men or biologists, who have studied malignant new growths in the form in which they come under observation in the operating and *post-mortem* theatres. Thus studied, cancer is almost always already fully developed. The stage at which it has arrived is alone presented for examination. The stages through which a tumour has passed, and those through which it will pass, are alike left to the imagination, and are supplied in accordance with any hypotheses which may find favour. The limits of objective observation do not extend beyond the stage at which a tumour has arrived, and it has been truly said that even the margins of a fully developed and growing cancer yield no information as to its origin. In this connection, however, it is important to remember that the histological features, especially the direction in which the cells tend to differentiate, are strong arguments in favour of the view that malignant new growths develop from cells of the normal tissues. These arguments grow in force when regarded objectively and free from the bias of the Cohnheim hypothesis which postulates an embryonic and atypical character for the cells of malignant tumours. Deviations from the typical character of the cells of the tissue "mimicked" are frequent. They are, however, of much less importance from the

standpoint of investigation than the universal occurrence of a single differentiation when any is present, and the occasional manifestation of all the features of malignancy by growths which show the most perfect differentiation and even exhibit the exercise of the secretory function of the tissue represented.

Investigation of cancer in man is so limited in its scope that it is not surprising if general credence has been given to the belief that it will be impossible ever to observe a cancer in process of formation,

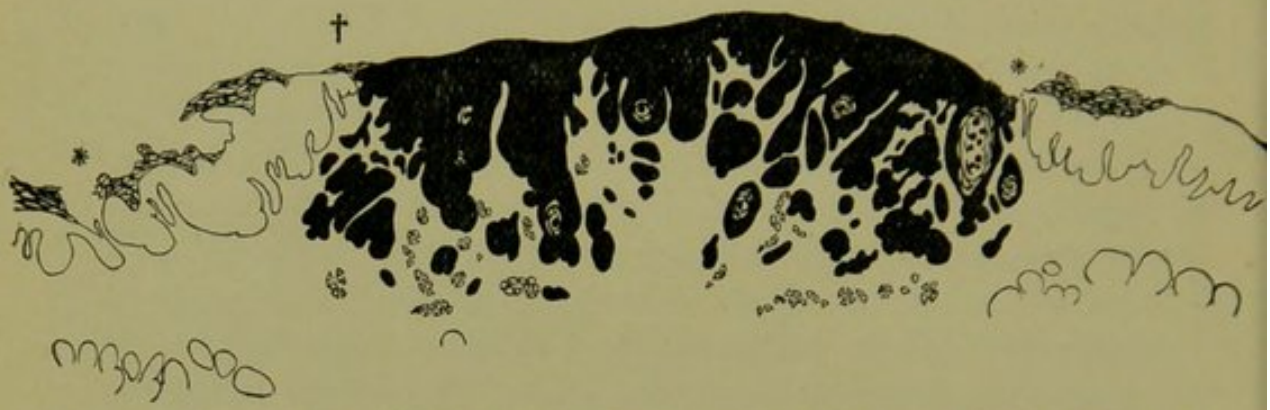

FIG. 1.—Early squamous-celled carcinoma of tongue, man. Shows two distinct carcinomata adjoining at †, completely independent of normal epithelium. × $\frac{2}{1}^{0}$

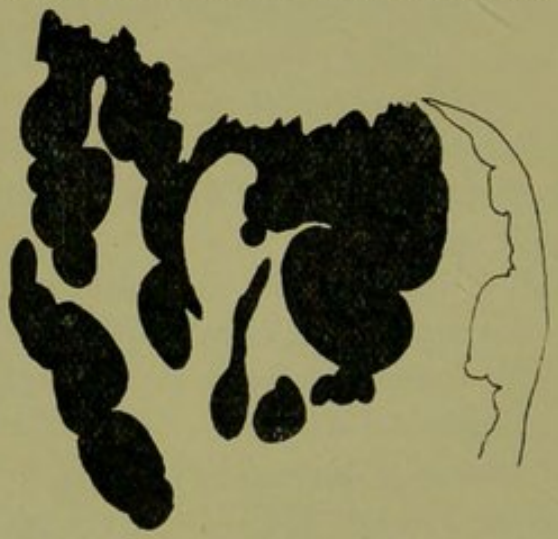

FIG. 2.—Squamous-celled carcinoma of jaw, mouse. Shows sharp separation of growth from normal buccal epithelium. × $\frac{2}{1}^{0}$.

and pathologists have in consequence remained content to modify the old explanations or to postulate anew other modes of origin whenever a previous conjecture has been shown to be untenable. All that could be ascertained by the study of human cancer appeared to have been elicited, [new facts were not forthcoming, and new explanations of the old facts did not have even the appearance of an advance. Is it surprising that pessimistic views obtained ascendance, and that medical men only cognisant of the seemingly insuper-

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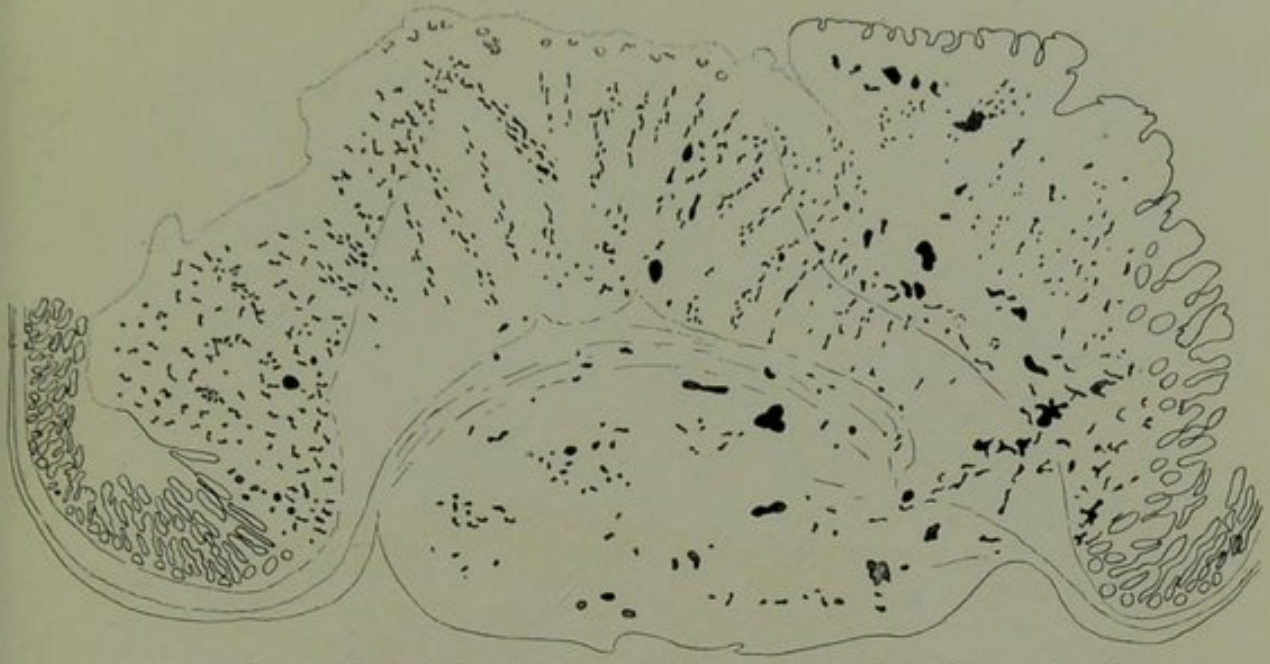

FIG. 3.—Adeno-carcinoma of small intestine, mouse. Shows greatest lateral extension in mucous membrane, arrangement of cancer in columns where it traverses the circular muscle, expansion into rounded masses under peritoneum. Carcinoma black, ulcerated surface dotted. The right margin is reproduced under higher magnification in Fig. 4. × $\frac{20}{1}$.

FIG. 4.—Adeno-carcinoma of small intestine, mouse. Margin of growth showing mode of extension laterally and through muscular walls of intestine. Higher power of right-hand side of Fig. 3. × $\frac{20}{1}$.

able difficulties presented by the study of cancer in man should declare that its nature can only be elucidated with the explanation of life itself? The method has been at fault. The investigator has been poking about in a corner, and the narrow scope of his enquiries has prevented him from forming a true conception of the problems and from making at the outset even a preliminary survey of the general features of the field of investigation. The study of cancer has been pursued not in a rational way but empirically, and the pessimism which has resulted from failure is logically ascribed to the methods which have been employed and not at present to the insoluble nature of the problem itself.

Features of Sporadic Growth.

The first essentials to the rational study of cancer are facilities for subjecting any hypothesis to the test of experiment and freedom from the restrictions which circumscribe its study in man. Hence it came to be one of the first duties of the Imperial Cancer Research Fund to determine the extent to which malignant new growths occur throughout the animal kingdom. These investigations, augmented by the results of other workers, have shown that if allowance be made for the differences in anatomical structure of the various animals, the problems of cancer present the same essential characteristics throughout the entire vertebrate phylum. This identity in nature—which, of course, involves identity in the character of the anatomical lesion upon which the diagnosis of malignant new growth can alone be based—is a matter of prime importance. It yields a secure comparative basis for deduction, and puts out of court as direct causative factors many external agencies which demand consideration in the higher forms of life, and of necessity attract attention in the case of mankind living under the artificial conditions associated with a high degree of civilisation.

The information elicited by studying the growth of cancer in the comparative and experimental manner thus rendered possible, must be brought to bear upon the nature of the disease in man and reviewed in the light of the knowledge which has accumulated during many years of clinical and pathological observation. The boundless cell proliferation proceeds with an energy which is only comparable with the initial proliferation in embryonic tissues, nevertheless it is intimately associated with another main feature of the disease, viz., its increasing relative frequency as life advances.

This is technically known as the "age incidence" of cancer, and must be explained before any claim to the establishment of the sufficiency of a hypothesis can be set up. All the well-known hypotheses, however, break down before the problem of the "age incidence" of cancer, and it does not necessarily follow from the primary assumptions which underlie any one of them. The comparative study of sporadic malignant new growths has proved that they occur in animals also with increasing frequency as age advances, both in species with a long and with a short duration of life. They appear in considerable numbers in mankind after from 45 to 50 years, in the horse after nine years, in the dog and cat after nine years, in the trout after from five to seven years, and in the mouse after two years. The higher incidence manifests itself after an interval which varies in different species in direct relation to the absolute duration of life. The interval of relative freedom is in consequence proportionately much the same for different animals. The maximum incidence also coincides with the decline in reproductive activity. This fact has given rise to speculation on the influence of the sexual organs. These speculations are deprived of any significance by the fact that cancer occurs in castrated animals at the same period as in entire animals. Neither the cessation of a normal secretion nor the appearance of an abnormal one can therefore be the cause of the maximum incidence of cancer at this time. The variations in the natural sporadic growth of cancer in different forms of life therefore yield some valuable information, and are of sufficient importance to claim further study.

The preliminary stages before the appearance of cancer, which may take 50 or more years in the case of man, are passed through in about two years in the case of the mouse. It would take so long to observe the various stages of the whole process in mankind that it is impossible to attempt it with hope of the practical results which are theoretically attainable in the case of short-lived animals. The relation which exists between the age incidence of cancer and the duration of life awakens expectations of another kind. There are laws which govern the varied but definite growth, which determine the size of body and the length of life in the different vertebrates. May they have a determining influence not only on the time at which the disease appears sporadically, but also set time limits to various phases in the development and growth of cancer itself? Just as the gestation period varies from 21 days to nine months in

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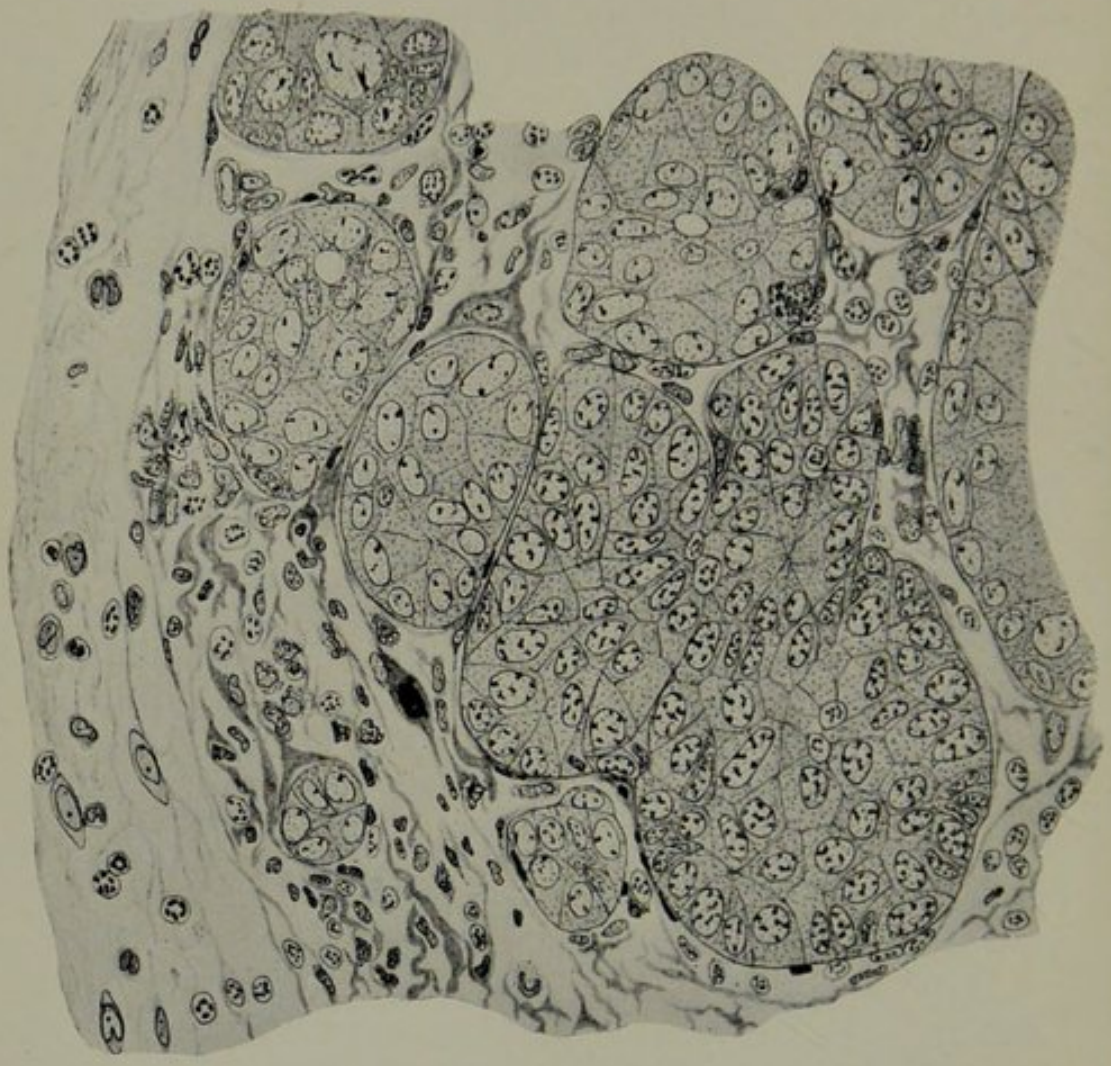

FIG. 5.—Transplanted carcinoma of mouse. Site of transplantation after twenty-four hours. Beginning degeneration of introduced stroma. × $\frac{400}{1}$.

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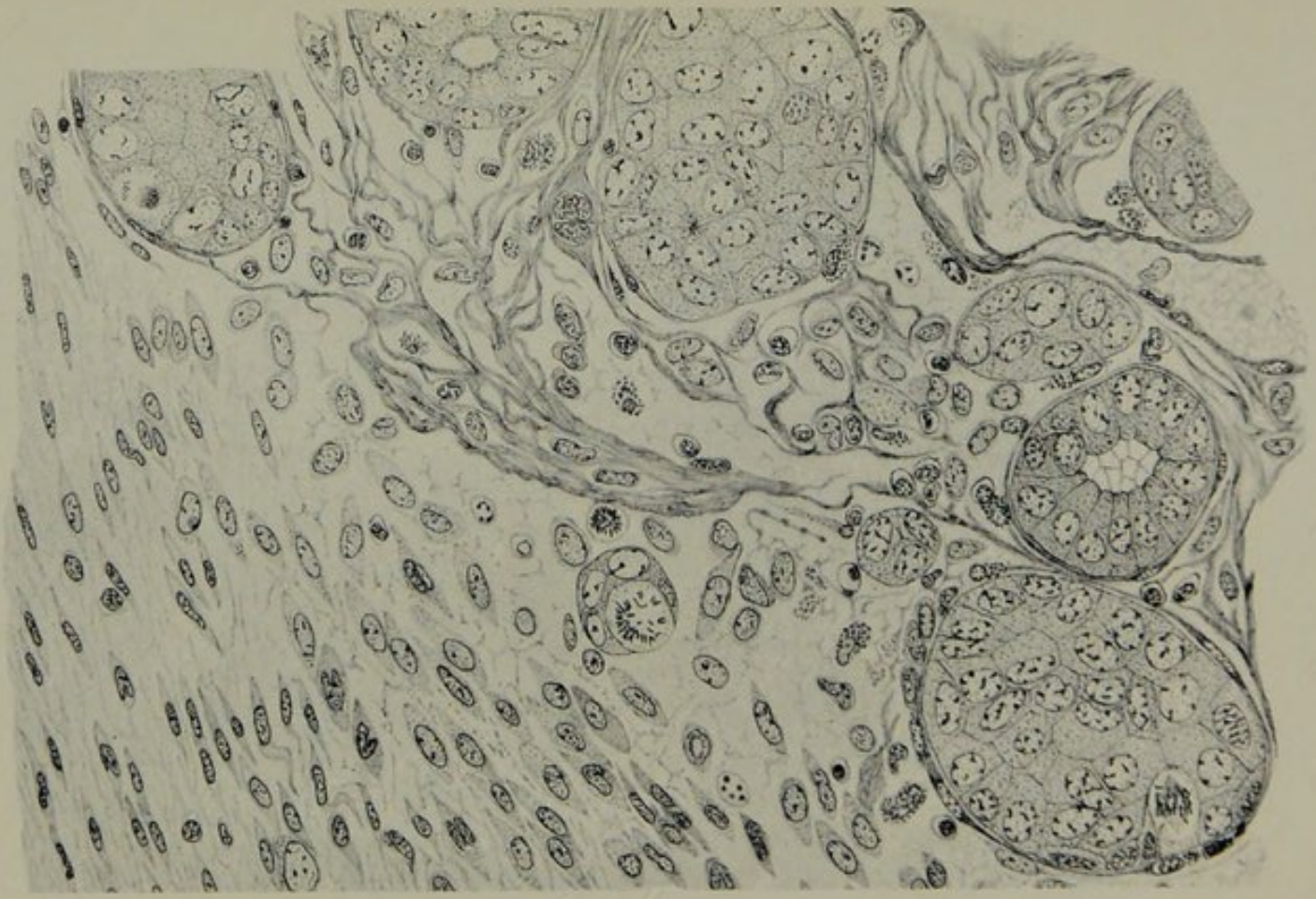

FIG. 6.—Transplanted carcinoma of mouse. Site of transplantation after three days. Two zones in surrounding connective tissue. Amitosis in outer zone, mitosis of connective-tissue corpuscles next the tumour. × $\frac{400}{1}$.

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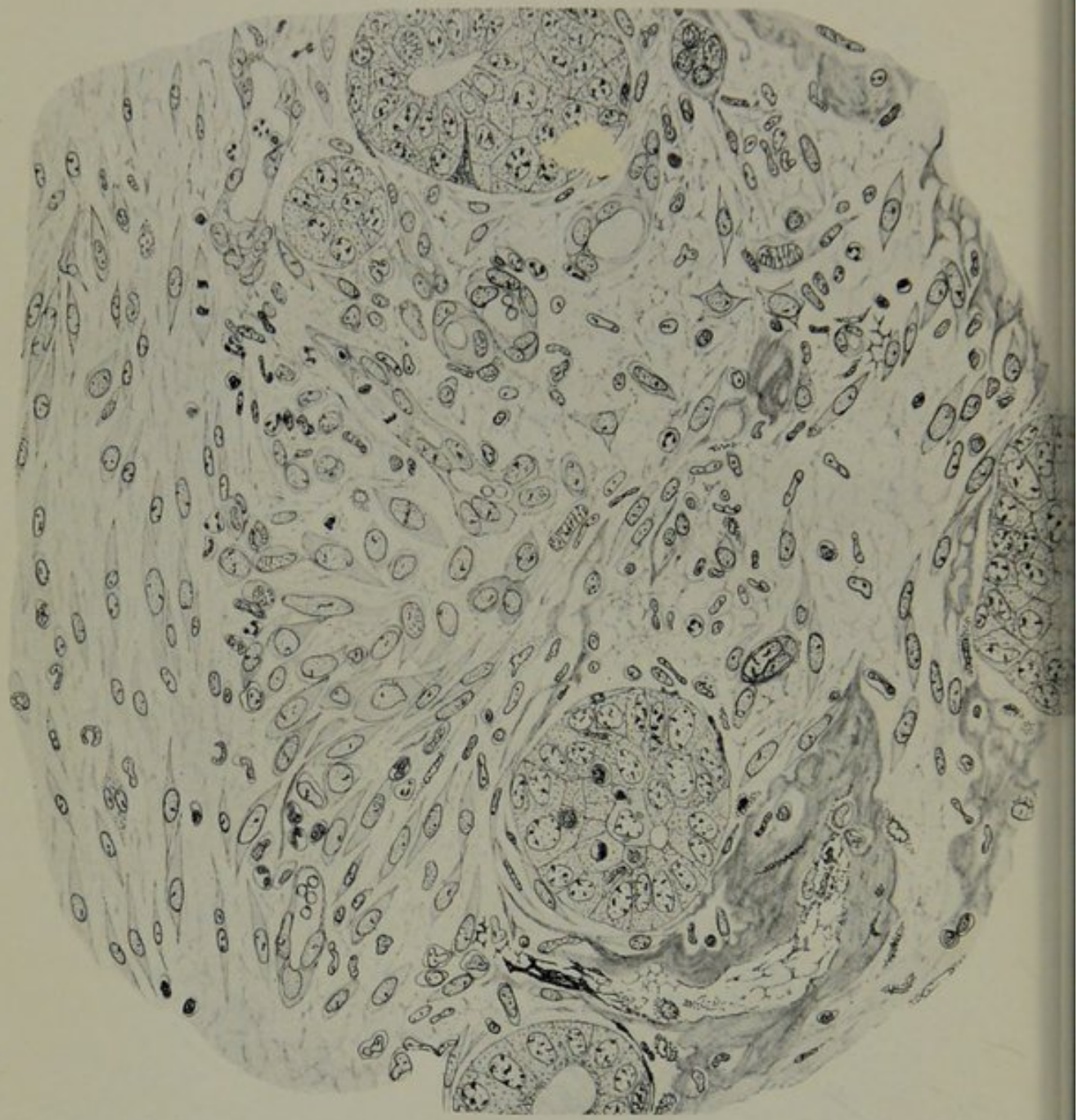

FIG. 7.—Transplanted carcinoma of mouse. Site of transplantation after four days. Late stage in degeneration of introduced stroma and early stage of vascularisation. × $\frac{400}{1}$.

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FIG. 8.—Infective venereal tumour of vagina of dog. Primary growth in vagina. Transformation of connective-tissue corpuscles into tumour cells. × 400.

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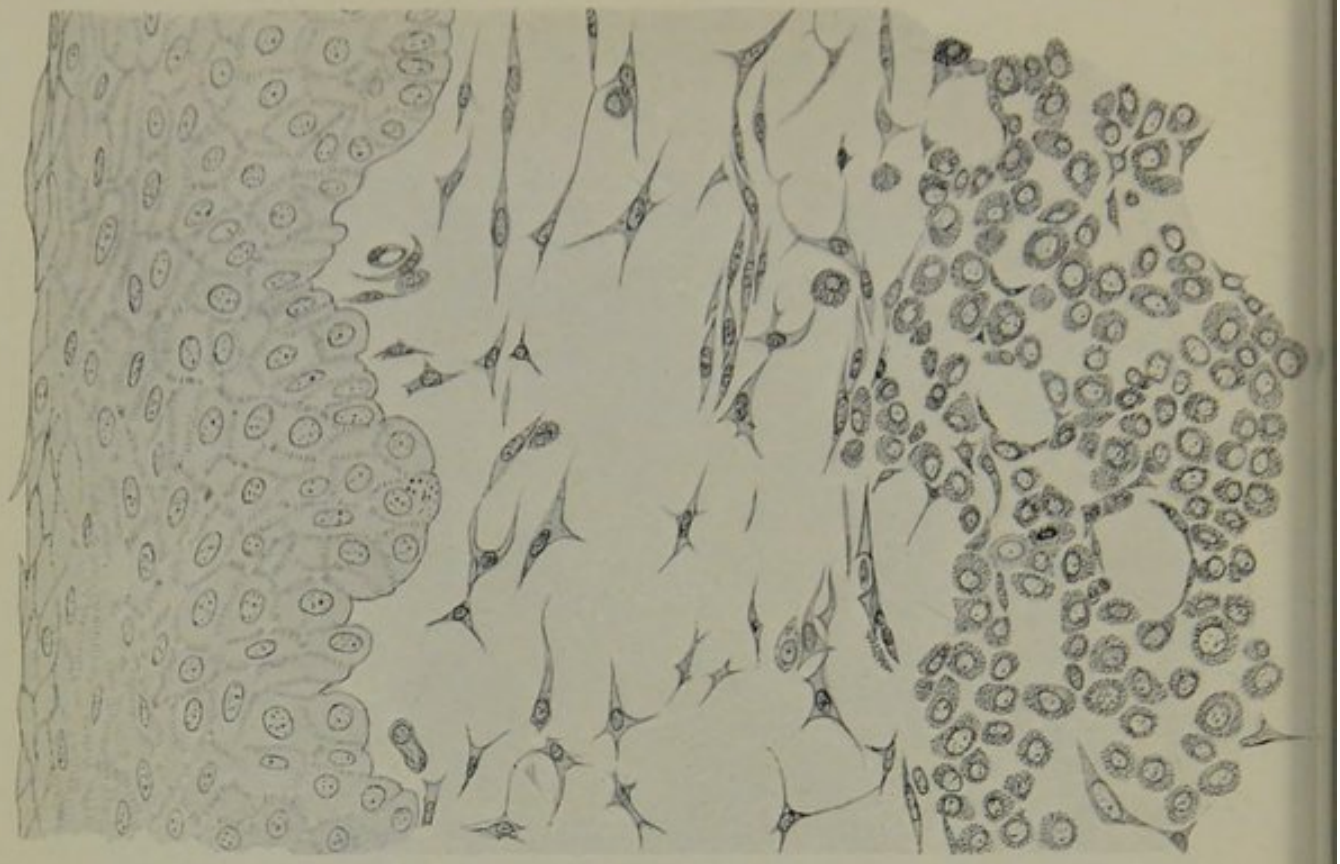

FIG. 9.—Round-celled sarcoma (mast-cells) of dog. Growing surface of primary tumour beneath skin. Shows absence of transformation of surrounding tissue. × $\frac{200}{1}$.

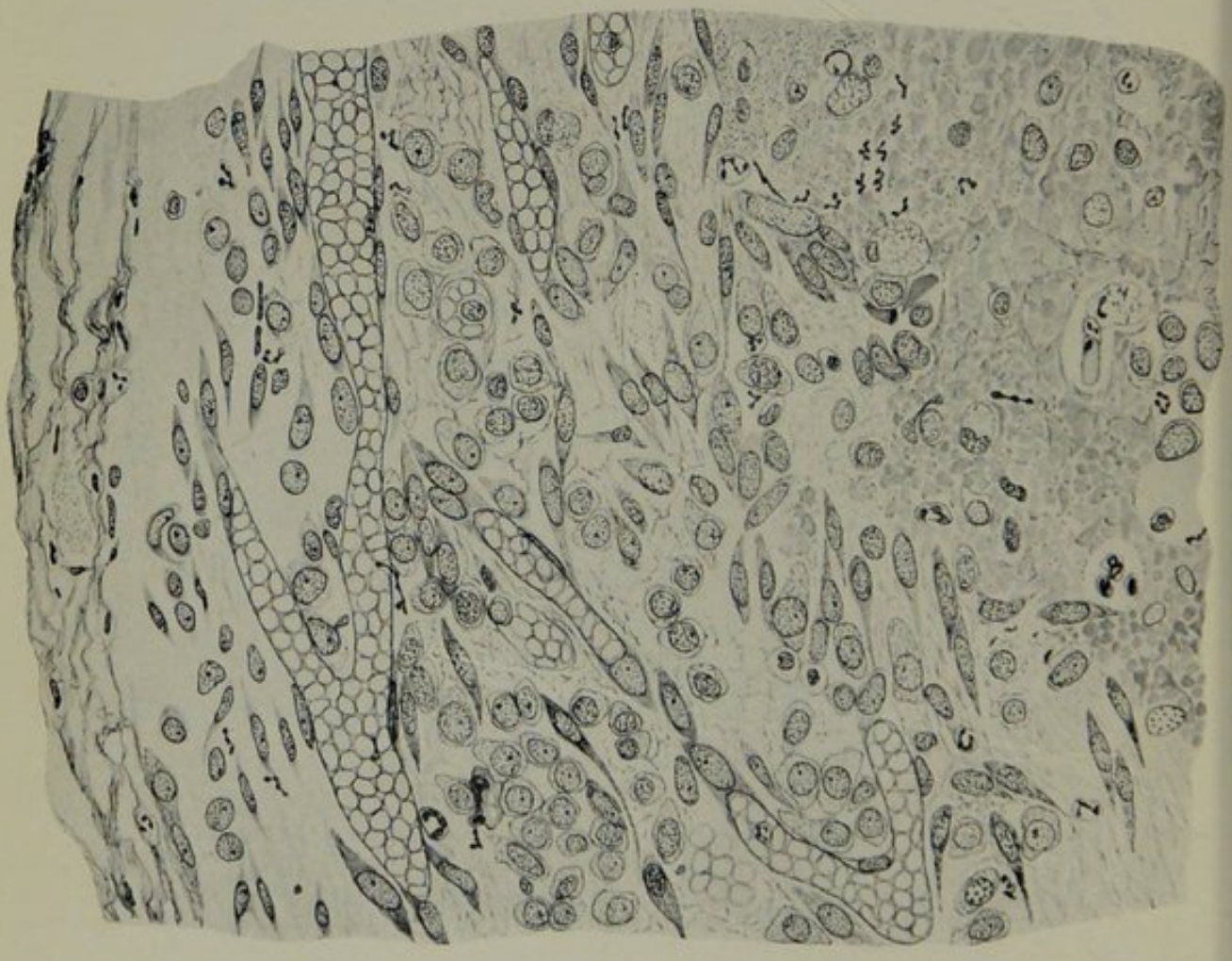

FIG. 10.—Infective venereal tumour of dog. Site of transplantation after forty-eight hours. Degeneration of introduced tissue and proliferation of new capillaries. × $\frac{200}{1}$.

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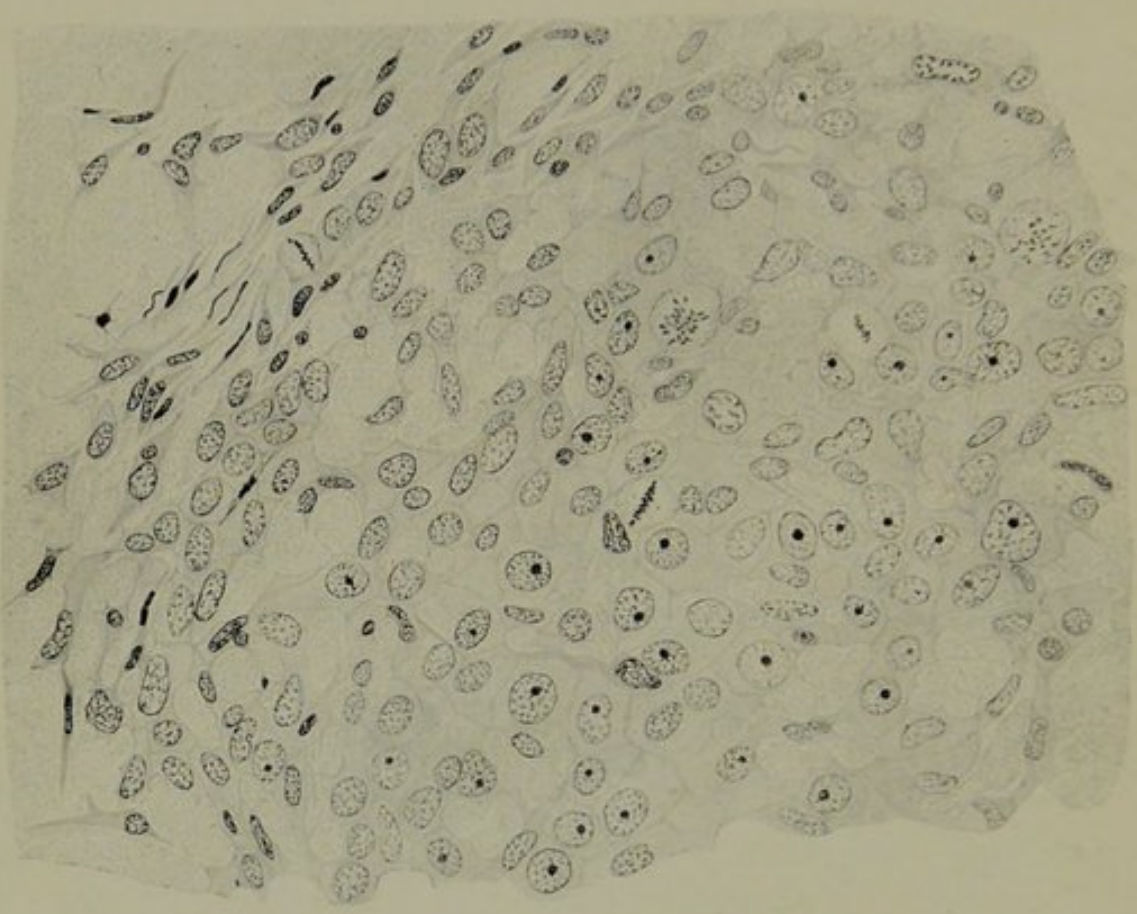

FIG. 11.—Infective venereal tumour of dog. Site of transplantation after four days. Transformation of connective-tissue corpuscles into tumour cells and mitoses in the latter. × $\frac{1}{12}$.

the case of the mouse and human subjects, in accordance with the laws which govern their respective developments, so if there be stages in the growth of cancer, they may also be adapted to the compass of life in different animals, and be gone through more quickly for the mouse than for man. As mankind and the mouse give evidence in their offspring of how their own growth has originated, is maintained, and declines, so it has seemed rational to look for evidence of a similar kind in the undefined and apparently continuous growth of cancer. This evidence has been most conveniently sought for in short-lived animals, and there also most readily interpreted with the assistance of experiments. Such observations are entirely impossible in the case of man, and are not always practicable in the case of animals.

Nature of Artificial Propagation.

Malignant new growths are said to be physiologically and morphologically independent of the needs of the organism primarily affected. This character of relative independence appears in its highest degree in the successful transference of malignant new growths to new hosts. The power of unbounded proliferation is also most clearly demonstrated in these circumstances. I need not pause to contrast the limited proliferation which follows the transplantation of other animal tissues with that of cancer under the same conditions. The artificial propagation of a malignant new growth by transplantation into a new host of the same species, or into a new site in the case of the organism primarily affected, is attended with difficulties which are not easily overcome. A large number of transplantation experiments have been performed in the horse, cow, dog, and cat, all with negative result.* In the rat malignant new growths have been transplanted successfully, and in the mouse about a dozen different tumours have been transplanted under the precautions which are necessary to establish unequivocal nature of the result. In what follows I shall rely mainly upon the details of the experimental observations of the Imperial Cancer Research Fund upon the successful propagation of five different sporadic carcinomata through several generations of mice, and for comparison on the

* In the positive cases reported, sufficient care has not been taken to exclude the mere inoculation of infective material from various forms of granuloma, and a detailed examination of the successive stages at the site of inoculation has not been carried out.

study of the processes which result in the production of large tumours in the case of an infective granuloma of the dog. An unfortunate misconception of the significance of the facts has led to the nature of the experimental propagation of cancer being confounded with that of the infective processes, from which it differs fundamentally. The experimental propagation of a malignant new growth means neither more nor less than the continued proliferation of the cells of one animal in another animal. It may also be practised on the same animal without, however, modifying its significance. The parenchyma cells of the tumours which arise at the new sites are the direct genealogical descendants of those introduced. They are not provided by the host. The process is as remote from being of an infective nature as that responsible for the formation of secondary deposits, with which it is strictly comparable. What reaction there is on the part of the host is limited to the supply of the vascular and supporting structures which the parenchyma cells—displaying again their independence—have power to make subservient to their needs. The process of infection is wholly different. The cells of an infective granuloma, introduced at the time of inoculation, are merely vehicles—living substitutes for the platinum loop—for the conveyance of the infective agent. There are infective granulomatous tumours closely resembling sarcomata, of which the causative agent cannot yet be isolated, and is not recognisable by any method known to us. In these cases also the process of infection which follows inoculation with portions of the granulomatous tissue is identical with that which occurs after inoculation with isolated pathogenic organisms. The introduced tissue only plays the part of a vehicle. It succumbs and is ultimately absorbed, and when new tumours result they are entirely composed of the tissues of the reaction on the part of the host. All the stages in the reaction can be traced, from the gradual transformation of the elements of the connective and vascular tissues, up to a fully-developed tumour identical in structure with that from which the original infection was derived.

In the experimental propagation of cancer the elements of the soil play the insignificant part of subserving the needs of the tumour, of which the essential part is genealogically derived from another animal. By these means a part of one animal, often long dead, is kept alive by what is really an artificial circulation provided by another. In tumours which result from infection the only con-

stituents, apart from the pathogenic organisms, are the elements of the soil themselves. Any comparison which may be drawn between the two processes is correctly limited to the differences and similarities which may exist between the nature of the reaction of the tissues of the host when pathogenic organisms or cancerous cells are proliferating in their midst. What we mean by disease is, in fact, the reaction of the tissues of the living animal to disturbing agencies of any kind. In infective conditions the reaction may result in the formation of masses of new tissue, but in the artificial propagation of cancer the reaction is a very subsidiary phenomenon, and the essential process is the continuous independent growth of the introduced parenchyma which constitutes the disturbing agency. The artificial propagation of malignant new growths yields conclusive experimental evidence, in keeping with accumulated clinical experience, that cancer *quâ* cancer does not produce specific symptoms of its presence. Malignant new growths have only been successfully transplanted from one animal to another of the same species. The cells of a malignant new growth of one animal are so much out of their element among the tissues and fluids of an animal of another species that they are unable to maintain their vitality. Their fate is probably the same as that of the blood corpuscles of a strange animal when employed in the manner in which transfusion of blood was originally practised in surgery.

General Features of Growth in Artificial Propagation.

I have already drawn attention to some of the comparative features of growth in sporadic tumours, and shall now briefly refer to some of the phenomena presented in propagated tumours. An attempt to propagate a tumour requires to be carried out under many precautions. Numerous factors have to be taken into account in interpreting the results of attempts at artificial propagation. Stated generally, the results of transplanting different carcinomata show a gradation from those which yield a uniformly high percentage of successes to those which yield a uniformly low percentage, and to others again which have given absolutely negative results. The contrast between the tumours at the top and those at the bottom of the scale, therefore, does not imply distinctions in nature, although it signifies that the respective groups differ in the degrees in which they possess the properties which adapt them to the conditions

obtaining in artificial propagation. Those specific qualities of the cells which determine the short or long duration of life of different species of animals appear to play an important part in the experimental establishment of tumours in a new host, and, further, there is also much evidence to show not only that the qualities of the cells of different tumours vary in the same species of animal, but also that they differ in apparently identical tumours, and even in the same tumour at different times. The variations in the percentage of successes, and the rate of growth in tumours of the same histological character have clinical bearings upon cancer in man, for they indicate that, in addition to the importance of the site of a primary tumour and the degree of vascularity, amount of movement, and other conditions, which have long been recognised to influence the early or late appearance of metastases (*e.g.*, in the cases of epithelioma of the tongue and the larynx), there is something else of great moment which is inherent, but not always present, in the tumour cells themselves, and without which even a suitable soil may remain free from invasion. The surgeon and the pathologist are familiar with the contradictory behaviour of malignant new growths which are reasonably supposed to be identical; how they present variations in malignancy, and how with uniform care in operative procedure uniform results are rarely obtained. The inconstancy in the qualities of the cells of the same tumour revealed in the course of our experiments is a contribution to the solution of these apparent contradictions, although it must not be forgotten that we are not yet able to express any definite opinion on the influence of the soil into which tumours are transplanted.

Cellular and Intracellular Phenomena of Growth.

When we turn to consider the more minute processes of growth—the cellular and intracellular phenomena—we find that the cells of carcinoma and sarcoma breed true. In saying that the cells breed true, I mean that any evidence they give of differentiation is in one direction only—that of the primary tumour. In the multiplication of the cells of a tumour there are several varieties of direct (amitotic) and indirect (mitotic) division. The phenomena of indirect division are the more prominent, and different authors have described the various features of the normal bipolar mitosis and several abnormal manifestations of the same process. A not infrequent abnormality

is cell division by multipolar mitosis, in which the rods of chromatin are arranged, not on one spindle with two poles, but on several spindles which converge towards a corresponding number of poles. The bipolar and multipolar mitoses, as a rule, proceed in a way which gives rise to symmetrical figures and distributes equal numbers of the chromatin rods to the nuclei of the daughter cells. However, both the bipolar and multipolar figures may occasionally appear to be asymmetrical and suggestive of an unequal distribution of the chromatin rods to the different poles. All the chromatin may not

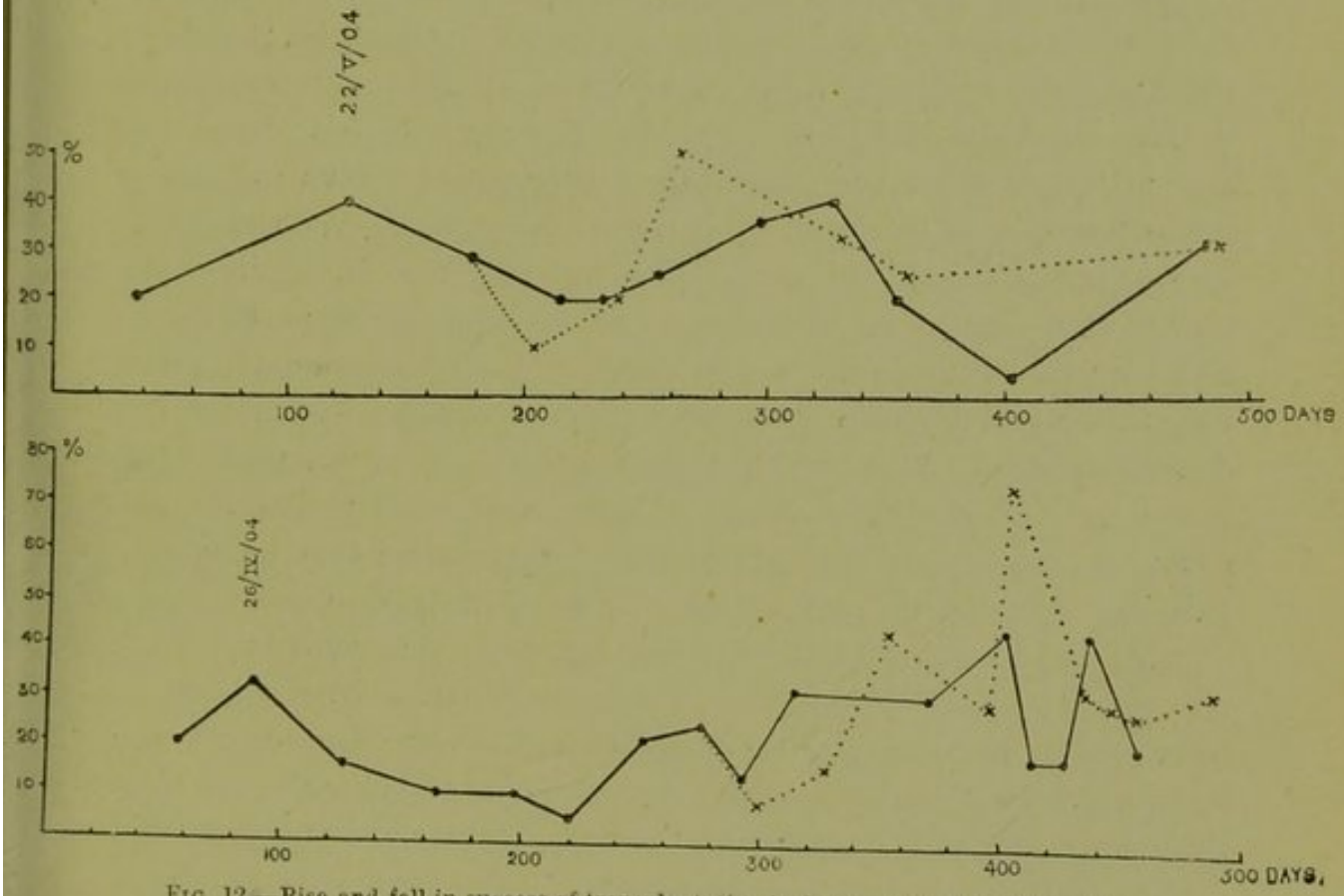

FIG. 12.—Rise and fall in success of transplantation in four strains of Jensen's tumour.

enter into the process in other dividing cells, and it is said to be "cast out." The peculiar form of cell division which prepares the reproductive elements for fertilisation has also been described in cancer, in the first instance by Farmer, Moore, and Walker. This form of cell division presents contrasts to the main features of ordinary bipolar mitosis, from which in the reproductive tissues it is readily distinguished in all its phases. Flemming, therefore, designated it heterotypical. In the reproductive tissues it results in each of the two daughter nuclei receiving exactly half the number of chromatin rods, which an ordinary bipolar mitosis would

distribute, and if the daughter cells proliferate the progeny retain the halved number of chromatin rods when in division. The halved number of chromatin rods is only restored to the full number when that fusion of nuclei occurs which is the one constant feature of fertilisation. We have pointed out that the cells which exhibit mitoses, which morphologically are heterotypical, differ in cancer from cells undergoing this process in the reproductive tissues. The differences extend also to the preparations for division and to the stages which follow it.

The various deviations in cancer from what is looked upon as the normal course of cell division are not exhausted by the above catalogue. There are other irregularities. Many dividing cells possess less than the proper number of chromatin rods; it may be half or less or more than half this number, others have too many. These two groups of nuclei were named respectively hypochromatic and hyperchromatic by von Hansemann. The hyperchromatic nuclei arise by preparation for a cell division which is, however, omitted, and perhaps also in other ways. The hypochromatic nuclei may arise by multipolar or by asymmetrical mitoses, by casting out of chromatin, or by the heterotypical mitosis. It is not possible at present to tell by what method a cancer cell which is dividing has come to possess too few chromosomes, even should they be exactly half as numerous as they ought. There is thus a confused series of normal and abnormal phenomena going on side by side. With one exception, all the abnormal phenomena have been shown to occur—although they are less frequent—in the processes of chronic inflammation, in benign tumours and elsewhere; but sufficient time has not yet elapsed to permit of a proper estimate of the significance of the heterotypical mitosis in cancer.* We have already stated that it is not a constant feature of malignant new growths.

All attempts to unravel the confusion of cell division in sporadic tumours have failed to pick out the essential from the negligible phenomena. If our knowledge of how the growth of cancer is maintained is to advance, the hitherto unsurmountable difficulties presented by the apparently disorderly phenomena of cell division must be overcome. In artificially propagated tumours the diffi-

* When this lecture was delivered, I was of opinion that certain mitoses observed in a case of chronic superficial glossitis exhibited the morphological features characteristic of the heterotypical mitosis. Further examination has not confirmed this opinion.

culties fortunately give promise of being more easily surmounted. Our long-continued observations on many generations of transplanted tumours have yielded the valuable results that a tumour maintains unaltered its general histological characters under the longest propagation yet attained, and also the minute cell characters, including the nature of the differentiation, and that constant number of chromosomes which is normal to the tissues of a healthy animal. Cell proliferation proceeds throughout all generations chiefly by typical bipolar mitosis. The various forms of irregular cell division which are such striking features of sporadic tumours are less prominent, and the process of proliferation becomes more orderly. Throughout many generations there can be no question of the proliferating cells showing too many or too few chromosomes. Yet at recurring intervals, which coincide with the reappearance of several other phenomena, the heterotypical mitosis is found distributing half the normal number of chromosomes to the daughter nuclei. Since in other dividing cells the normal number of chromosomes is retained, it follows that if the heterotypical mitosis is anything more specific for cancer than the other irregularities present in sporadic tumours, it must be an essential phase intercalated in the process of growth. Fusion of the daughter nuclei would be necessary to restore the normal number of chromosomes, and might be expected to establish powers of proliferation and of relative independence such as follow the nuclear fusions of fertilisation, and to result in behaviour similar to that of an organism of a succeeding generation towards the one which has preceded it. Otherwise the heterotypical mitosis can only be an incident by the way in a continual vegetative proliferation by normal bipolar mitosis. If the first interpretation is correct, then the apparently uninterrupted growth may be further analysable. We may then expect it to be a discontinuous process maintained by an orderly series of cell changes—though with our present knowledge they appear disorderly—and the explanation of the stages through which the cells of fully developed tumours pass in the incessant renewal of proliferation, will indicate the nature of the changes which set the growth agoing.

We can form an opinion of the stage at which the heterotypical mitosis will be intercalated in the growth of cancer. In animals and plants this mitosis marks a terminal phase in cell proliferation, and ushers in the preparatory stages for the sexual production of a succeeding generation. It is permissible to draw an analogy with

cancer and to interpret the heterotypical mitosis there as a terminal phase of growth. In the artificial propagation of Jensen's tumour, we have only been able to convince ourselves of the occurrence of the heterotypical mitosis at definite intervals, and then always in association with other recurring phenomena, notably the establishment of intimate secondary connections between the nuclei of adjacent parenchyma cells. It will be obvious why cancer need not always follow upon the final stages of cell multiplication but only when the process of nuclear fusion, in whatever manner it be attained, has been properly consummated, to secure which there is no special mechanism, and consummation is therefore attained even more rarely than in the case of the sexual elements, to secure the union of which one is provided.

Attention has been drawn to the fact that all hypotheses in explanation of the origin and nature of cancer break down, not only in not explaining how growth is maintained, but also before the problem of the peculiar age incidence of the disease. Several investigations have shown that time limitations modify the fundamental features of cancer in an important way. The effects of time cannot be explained on the assumption that the growth of cancer is uniform and continuous. They harmonise with the features of a form of proliferation which is incessantly renewed and therefore support the cytological observations. The relations which exist between time and various features presented by cancer all bear upon the explanation of the increasing frequency of the disease as life advances. Different but definite limits are set to the rate of growth, to the size of the body—*i.e.*, total amount of growth—and to the duration of life in man and animals. A parallel can be drawn between those specific characters and the equally specific age incidences of cancer. They are all dependent on factors innate in the different forms of life, and the time when malignant new growths appear is as much determined by the biological laws peculiar to each species of animal as are the form of the body and the absolute length of life.

The span of life of the individual is not the same as that of the separate organs and tissues which have contributed to its maintenance. Some organs and tissues early attain full development and disappear; others are only active during adult life; and others, again, as long as life lasts. The age incidence of cancer in different organs presents contrasts similar to those found in species with long

and short lives. Other factors, however, greatly modify the mere influence of time, and we do not perceive in the organs of an individual the sharp distinctions exhibited in the representatives of different species. There are, however, indications of such differences. To take only one or two instances from human pathology, the chorion has a short life, and chorion epithelioma appears at an interval after fertilisation which corresponds to its old-age stages of proliferation. The mamma and the uterus attain maturity more slowly, and are active for a relatively longer time, but carcinoma

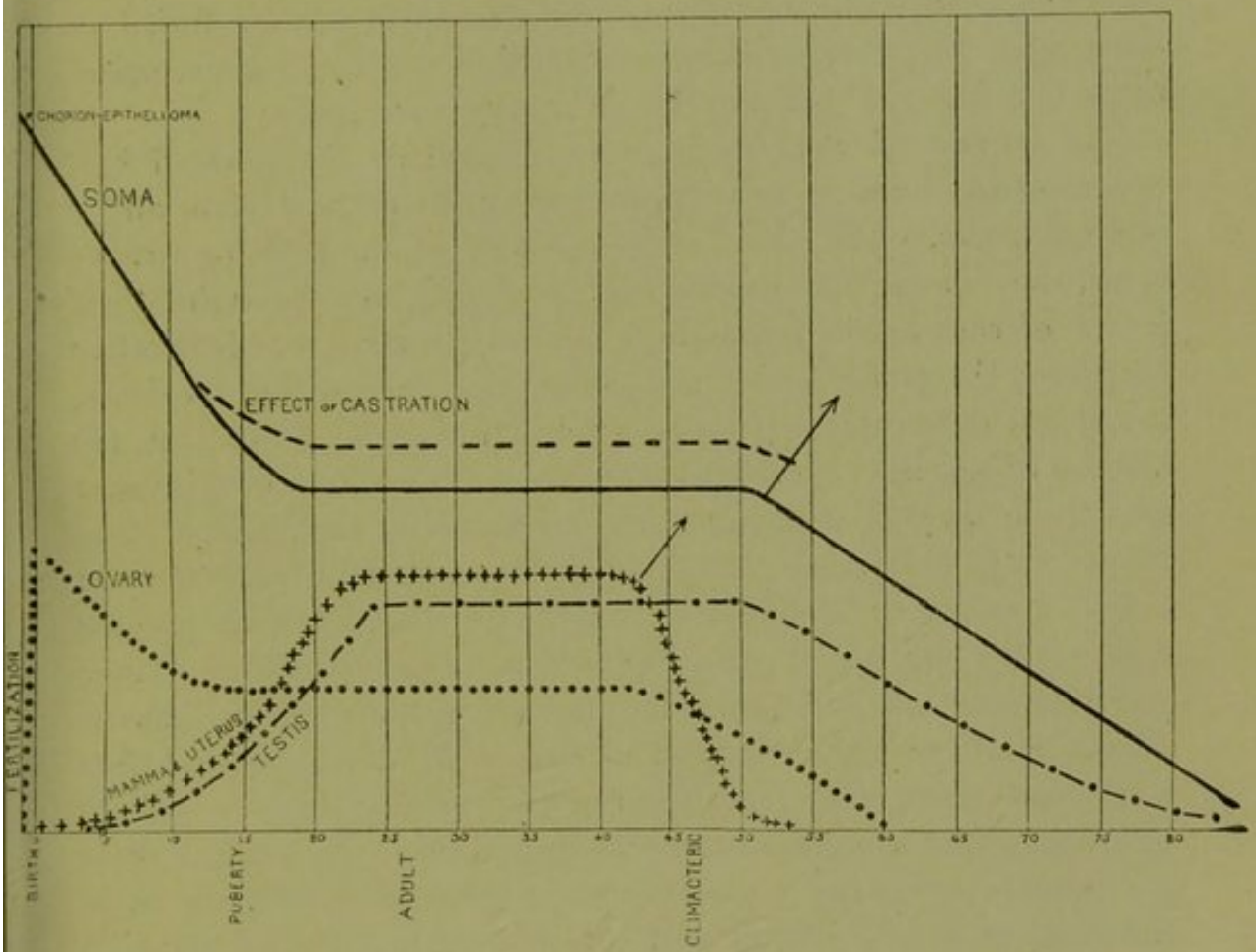

FIG. 13.—Diagram representing the progressive diminution in cell proliferation as life advances in the body generally and in some of the more important tissues. The time of frequent appearance of carcinoma in different tissues (chorion, mamma, and uterus, skin) is indicated by an arrow at the time when their proliferative activity begins to decline The skin is taken as a type of the strictly somatic tissues, and is represented by the continuous black line.

has its highest incidence when the organs are undergoing involution. The skin remains functional long after middle life, and the age at which squamous-cell carcinoma is most frequent corresponds. As the compass of life determines the general incidence of cancer in a species, so also the same factor helps to determine the occurrence of malignant new growths in different sites in any one animal. The

age at which the maximum incidence of cancer occurs in any one species results from the combined action of the factors which have been discussed ; but at special sites there may be contributory causes whereby the final stages of proliferation are attained more early, where, *e.g.*, chronic irritation or injury has led to excessive cell multiplication. All the many modifications which time limitations effect on the characteristic features of cancer support the conclusion from the experimental and cytological observations ; and the view that the unbounded growth of cancer follows on the terminal phases of normal cell multiplication in consequence of nuclear fusion, or some other at present unknown equivalent for fertilisation, makes the age incidence of the disease a necessary consequence.

The provisional working hypothesis based on the study of how cancer grows requires no subsidiary assumptions to explain all its other features. The circumscribed nature of the primary area, or areas, the relative independence of malignant new growths, their power of continued proliferation, their destructive and infiltrative character, the formation of metastases, the peculiar age incidence, the single differentiation, transmission with all its limitations, the absence of a specific symptomatology, and the addition of malignant growth to congenital tumours, are all naturally explained if it be true that the cells of the body and embryomata tend sometimes in the final stages of proliferation to undergo changes which prepare them for nuclear fusion which is occasionally consummated. These investigations are still proceeding on other tumours of different character, and no claim whatever is made to finality in laying before you some provisional conclusions which must stand or fall in accordance with the results of future experience. At present these provisional conclusions possess the great value of stimulating us in our study of a very difficult and involved subject, and of assisting us to devise means for experimentally attacking it. I may now briefly summarise the main results of the investigations.

1. Cancer is identical in all vertebrates, and in growing accommodates itself in a striking manner to the time limitations imposed by the compass of life in different animals.

2. Under favourable experimental conditions the growth of cancer is undefined, of enormous, and, so far as we can judge, limitless amount.

3. Artificially-propagated cancer displays all the characteristic features of the growth of sporadic tumours. Secondary growths

(*To face p.* 16.)

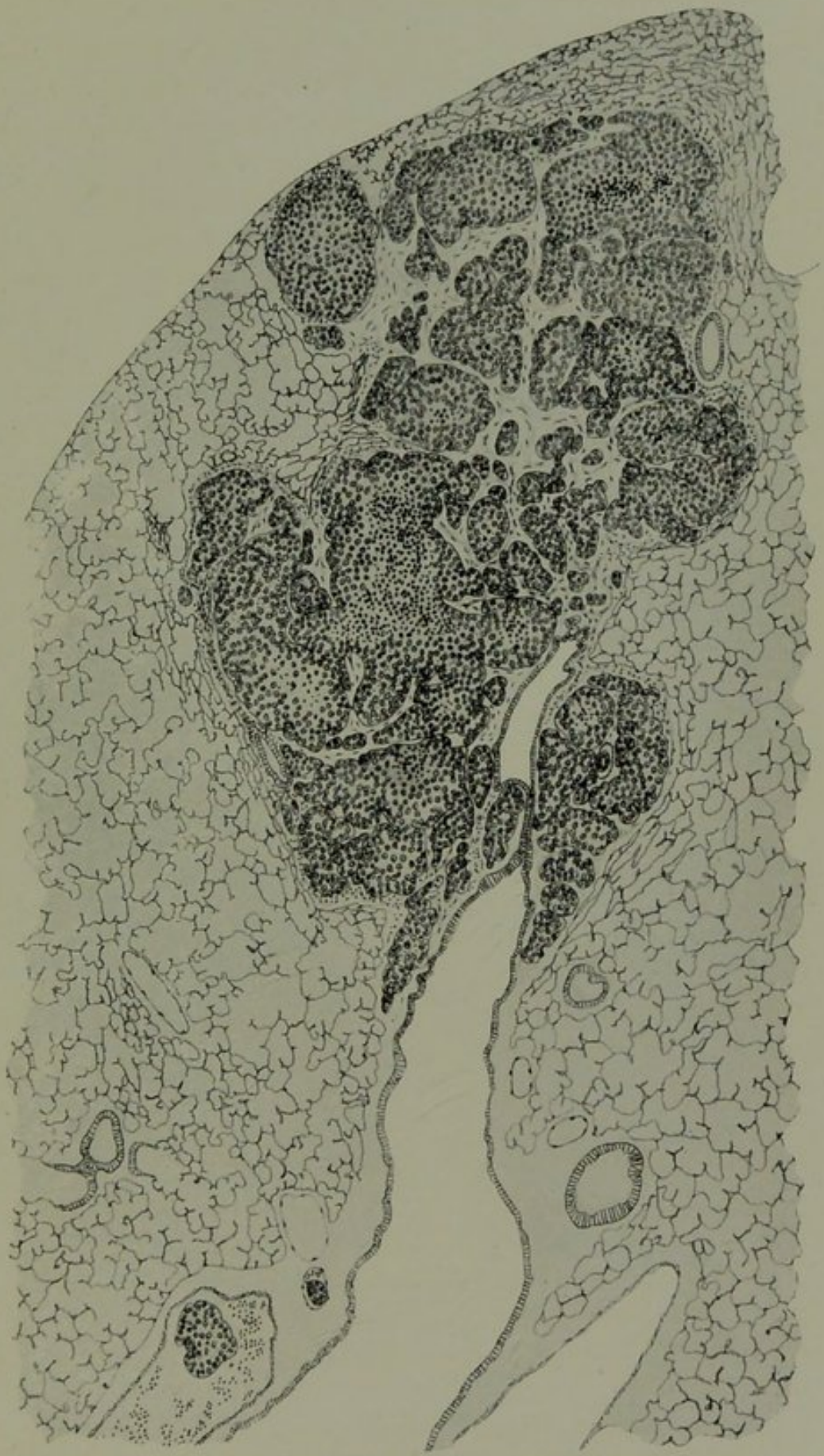

FIG. 14.—Transplanted carcinoma of mouse. Infiltrative and expansive growth of metastases in the lung twenty-six days after intraperitoneal inoculation. × $\frac{4}{1}$.

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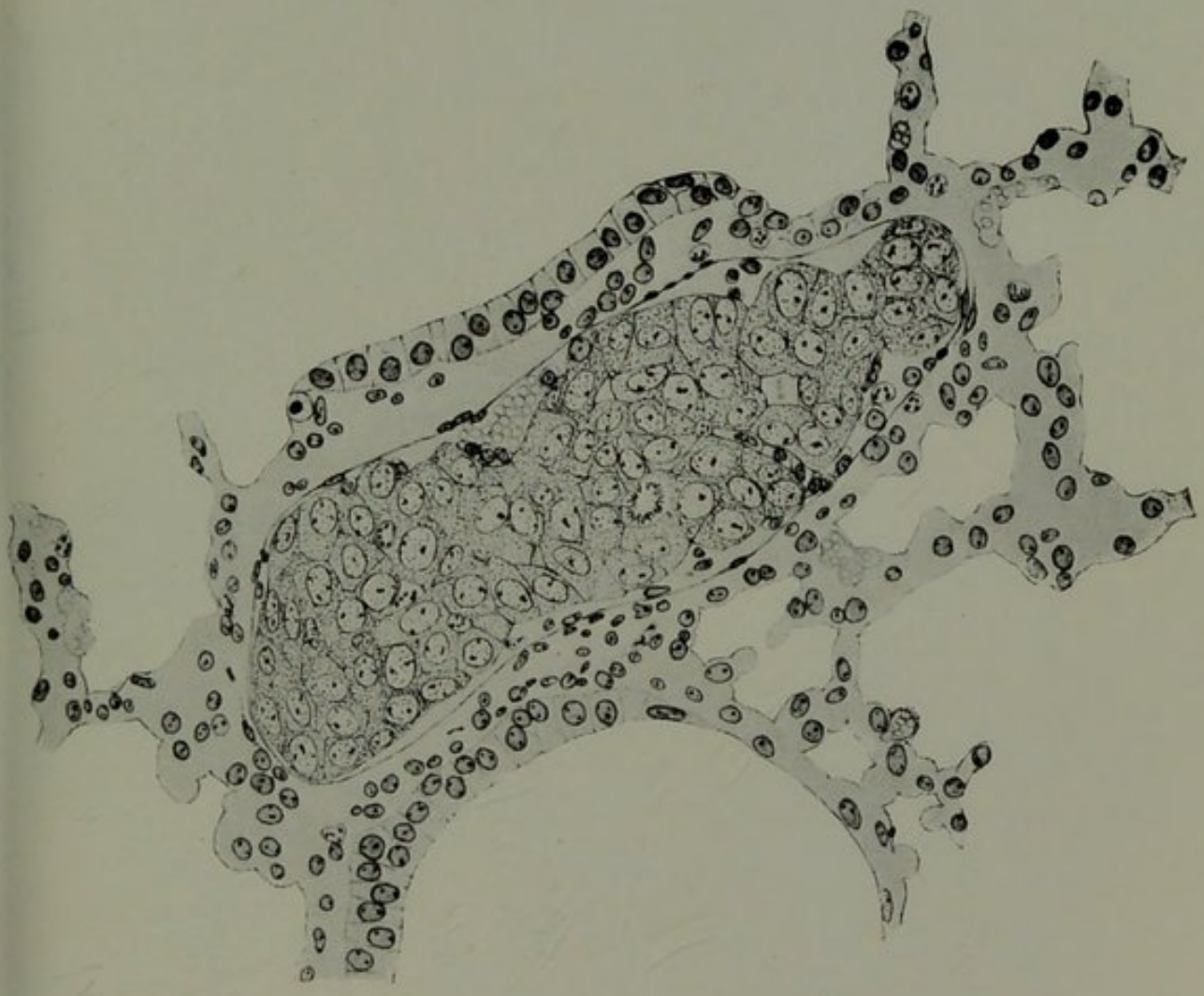

Fig. 15.—Carcinomatous embolus in pulmonary artery forty-six days after subcutaneous inoculation. × $\frac{200}{1}$.

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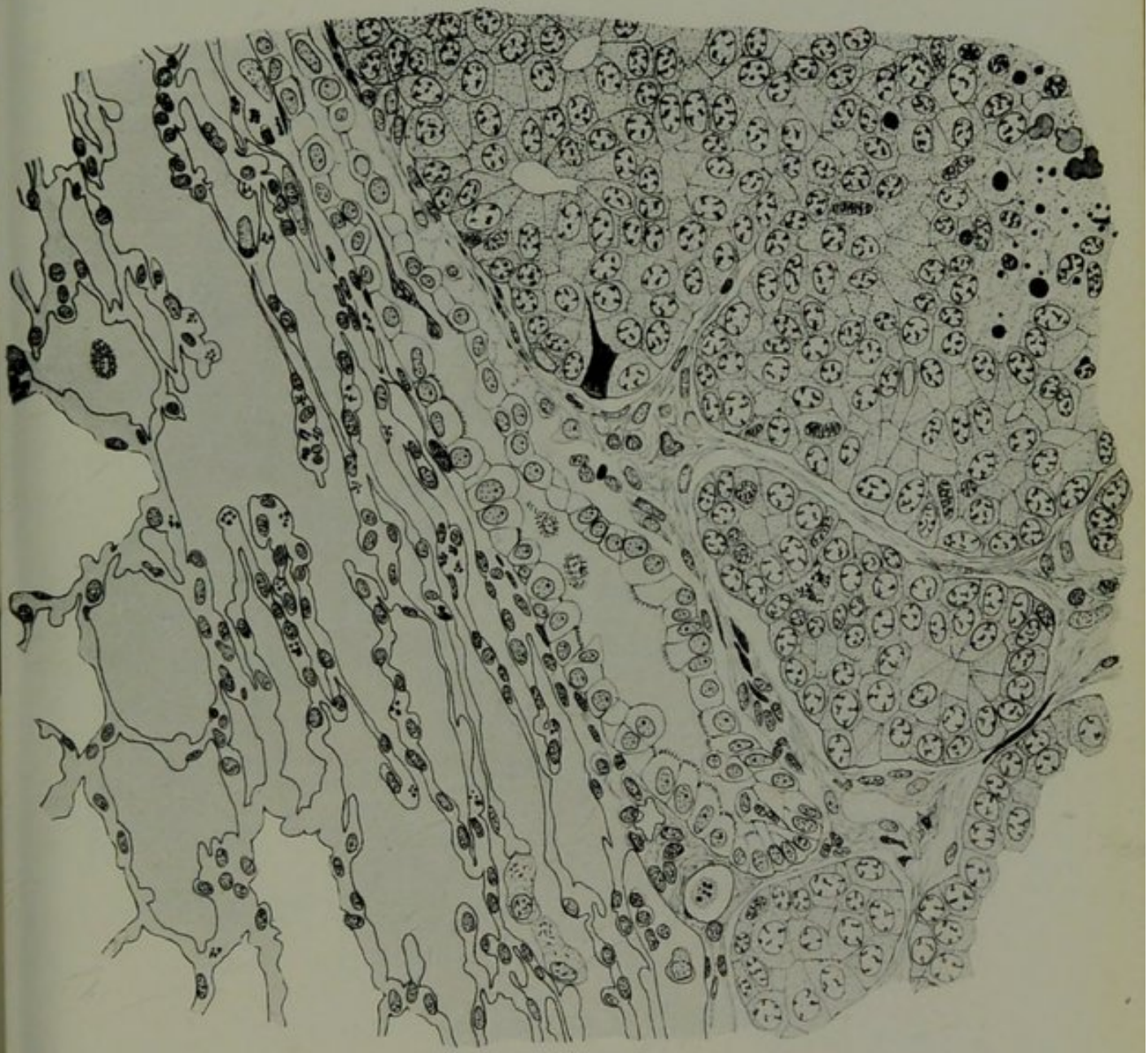

FIG. 16.—Invasion of alveoli of lung. High power of left side of Fig. 14. × $\frac{400}{1}$.

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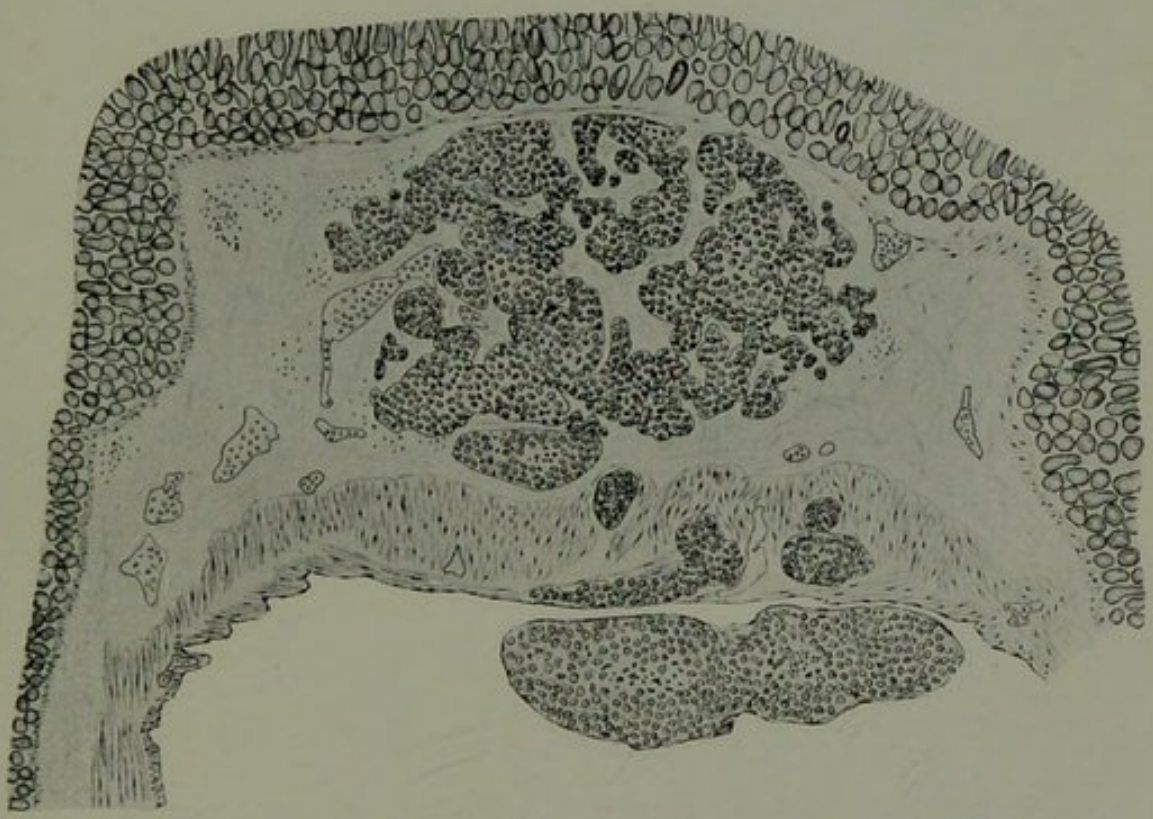

Fig. 17.—Growth invading wall of small intestine. Narrow columns of cells in the lymphatic channels of the muscular coats. Expansive growth in sub-mucous tissue. *Cf.* Figs. 3 and 4, showing the same mode of extension of a sporadic tumour. *Cf.* also Fig. 16. × $\frac{10}{1}$.

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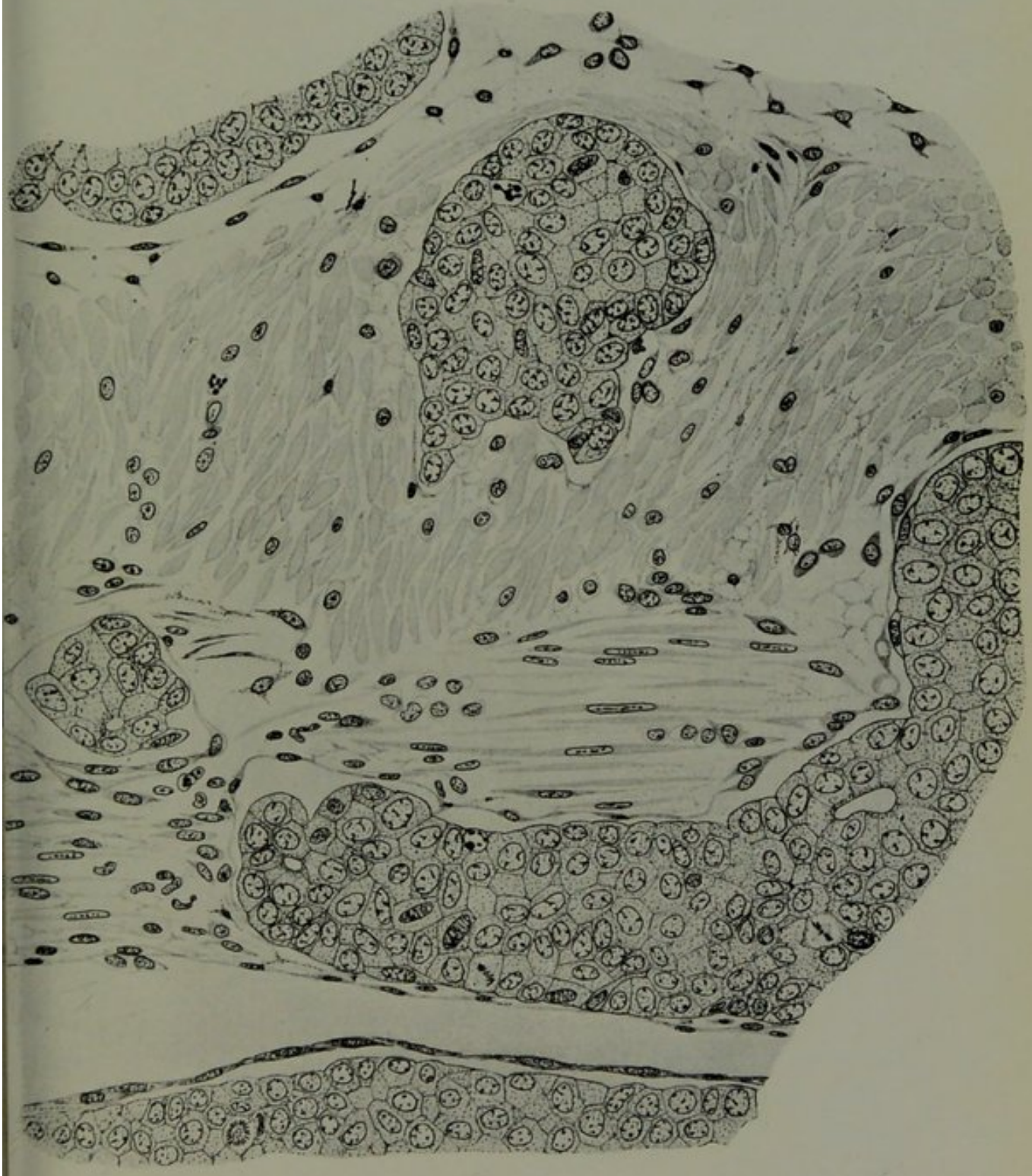

g. 18.—Details of infiltration of muscular wall of small intestine. Same preparation as Fig. 17. The lymphatic endothelium is not destroyed. × $\frac{1000}{1}$.

occur, extension taking place both by blood vessels and by lymphatics.

4. The growth of artificially-propagated cancer is due to the continued proliferation of the parenchyma cells. We have confirmed this conclusion, originally advanced by Jensen on his own tumour and on four other different carcinomata.

5. The artificially-propagated parenchyma makes the reaction of the host subserve its own needs.

6. Artificially-propagated tumours cause no symptoms in the organism to which they have been added.

7. The power of differentiation is definitely in one direction only, even three and a half years after separation from the original host.

8. The number of chromosomes constant for the healthy body tissues is retained, notwithstanding the recurring reduction of this number to the exact half, and the apparent intercalation of other irregularities.

9. The balance of evidence is in favour of the growth being interrupted and not uniform and continuous.

10. From the standpoint of therapeutics, the investigations of the Imperial Cancer Research Fund thus far establish the early surgical treatment of cancer and of the conditions suspicious of cancer, upon that experimental and rational basis which has hitherto failed. Artificially-propagated tumours produce metastases, as do sporadic tumours. Sufficiently early removal of the local transplanted tumour removes metastasis from the region of possibility, and the immediate practical outcome of the whole investigation is a strong experimental justification of early operation in cancer. We have made many attempts to modify the growth of propagated tumours; they have been, however, purely empirical, and must continue so until the fundamental problem which I have outlined has been solved.

We have certainly not ascertained all the truth, and it would be rash to forget that the positive experimental results are at present based upon observations in mice only. This may be too narrow a basis, and I must therefore protest that I do not appeal to you in support of any hypotheses explanatory of the nature and origin of cancer, but simply in advocacy of the necessity for further investigation into how cancer grows, in the hope that we may determine why it grows. I have laid before you a provisional interpretation

of the few isolated observations we have made thus far, with the conviction that it is capable of being tested by investigations now progressing, and this is a very different matter from taking refuge from criticism in a postulate which cannot be submitted to objective investigation.

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