Carcinoma mammae in the mouse / by E.F. Bashford and J.A. Murray.

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CARCINOMA MAMMÆ IN THE MOUSE.*

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FROM the outset of the investigations of the Imperial Cancer Research Fund, in October 1902, every effort has been made to give effect to the desire of the Executive Committee to develop the experimental aspects of the study of cancer. In directing the attention of other investigators to the experimental study of cancer we pointed out that, in the first place, it was essential to be sure we were dealing with malignant new growths comparable to those of the human subject [1]. We have carefully satisfied ourselves of the carcinomatous nature of the growths on which our experimental observations have been based, but have purposely avoided burdening our papers with details of descriptive pathology [2]. We have been equally careful in regard to sarcomata and have even excluded growths which other observers have claimed we should have included—*e. g.*, certain venereal tumours of dogs. As regards the latter, we may say at once that we believe the course of events during the past four years has justified our caution. The high degree of natural infectivity, the constancy of the site of occurrence—viz., the genital organs—and the ease of artificial infection of healthy animals, as well as the processes responsible for infection, showed that those tumours differ from other sarcomata which they resemble histologically. We concluded that the tumours were an infective venereal disease of dogs, perhaps comparable to syphilis of man [3], or better to granuloma pudendi. Sticker [4], Ewing

* The superior figures occurring throughout the article refer to the bibliography at the end.

and Beebe [32], and others, have opposed this conclusion, but Apolant [5] in the most recent paper from Ehrlich's Institute acknowledges its correctness practically in our own words [3], even to adopting the analogy with syphilis.

In some of our earlier papers we have devoted great attention to the artificial reproduction of the natural lesions of cancer in mice [6] owing to its importance as a starting-point for experiments. Detailed attention has been given to the nature of transplantation, to the interchangeability of expansive and infiltrative growth, and to extension by the blood-vessels and lymphatics ; in short, to the reproduction of all the features of the primary or sporadic tumours. Although the evidence thus advanced must appear convincing to all who have studied it in unbiased fashion, the experimental study of cancer has been subjected to much criticism, both at home and abroad. It seems necessary to meet this criticism in the frankest manner. At home some of it has been deliberately designed to inspire distrust in the experimental study of cancer, and particularly in that aspect of the work of the Imperial Cancer Research Fund, the only institution avowedly engaged in its pursuit in this country.

In the present paper are described certain anatomical and pathological features of sporadic tumours of the mouse. Detailed descriptions of a large number of similar tumours will be given by Bowen, Haaland, and ourselves in the Third Scientific Report now in course of preparation. The anatomical distribution of the tumours will be shown to correspond to that of the mamma. The histological differentiation they present will be referred to the normal histology of this organ in the mouse. The local infiltrative extension of the growths at their primary sites will be described. The formation of metastases by way of the blood and lymph streams will be clearly set forth. The evidence, added to what we have already published, leaves absolutely no reason to doubt that these tumours are epithelial new growths of the mouse, that they are malignant, and identical in nature with similar malignant new growths of the human subject. Therefore the results of experiments based on them must have direct importance with reference to the study of the disease in man, provided of course due caution be exercised when making comparisons between man on the one hand and the mouse on the other.

The development of the experimental study of cancer in the last four years has been achieved almost entirely as a result of the relative ease with which certain tumours of the mammary region of the mouse can

be propagated artificially in normal animals of the same species. This line of inquiry has advanced rapidly. The new and interesting points of view opened up have engrossed those actively engaged in the work. They have proceeded to obtain new light on the nature of cancer, without engaging in the laborious task of convincing all and sundry of the soundness of the anatomical and histological basis of their investigations. The negative criticism to which experimental cancer research has been continuously subjected has repeatedly shifted its ground, while new facts coming to light have more and more fully justified confidence in experimental investigations.

The objections raised against regarding these tumours as mammary carcinomata are as various as the authors who have raised them; practically no two are agreed either on their actual features or on those of malignant growths in the human subject justifying the objections. They can be grouped in three classes. 1. The sporadic tumours in mice are stated to be not cancer at all. 2. The facts elicited in the course of their experimental propagation are stated to be so out of accord with clinical and pathological observations on the human subject as to have little or no value. We shall refer to the preceding objections in detail below. 3. The third class of objections can be summarily dismissed, since they are entirely misdirected. They pertain to matters of quite subsidiary importance, compared with the larger question of whether these tumours permit us to study any form of cancer experimentally. The resuscitation [7] of the opinion of Eberth and Spude [8], now only maintained by Lazarus-Barlow, that such tumours are endotheliomata, is one example. Ribbert, while regarding them as epithelial tumours of the mamma, denies them malignancy [9] in the sense that they present characters associating them with the malignant tumours of man, mainly, it would appear, because of the difficulties of harmonising the results of experiment with Ribbert's own hypothesis of the origin of cancer. Ribbert has overlooked the fact, that the transplantation of these growths affords the experimental demonstration of his contention, that malignant new growths grow from their own resources only. Others profess to see a quite usual phenomenon in the extraordinary powers of proliferation exhibited by a mouse tumour when artificially propagated [10], namely, "nothing more than a universal and long recognised capacity in cells." The normal tissues of a mouse, or any other vertebrate, are devoid of similar powers of proliferation. They present a contrast to cancer and cannot be transferred an infinite number of times from one animal to another with retention of

undiminished powers of growth. Nor can the transplantation of cancer in the vertebrates be explained by an analogy with the propagation of the higher plants by means of grafts or cuttings. We have already considered this analogy, which so naturally suggests itself, and dismissed it [11]. Apart from its theoretical importance, the value of the artificial propagation of cancerous tissue rests on the fact that it affords opportunities for experimentally modifying the rate of cell growth and multiplication : in other words, for directly attacking that property of cancer by virtue of which it destroys human life [6].

The objection that the tumours under discussion are not cancer can be dissipated by a knowledge of their pathology and of the normal anatomy and histology of the mouse's mammæ in the immature

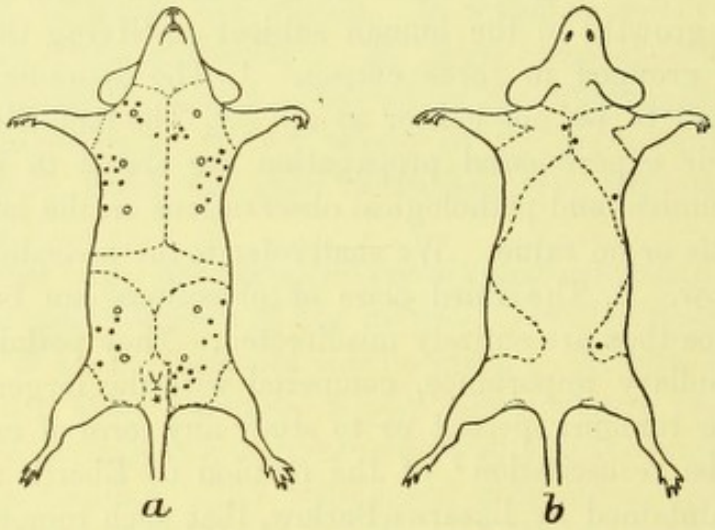

FIG. 1.—*a*, Ventral, and *b*, dorsal view of a mouse to show distribution of normal mammæ (dotted lines, nipples = 0) and the position of 42 spontaneous mammary carcinomata of which three were in males.

condition, in rest, and in functional activity. The mammæ in the mouse usually consist of five pairs of glands, occupying the sides and front of the body from the neck to the anus. In the shoulder region the gland-acini extend round the sides of the body in front of and behind the fore-limbs, meeting dorsally in the middle line. In the inguinal region there is a similar extension along the crest of the ilium and on the inner aspect of the thigh. The general distribution is shown in fig. 1, in which the position of 42 spontaneous tumours is indicated also. In figs. 5 and 6 the extension at the level of the shoulder-girdle is shown on the right side of the body, in transverse sections of a mouse with a large carcinoma in the left axilla. It is evident that the tumours

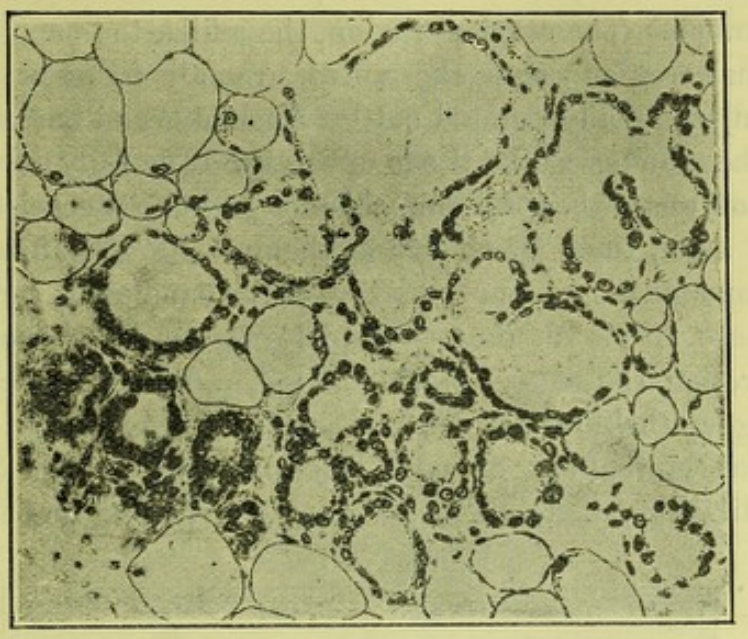

FIG. 2.—Normal adult mamma. The mouse had borne young but was not suckling. Shows variability of lining epithelium from cubical to flattened cells, according to the degree of distension of acini by secretion.

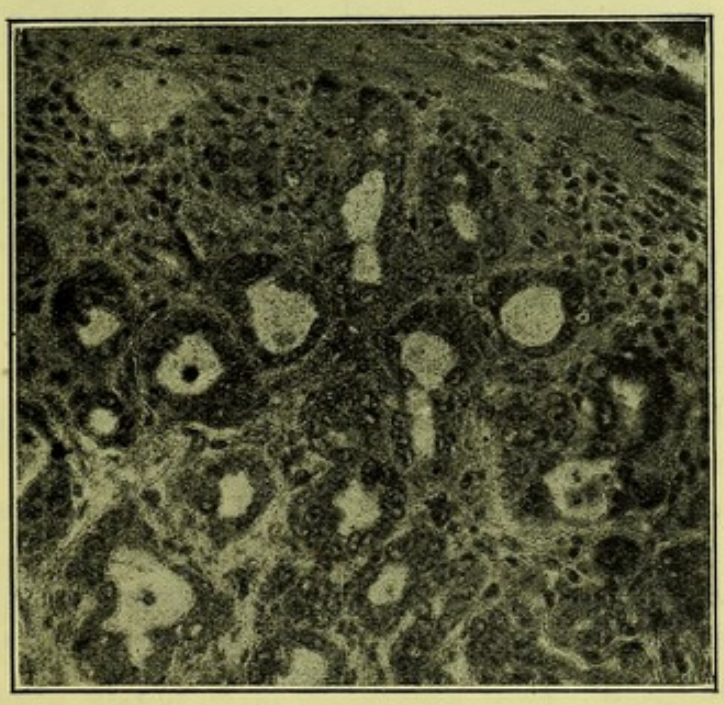

FIG. 3.—Adeno-carcinoma mammæ showing many small acini, like those of normal mamma. Figs. 2 and 3 same magnification. Note fibres of panniculus carnosus at upper part of the figure.

with which we are concerned correspond in their distribution to the normal mamma. The cervical region, the axilla, the nape of the neck, the inguinal region, and the vulva are all frequent sites. This distribution, as already pointed out by Apolant [12] and ourselves, of itself indicates the mamma as the tissue of origin. The fully developed gland in a state of rest (when the animal is not suckling), consists of delicate branching acini, lined by cubical epithelium (fig. 2, p. 5) and lying in loose areolar and fatty tissue subjacent to the panniculus carnosus which, in the mouse, forms an almost complete sheath to the body. During active secretion the acini become dilated and form branching sinuses. The lining epithelium frequently becomes stretched till it resembles a pavement epithelium or endothelium. Fig. 3 (p. 5) illustrates the gland-like characters of an adeno-carcinoma and that its relation to

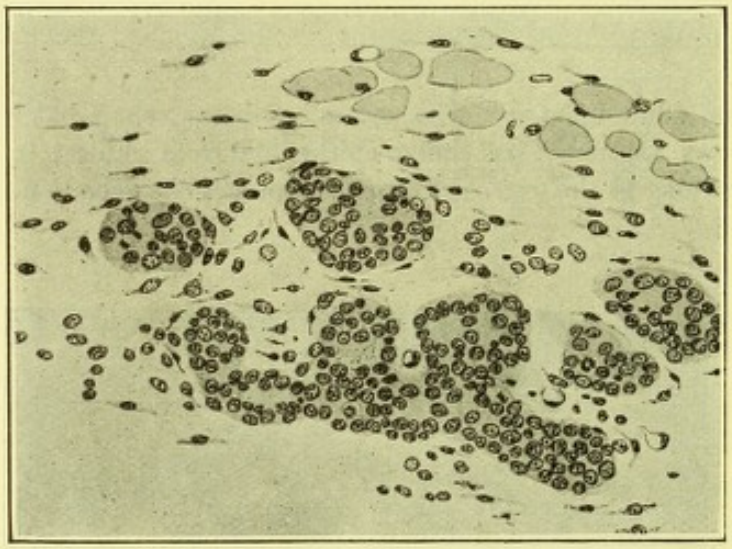

FIG. 4.—Mammary foundation of new-born female mouse. Alveolar arrangement of cells in strands subjacent to panniculus carnosus.

the panniculus carnosus corresponds to that of the mamma. In the new-born female the gland is much less extensive and forms a few branching columns of cells in the vicinity of the nipples. The acini are usually solid, although lumina can be recognised in places. For the most part, the position of the future lumen is merely indicated by the recession of the closely packed nuclei from the central part of the cellular strand (fig. 4). Cell division is frequent at this period. The gland is growing rapidly. The cells are small, and it is often difficult to say whether an individual nucleus at the surface belongs to the gland parenchyma or to the connective tissue. The tumours first

appear as roughly spherical swellings usually placed asymmetrically with reference to the nipple as in the human subject. The small size of the mouse, and the looseness of its integuments often permit this shape to be retained till the increase in size is incompatible with existence, there being a limit to the amount of tissue which the animal can support. The looseness and elasticity of the skin may permit growth to proceed without invasion of the chest wall in tumours in the axillary

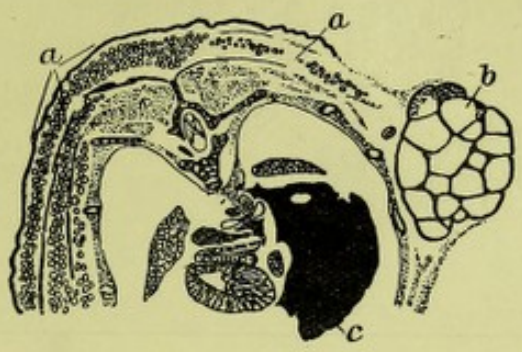

FIG. 5.—Transverse section of a mouse with spontaneous carcinoma mammæ ([19]). *a*. Hypertrophied normal mamma (lactation). *b*. Cystic mamma anterior to growth. *c*. Mass of growth replacing left lung, lower lobe.

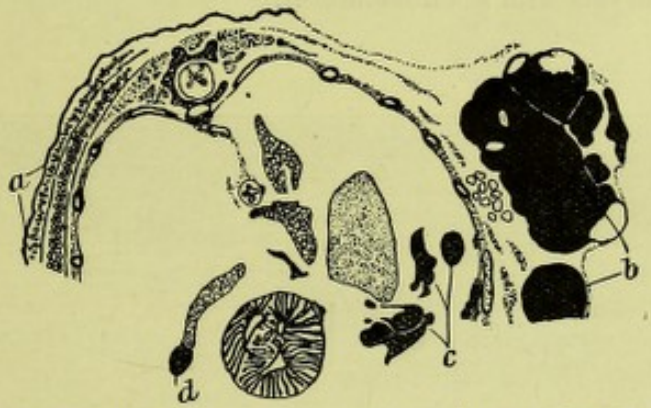

FIG. 6.—Transverse section of same mouse through growth at level of diaphragm. *a*. Normal mamma. *b*. Growth. *c*. Posterior end of growth in left lung. *d*. Metastasis in right lung, upper lobe.

region, although the lungs may be almost completely replaced by metastatic growths. Lymphatic glands in the neighbourhood may also present secondary deposits, as in figs. 7, 9, and 11. These mammary growths frequently appear, on removal of the skin, to be encapsuled completely by a fibrous layer of varying thickness. This "capsule," however, is usually invaded by strands and columns of tumour cells, as in the accompanying figure (fig. 8). The complete surgical removal of the tumours can be effected only by removing the capsule and

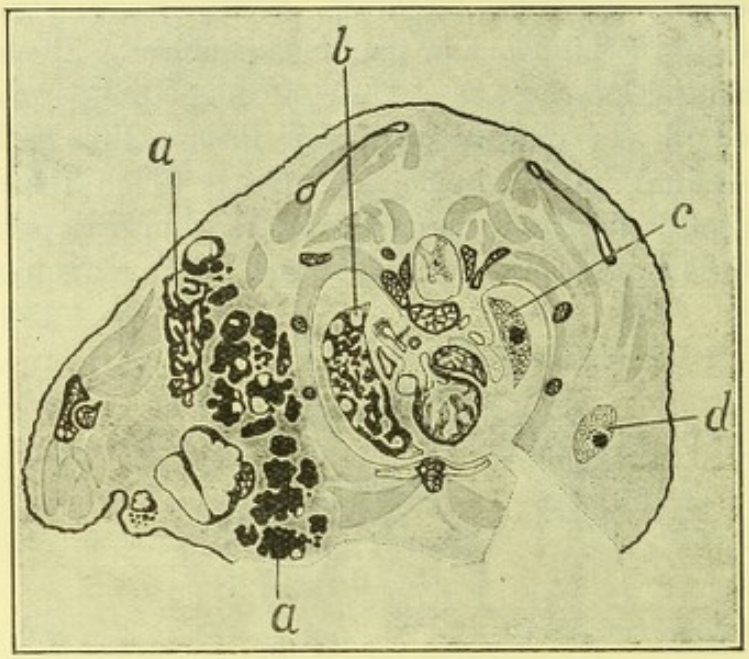

FIG. 7.—Transverse section of a mouse with spontaneous carcinoma mammæ ([25]). *a*. Primary growth in right axilla. *b*. Right lung replaced by growths. *c*. Small metastasis in upper lobe of left lung. *d*. Lymphatic gland of opposite side with small metastasis.

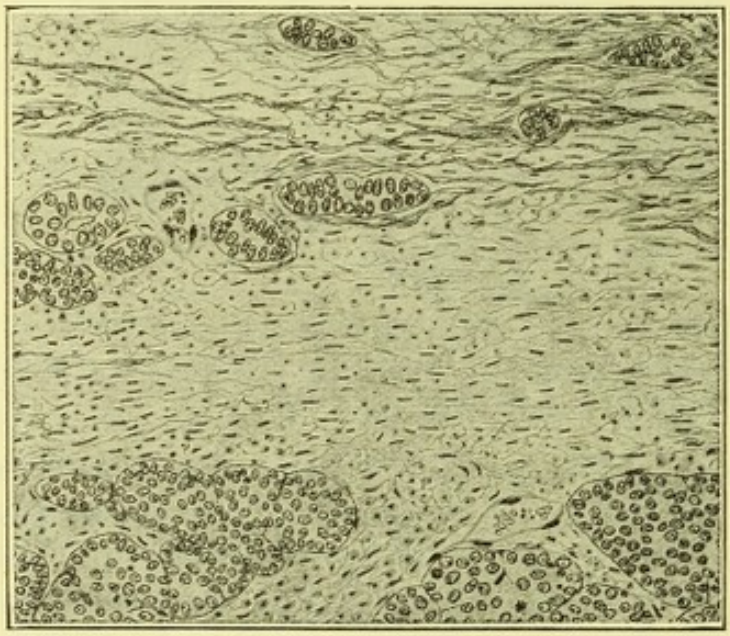

FIG. 8.—Section through "capsule" of a spontaneous carcinoma mammæ of the mouse, alveolar form. Shows infiltration of the apparent capsule by strands of tumour parenchyma.

surrounding tissues and not by shelling the tumour out of its "capsule" after incision.

When a growth arises in the limited space between the thigh and the pelvic outlet it soon fills up all the available room and then its further extension takes place in an infiltrative manner, as in the case represented in figs. 9 and 10. The thigh on the affected side is seen to be twice as thick as that on the healthy side, due to the intercalation of the growth between the muscles. Fig. 10 represents in silhouette the manner in which the growth penetrates between the muscles. The muscle fibres disappear from between the alveoli of the tumour

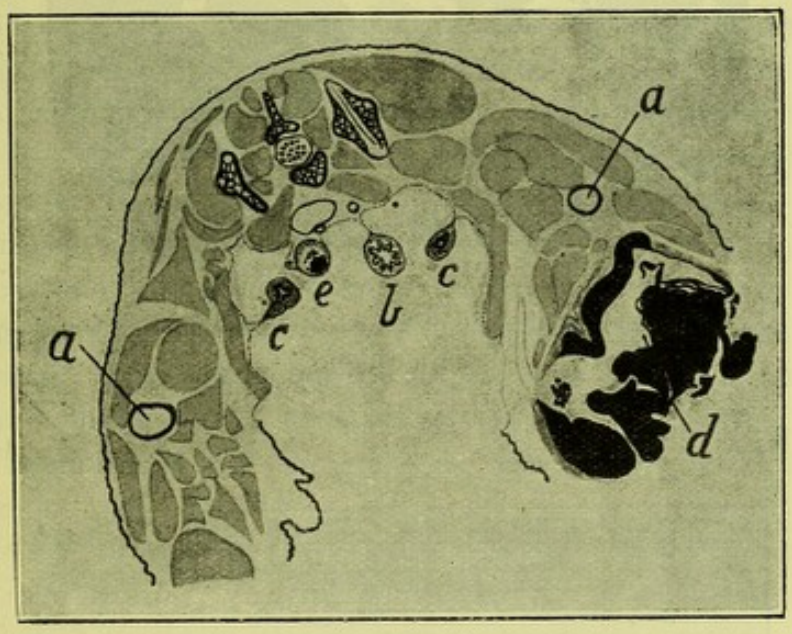

FIG. 9.—Transverse section of a mouse with spontaneous carcinoma mammæ $\left(\frac{46}{0}\right)$ of the inguinal region. *a a*. Femur. *b*. Rectum. *c c*. Uterus. *d*. Extension of primary growth into muscles of thigh; note thickness as compared with right limb. *e*. Aortic lymphatic gland with metastasis. See fig. 11.

parenchyma, apparently by pressure atrophy; there is nothing to indicate a digestive action of the tumour on the surrounding structures any more than in the new growths of man. In this case there is also extensive infiltration of the connective tissue between the vagina and rectum. After death this mouse presented large metastases in the lungs and, in addition, in the aortic lymphatic glands, as indicated in the section of the whole mouse (fig. 9) and for a lymph gland alone, under a higher magnification, in fig. 11. The asymmetrical position of the tumour nodule and the displacement of the lymphatic tissue to form a crescentic

margin indicate that growth has commenced in the marginal sinus of the gland as in lymphatic metastasis in the human subject. These illustrations show that we are dealing with new growths of the mammary region of the mouse, which grow progressively (recur after incomplete

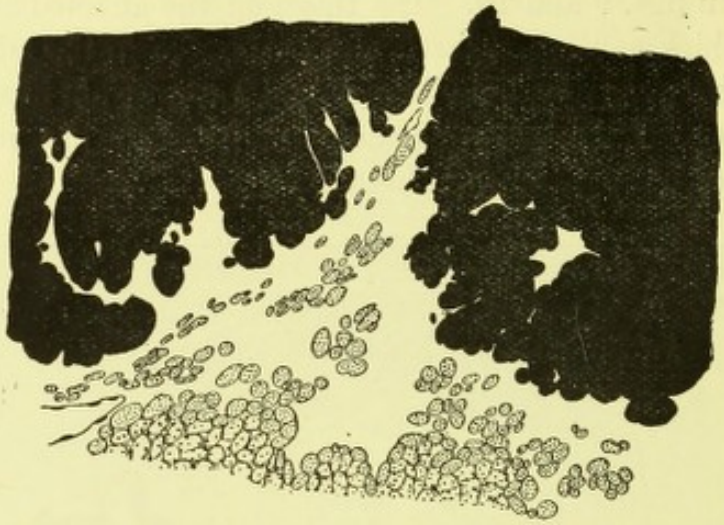

FIG. 10.—Silhouette of margin of growth where invading the muscles of the thigh.

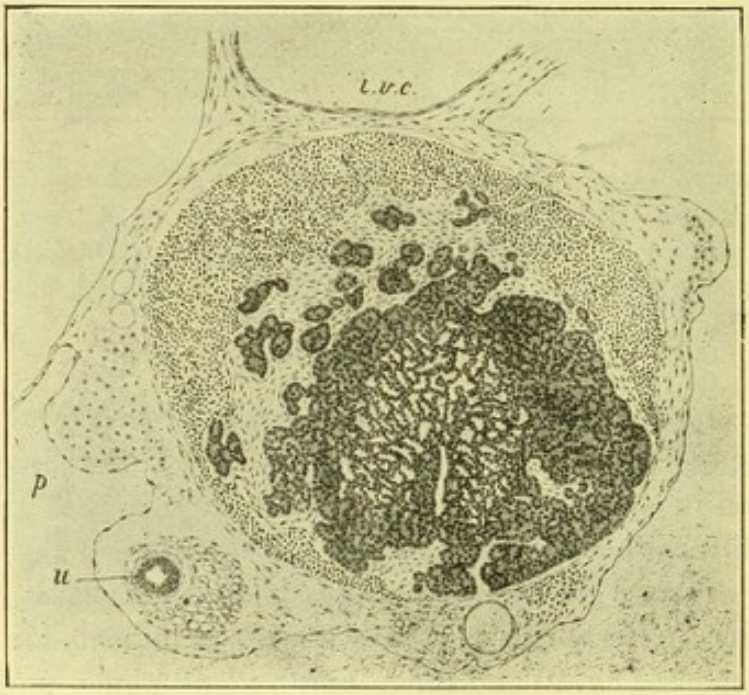

FIG. 11.—Aortic lymphatic gland with metastasis from same case.
i.v.c. Inferior vena cava. *p.* Peritoneum. *u.* Ureter.

removal), infiltrate the surrounding normal tissues, and produce metastases of the same histological type in the lungs and lymphatic glands. They lead to the death of the animal. The conclusion is inevitable that they are malignant new growths of the mamma.

We now approach the subsidiary question : Do these tumours arise from the epithelium of the acini of the mammary gland (adenoma, carcinoma), from the endothelium of the blood or lymph-vessels (endothelioma), or from the connective tissue (sarcoma) ? There are no other possibilities. The third mode of origin may be discarded at once. They are not sarcomata. A conclusion as to the histogenesis of a tumour is a reasoned judgment based on a knowledge of the histological differentiation of the tumour parenchyma and of the normal tissue implicated, in the various stages of its growth and functional activity. The actual connexion of the tumour with its parent tissue is very rarely seen, and the conclusion is adopted which harmonises most naturally with these two sets of facts—the normal histology on the one hand, and the tumour histology on the other. Bearing this in mind, it is easy to show that these mammary tumours of the mouse present a graduated series, from growths built up of small acini, indistinguishable from those of the normal resting mamma, through others, in which the acini are dilated into cystic spaces, reproducing in an exaggerated form the puerperal condition, to alveolar growths, built on the plan of the rapidly growing mammary foundation of the new-born mouse. We do not regard this similarity of alveolar carcinoma to immature normal mamma as indicating a return to an embryonic condition [13], but merely as showing that an epithelium which will certainly differentiate into a mass of acini lined by one layer of cubical cells may pass through a growth-form in which many layers of cells or solid columns of cells predominate. Therefore the presence of similarly constituted alveoli in a tumour does not preclude that they have arisen from simple acini lined with one layer of cells. These tumours present us with every imaginable intermediate stage from pure adenoma to alveolar carcinoma, and our classification must recognise the continuity of this series of histological appearances. Adenomatous and solid alveolar portions are frequently encountered in the same growth. The situations in which they occur indicate clearly, in many instances, a mechanical influence as determining the histological appearances. The transplantability of many of these tumours gives further opportunities for determining the share of mechanical conditions in modifying the histology. With the development of this line of inquiry we shall soon see that, instead of attempting

to classify mouse tumours in accordance with human histology, the results of experiment will force us to modify the rigidity of the classification now in vogue. The clinical, pathological, and cytological distinctions which even to-day it is sought to draw between benign and malignant growths break down entirely in the face of the facts revealed by the comparative and experimental study of cancer. It is becoming more and more certain that the explanation of growths in the one class will also elucidate the nature of those in the other.

Our knowledge of cancer in mice is by no means limited to carcinoma mammæ as seems to be generally believed. We have described and figured an adeno-carcinoma of the duodenum [6], and a similar case has been described by Bulloch and Twort [14] in which extensive secondary growths were present in the liver. We have also described a case in which the histological appearaces were those of the pancreas [6]. In yet another case Jensen found a large growth surrounding the kidney in a mouse which we had sent to him : it had the structure of a spindle-celled sarcoma. Haaland has described [15] a number of malignant growths in mice observed in Borrel's laboratory, and we have already reproduced a figure [16] of one of several cases of squamous-celled carcinoma of the floor of the mouth described by him. The carcinomatous ulcer in that case reproduced the appearances in the same site in the human subject very closely. The secondary growths in the marginal sinus of the submaxillary lymphatic gland are typical. The invasion and destruction of the ramus of the lower jaw complete the clinical and pathological picture in this most interesting case. Haaland has also published [17] preliminary accounts of multiple enchondromata, of chondro-sarcoma, and of squamous epithelioma of the vulva. The typical features of the last case entirely dispose of the doubts expressed by Erdheim [18] in regard to a similar growth. Haaland will describe these cases in more detail in a future communication. We cannot refrain from referring to Ehrlich's [12] important material, which includes not only very numerous mammary growths, but also chondroma and spindle-celled sarcoma. In the papers published by the many investigators who have large personal experience of cancer in mice there is not one discordant note. Michaelis has authorised us to state that he is wrongly quoted [10] as holding that the growths in mice are not cancer.

The criticism that the facts elicited by the experimental study of cancer are out of accord with clinical and pathological observations on the human subject, has done duty repeatedly with reference to other diseases. It has been brought forward whenever the first fruits of

experimental investigations have clashed with empirical conceptions—clinical or pathological. It is matter of history that it was used with effect on Villemin's early experiments on the infective nature of tubercle and applied also to Koch's monumental research in which he finally demonstrated the cause of the infection. The same battle had to be fought in the case of diphtheria. This form of criticism is one to be welcomed, for on the whole it has a salutary influence, although its volume in the past has often been merely an indication of the number of those who were unable to grasp novel conceptions or unwilling to appreciate their importance.

We wish to refer briefly to certain specific objections. Wilks[19] pointed out over 40 years ago, on the basis of experience gained in the performance of 2000 necropsies at Guy's Hospital, "the cachectic condition spoken of in cancer is a result of the disease, and does not pre-exist, and in very many cases is not present at all, and depends, as we have before remarked, upon accidental circumstances." Sir Samuel Wilks's words can be applied equally to mice suffering from cancer, either natural or induced. If we interpret recent surgical papers correctly, *e. g.*, those by Mr. G. L. Cheatle[20], our opinions coincide with his in this matter. The spontaneous disappearance of tumours in the human subject in its relation to the similar phenomenon in mice after successful inoculation, was first referred to by us in the course of a discussion at the Medical Society of London in March 1905[21]. At that meeting Mr. J. Langton and Mr. H. J. Waring recorded their personal experience of its occurrence and other surgeons have done so since. A most interesting case has been recorded quite recently by Mr. W. Bruce Clark[22]. With Cramer we have fully described the nature of the process in mice and pointed out its identity with what Orth[23] had described for epithelioma of the human tongue. In regard to mice with inoculated tumours, the importance of the phenomenon has also been emphasised independently by Clowes[24]. Clowes and Gaylord[25] tabulated the recorded cases in the human subject and confirmed our description and figures in the case of mice. Those objecting that its relative frequency shows cancer in mice is not comparable with cancer in man have entirely overlooked the fact of our statements referring to cancer when transplanted in normal animals rather than to sporadic growths in the animals spontaneously attacked. The great importance of this phenomenon cannot be denied. Its apparent novelty has, perhaps, much to do with the incredulity with which our statements have been received. In the human subject, in chorion epithelioma,

spontaneous healing of the secondary growths presents the closest parallel to its occurrence in experimental cancer. In chorion epithelioma we have a form of cancer which is naturally transferred from one individual to another by transplantation—viz., from the cancerous chorion to the healthy mother. The frequency of the spontaneous healing of the secondary growths thus occurring in the mother is a matter of common knowledge among pathologists. Mr. Pearce Gould has drawn attention to spontaneous healing of cancer of the human breast and of the secondary nodules in melanotic sarcoma. Mr. W. S. Handley has emphasised the significance of the phenomenon. On the one hand, the human organism is able to protect itself against malignant growths, at least occasionally, and perhaps more frequently than we are yet aware of. On the other hand, mice inoculated with cancer are very frequently able so to protect themselves in certain favourable circumstances.

As regards statements which have been made about the frequency of infection in mice, we have discussed this subject so often that we can dismiss it by reiteration of the facts. We have taken every care to show how absolutely distinct from all known processes of infection is the artificial transference of the disease. The establishment of this distinction by Jensen [27] and by us [1] [2] is one of the salient results of the experimental study of cancer. We have observed the effects of inoculating 60,000 mice with carcinomata. The animals have been kept under painstaking observation. The development of tumours that could be referred to infection or contagion has been observed in not one single instance. Ehrlich [12] has performed a somewhat smaller number of inoculations but has employed a greater number of sporadic growths. His experience agrees with ours. The housing of mice suffering naturally from cancer with normal animals has yielded no evidence of infection or epidemics, although our observations have now been extended over a longer period than any previous investigation and much longer than a mouse lives. The spontaneous appearance of tumours in our own and other experiments is to be explained in an entirely different way. The positive statements made in regard to infection when small animals suffering from cancer are housed with normal animals can be referred with confidence to (1) fallacious observations ; (2) erroneous deductions as we have already pointed out [28] (Morau [29], Gaylord [30]) ; and (3) unwarranted assertions by those without personal experience. In our experiments mice have developed cancer spontaneously, though not by infection. We shall have occasion to revert to this topic. We shall show also how large an allowance must be made when large numbers of

small animals are kept under careful observation, since the relative number of cases of cancer developing then more nearly approximates to the absolute incidence of the disease in animals alive in the later adult and old-age periods of life. The very positive statements about infection in the case of mice are at present devoid of all scientific value.

We are unable to comprehend why there should be a feeling that there is something mutually exclusive in the clinical, pathological, comparative, and experimental methods of investigating cancer. They are really complementary to one another, and those who have studied the publications of the Imperial Cancer Research Fund must have perceived that every effort has been made to give each line of inquiry its due importance, and to coördinate them as the respective parts of one extensive investigation. The purely clinical and pathological aspects of cancer have received a large share of attention. The statistical investigations of the Imperial Cancer Research Fund are based on the most numerous and reliable clinical and pathological data yet tabulated. In certain investigations on the earliest stages of squamous-celled carcinoma of the tongue, the ripe clinical experience of Mr. H. T. Butlin was supplemented by experience of a different kind, gained in purely pathological and experimental studies on human and animal material, with most important clinical results [16].

We beg leave to conclude that the comparative, the biological, and the experimental investigation of cancer is based not only on sound foundations, but that it is advancing our knowledge [31] of the disease more rapidly than any other line of inquiry at the present time.

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