Illustrations OF PROPAGATED CANCER.

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THE experimental investigation of cancer, long the dream of the pathologist, has emerged from the domain of probabilities into the realm of accomplished fact. Following on those of Jensen and Borrel the investigations of the Imperial Cancer Research Fund have shown that the attributes of cancer can be studied in experimental growths whose origin is not problematical but definitely known. The essential condition of possessing controls to attempts to modify cancerous proliferation has thus been fulfilled, and a new era initiated in the investigation of malignant new growths. The extent of the revolution which has thus

Fig. 1.—Sporadic mammary carcinoma of mouse. Large haemorrhagic growth (G, G) invading the muscles of the chest wall and extending into the axilla; (S) margin of reflected skin.

been effected is perhaps not yet sufficiently appreciated by the medical profession as a whole, because the quality and amount of the results already achieved are unknown to all but a few workers in laboratories who have opportunities for direct individual study. In the present paper I propose to illustrate the identity of the sporadic malignant new growths of the mouse in all their anatomical features with those of man, and the reproduction of the gross morbid anatomy of malignant disease as met with in the human subject, in the artificially-propagated cancer of the mouse.

In the first instance it is necessary to point out the great inherent difficulties of these investigations. Although malignant new growths are far from rare in the mouse, it is the exception to obtain a growth which can be propagated with certainty in a large number of animals for long periods. Thus, although we have attempted the experimental transmission of 28 sporadic malignant new growths discovered in a total of 50,000 mice, none of these tumours has approached in rapidity and amount of

growth that which we have obtained in English mice with Jensen's tumour.

In our hands this tumour grows with a rapidity and infiltrates and forms large metastases to a degree unsurpassed by any growth yet propagated. The general impression that this tumour cannot be got to yield a higher ratio of success than 30 or rarely 40 per cent. of the animals inoculated, supported by Ehrlich in his latest paper, is erroneous. We have repeatedly obtained success in 90 per cent. of the animals used, and tumours of 1.5 grams weight in the course of ten days after inoculation of a piece of tissue not more than 0.02 gram in weight—that is, about as big as the head of a pin.

Tumours occur naturally in the mammary region of the mouse from the axilla to the groin. The accompanying photograph (Fig. 1) shows such a tumour *in situ*. Its highly malignant character is evidenced by the fact that it recurred three times after operation, had invaded the muscles of the chest wall, and as is shown in Fig. 2, had produced extensive metastases in the lungs.

Such tumours constitute the majority of those we have encountered in the mouse. Growths also occur in other situations. Fig. 3 represents a transverse section of the

Fig. 2.—Front view of same case as Fig. 1. Note nodule in pectoral muscles (N), left side of chest filled by new growth (G), and small nodule in upper lobe of right lung (L); lower lobe of right lung removed for microscopical examination. Note absence of cachexia as indicated by outline of tail. Compare Figs. 9 and 10.

two rami of the mandible of a mouse, in the left one a squamous cell carcinoma has produced great deformity by invading and completely disintegrating the bone, and presenting an ulcerated surface towards the buccal cavity. We owe the preparation from which this figure is made to the generosity of Professor Borrel of Paris; it has already been described by him, and the metastases in the lymphatic glands of the neck were figured in his memoir in the *Annales de l'Institut Pasteur*. The lesions at the primary site and in the lymphatic glands permit no doubt as to the complete identity of the disease in this case with epithelioma of the jaw as met with in man.

A general view of an adeno-carcinoma of the small intestine of the mouse is given in Fig. 4. Although not more than 3 mm. in greatest extension, it has already nearly encircled the gut, is deeply ulcerated, and has penetrated both the muscular coats, forming large nodular masses on the peritoneal surface. Apart from the small

compass within which the whole process is displayed, the anatomical features are identical with those of human carcinoma in the same situation.

The number and the variety of the malignant new growths met with in the mouse is increasing as attention

Fig. 3.—Borrel's case of squamous-celled carcinoma of jaw of mouse. Left side of jaw healthy. On the right side a carcinomatous ulcer (U) of the mucous membrane. The growth has invaded and disintegrated the bone; the incisor tooth (I) is seen in transverse section at the lower and inner part, the spicules of osseous tissue (O) to the right representing the compact but less bulky bone on the healthy side; (J) healthy jaw with incisor; (T) transverse section of tongue.

is more closely directed to them, and the multifarious histological types which have been recognized as a result of the long-continued studies of human pathologists bid fair to appear in the mouse also.

The tumours which result from the subcutaneous implantation of cellular grafts in mice are usually of an irregular rounded form and show little tendency to

Fig. 4.—Adeno-carcinoma of small intestine of mouse. Shows greatest lateral extension in mucous-membrane (M), and arrangement of cancer in columns where it traverses the circular muscle; expansion into rounded masses (R) under peritoneum. Carcinoma black, ulcerated surface dotted. Compare Fig. 7.

infiltrate deeply into the subjacent tissues. How fallacious it would be to regard this expansive mode of growth as an indication of a low degree of malignancy is shown by the accompanying photograph of such an inoculated tumour. In this case (Fig. 6) a slight injury to the muscles of the back at the time of transplantation sufficed to open the way for an infiltrative extension of the resulting tumour, through the parietes, into the abdominal cavity. The kidney (K) and ovary are pushed forwards by the new growth. A much more infiltrative mode of growth, presenting a perfect parallel to the sporadic growth of Fig. 4, is shown in Fig. 7, which represents a minute growth in the intestinal wall following intraperitoneal inoculation. Growth has commenced as a small nodule (N)

Fig. 5.—Thoracic viscera of a mouse after subcutaneous inoculation of carcinoma; both lungs show numerous secondary nodules.

on the peritoneal surface of the intestine, has extended through the longitudinal and transverse muscular coats by the lymphatic channels (L), and has expanded in the sub-mucous tissue to a spherical mass (G), which, had it been allowed to grow, would inevitably have stretched the mucous

Fig. 6.—Transplanted carcinoma of mouse. Infiltrative growth of tumour through abdominal parietes, pressing upon and displacing the left kidney and ovary. (S.G.) Subcutaneous growth; (P.G.) peritoneal growth; (P) point of penetration of abdominal wall; (K) kidney.

membrane and led to an ulceration indistinguishable from that of the sporadic growth already referred to (Fig. 4).

Metastasis formation follows the development of experimental tumours in the subcutaneous tissue, peritoneum, and elsewhere. Fig. 5 shows extensive secondary growths in the lungs following a subcutaneous growth, and Fig. 8 shows the microscopical appearances of the lower lobe of the right lung in another similar case.

Microscopical emboli of cancer cells are very frequent

Fig. 7.—Transplanted carcinoma invading wall of small intestine. Narrow columns of cells in the lymphatic channels (L) of the muscular coats; expansive growth (G) in submucous tissue; (N) nodule on peritoneal surface. Compare Fig. 4, showing the same mode of extension, but in the opposite direction, of a sporadic tumour.

in animals whose lungs appear free from secondary deposits to the naked eye, but enormous metastases replacing almost entirely the whole respiratory area are not infrequent when animals are allowed to live for longer

periods. (See Fig. 8 and also Fig. 2 of a sporadic case.) Direct extension of the growth along venous channels into the chambers of the right heart has been described by Haaland, recalling the mode of extension within the inferior vena cava more familiar in the human subject. These few instances, selected from our very extensive collection, must suffice to show that sporadic and transplanted cancer in the mouse reproduce closely all the anatomical lesions met with in the disease in man.

The experiments have given conclusive evidence that a

Fig. 8.—Transverse section of entire lower lobe of lung showing extent of secondary growths (G G) and destruction of lung tissue (L). (Microphotograph.)

specific cachexia or a symptomatology of cancer do not exist in mice. The experimental tumours when situated in the subcutaneous tissue of the back may attain a large size without invading the deeper tissues, or causing rupture of the skin. Malnutrition in the mouse shows itself at first by a shrinking of the soft parts in the tail, so that the vertebrae become prominent. This constantly occurs when mice suffer from any acute or chronic infectious disease. Mice with enormous tumours more than half the weight of the animal may not show the slightest

Fig. 9.—Two mice with large subcutaneous transplanted carcinomata of three weeks' growth. In A skin intact, no signs of emaciation in the tail. In B ulceration present for three days, caudal vertebrae prominent (artificial production of cachexia).

emaciation of the tail so long as the integument covering the tumours remains intact. (See Fig. 9.) A small ulcerated surface on a much smaller tumour suffices, as shown in Fig. 10, to cause well-marked emaciation in two or three days. The absence of emaciation even with extensive

lung metastasis is shown (in Figs. 1 and 2) in a case of sporadic mammary carcinoma with extensive metastases, and the other mice figured are likewise free from it. The frequency of pain as a symptom of cancer in man is now generally recognized as belonging to a late stage of the disease. So far as it is possible to judge by free manipulation which mice quickly resent if performed on an abscess or other inflammatory swelling, the experimental carcinomata are painless. The only evidence of their presence is a lump at the site of inoculation; specific symptoms such as are generally comprised in the term cachexia cannot be recognized. When inoculations are made into the

Fig. 10.—Intraperitoneal transplantation of carcinoma. Extensive multilobular growths (G) attached to the mesentery. Thoracic viscera removed; very large metastases were present in both lungs.

peritoneal cavity growths may attain a large size before their presence is detected (Fig. 10). If such intraperitoneal growths invade or interfere with the alimentary tract, malnutrition and wasting speedily supervene.

These facts—only a very few of those which have direct clinical bearings—are of the greatest practical importance. As is well known, a malignant new growth in the human subject may be present for a long time and attain considerable dimensions without attracting attention. In how many cases is the presence of malignant disease discovered accidentally, as it were, at a stage when all hope of operative treatment has passed!

It is certain that the early diagnosis of cancer and its successful treatment depend, not on insistence on the search for supposed early symptoms of the disease, but on the recognition by the practitioner of the absence of symptoms apart from an anatomical lesion of minute dimensions.

I need only illustrate this contention by a brief

Fig. 11.—Squamous-celled carcinoma of tongue in man. Shows two distinct carcinomata adjoining at †, completely independent of normal epithelium. Note the extent to which the muscular fibres (M F) of the tongue lie between the columns and masses of epithelioma and have been drawn up above the level of the muscles (M M) outside the limits of the growth. Extreme dimensions of growth, 5 mm. (Removed by Mr. H. T. Butlin.)

reference to the remaining figures which represent three small malignant new growths from the human tongue. These were diagnosed as precancerous or very early cancers. The figures show that in one (Fig. 11) deep

infiltration of the muscles had already occurred, and the growth was sharply marked off from the adjacent mucous membrane. In the second (Fig. 12), muscular infiltration has begun, although it is not so far advanced, and the new growth is still in cellular continuity with the adjacent epithelium, while in Fig. 13, what was clinically a small elevated vascular swelling, 3 mm. in its greatest diameter, is seen to be in reality an endothelioma or angio-sarcoma which had stretched the covering endothelium and had extended some way among the muscles. In these cases the histological lesion, as revealed by the microscopical examination of many consecutive series of sections, is the only criterion by which they have been dis-

Fig. 12.—Squamous-celled carcinoma of tongue in man. The growth (G G) is not sharply marked off from the adjacent epithelium, and the normal level of the muscles (M) is undisturbed. The small nodule of growth (N) to the right is completely separated from the larger growth by apparently non-cancerous epithelium. Extreme dimensions of growth, 5 mm. Thin slice removed from growth (G G) for microscopical examination of the margins of growth in the diameter at right angles to that of this figure. (Removed by Mr. H. T. Butlin.)

tinguished from other morbid conditions occurring in the tongue.

A small piece of a mouse cancer transplanted into the subcutaneous tissue, if it grow, ultimately gives rise to a mass of new growth nearly as great as the mouse itself. It produces metastases in the lungs, and leads to the death of the animal. If the tumour be removed by operation when it has reached the size of an almond, these results do not follow. The mouse remains well indefinitely, although the tumour transplanted into other mice continues to grow. In the same way, in the human subject, carcinoma and sarcoma are at first local processes taking place in circumscribed areas; their complete removal prevents the further extension of the disease. In

Fig. 13.—Endothelioma or angio-sarcoma of tongue in man. Note stretching of epithelium over the growth (G) and extension on the deep surface into the muscles. Extreme dimensions of growth, 3 mm. (Removed by Mr. W. H. Parker.)

this early state, however, the anatomical (and histological) lesion constitutes the most reliable criterion of the presence of cancer: symptoms are absent, and the removal of a piece of tissue, which cannot be shown to be cancerous, or ultimately proves to be non-cancerous, is to be preferred to delay until the naked-eye appearances have raised suspicion to probability. Are not the consequences of the growth of a small piece of mouse cancer no bigger than the head of a pin sufficient to convince the most sceptical of the justice of this attitude?

THE RADICAL OPERATION FOR CANCER OF THE LOWER LIP.

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In every case of epithelioma of the lip the submaxillary triangles and the submental space should be cleared of their contents at the time the primary growth is removed.

This is putting into precise words what has been elsewhere suggested in more or less vague terms. In the excellent *Manual of Surgery* by Messrs. Alexis Thomson and Miles (1904, vol. ii, p. 130) it is stated that:

It is advisable in all cases of cancer of the lip to remove the lymphatic glands below the jaw, whether they are palpably enlarged or not.

No details are given as to how this should be done. The rare cases in which the upper lip is involved may be included under the general term "cancer of the lip," for the same indication for radical treatment would apply. The disease is remarkably frequent in Ireland, and Sir Thornley Stoker's opinion from an experience of 350 cases is of special value. He writes:¹

The removal of a portion of the lip for a small epithelioma is a simple matter, and is not much complicated by a moderate engagement of the submental lymph glands. Whatever incisions may be considered necessary should be carried at least $\frac{1}{2}$ in. to $\frac{3}{4}$ in. free of the disease, and should be extended sufficiently to remove any infected glands.

He further remarks that sometimes special incisions may be required to expose doubtful glands, and that it is often possible only to find enlarged lymph glands in the submaxillary space after this has been opened up. This comes far short of advocating what may be fairly termed the radical operation for all cases of cancer of the lip. A brief description of it may, I trust, be allowed here. The case is supposed to be a typical epithelioma at or near the middle line of the lower lip, probably of at least six months' duration.

It is impossible to say on which side glandular infection has taken place or whether the submental glands will be first involved; the only safe plan is to clear the space from one angle of the jaw to the other. A curved incision is made through skin, platysma, and fascia, which starts at one angle, extends down to the hyoid bone, and finishes at the symphysis. (See Fig. 1.) The facial vein which emerges from the submaxillary gland at its lower and posterior angle is isolated and ligatured. The facial artery entering the gland higher up from beneath the digastric muscle is then sought for, secured between two ligatures, and divided. The salivary gland is then lifted up and separated with the numerous lymphatic glands at its upper border from the lower jaw, the facial artery and vein being again ligatured as they cross the latter. The gustatory nerve is carefully isolated and its branches to the gland divided. Wharton's duct is then ligatured and cut across. Thus the whole glandular contents of the submaxillary triangle can be drawn forwards towards the middle line, leaving both bellies of the digastric, the mylohyoid, and part of the hyoglossus bared by the dissection. The patient's head being now turned over, a second incision is made continuous with the first, curving down to the hyoid and back to the opposite angle. By reflecting the skin at the middle line the space between the two anterior bellies of the digastric can be completely cleared from the symphysis down to the hyoid bone. In this way the glands from one angle of the jaw to the other can be removed in one piece. (See Fig. 2.) Care should be taken that the lymphatic glands situated just under the angles of the jaw are removed, and it is well that those over the carotid bifurcation should be dissected out at the same time. The lip cancer is now freely excised by two independent incisions in the usual way, the procedure being made simpler by the previous ligature of both facial arteries. A small drainage tube should be inserted at each side of the submaxillary wound, which is then sewn up and well supported by a copious dressing of moist sterile gauze.

The operation cannot be done satisfactorily under an hour, and therefore is a contrast to the time-honoured method of V excision, which was almost dramatic in its rapidity and was frequently performed without an anaesthetic. But in no other region of the body is it