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INVESTIGATIONS ON THE SPIROPTERA CANCER VI

A TRANSPLANTABLE SPIROPTERA CARCINOMA OF THE MOUSE

BY

JOHANNES FIBIGER

WITH THREE PLATES

KØBENHAVN
HOVEDKOMMISSIONÆR: ANDR. FRED. HØST & SØN, KGL. HOF-BOGHANDEL
BIANCO LUNOS BOGTRYKKERI
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(From the Anatomo-Pathological Institute of the University of Copenhagen.)

Transplantation experiments having during the last decenniums demonstrated the enormous power of continuous proliferation presented by the cells of the malignant new growths, such experiments must consequently claim a principal place within experimental investigation carried out for the purpose of proving that malignant tumors possess all characteristical features.

But, as known, transplantation experiments are far from giving positive results in all cases. It is certainly beyond doubt that many of the experiments in hand have failed owing to the fact that only a comparatively small number of young experimental animals has been employed. But even when transplantation is effected into numerous individuals, some tumors prove less easily transplantable than others, and, no doubt, great difficulties will occur with regard to the propagation of certain types of new growths.

As may be seen a. o. from the experiments due to HAALAND[1] this especially seems to be the case with the strongly keratinising types, as far as the tumors in mice are concerned. And there is a priori no reason to suppose that such tumors in rats would offer more favourable conditions of propagation although transplantation has been successful and caused no difficulty in a few cases of carcinoma observed in these animals (HANAU[2], LEWIN[3], NICHOLSON[4]).

[1] Spontaneous Tumours in Mice. Fourth Scientific Report of the Imperial Cancer Research Fund 1911.

[2] Fortschritte der Medizin VII 1889.

[3] Zeitschrift für Krebsforschung VI 1908.

[4] The Cancer Hospital Research Institute. Selected Papers Vol. I. 1913.

Thus, it cannot surprise that experiments which I have carried out repeatedly during these last years for the purpose of transplanting the Spiroptera carcinoma into black and white rats have given negative results, and all the more so, because I have not been able to use a greater number of young rats for these investigations. Add to this the fact that owing to technical difficulties I may not in all experiments have succeeded in getting a sterile material for inoculation from the organs (the fundus of the stomach and the tongue) affected with the primary Spiroptera carcinoma, — and, furthermore, that transplantation of metastases has been precluded in nearly all cases, these secondary deposits being most frequently of so tiny dimensions that only microscopical examination could establish their existence.

In a previous paper[1], in a preliminary report on the results of my examinations regarding the influence of the Spiroptera infection upon white mice, I have, however, given a brief communication concerning 3 albinotical mice, infected with the Spiroptera and in whose stomach carcinoma had developed, — noting, that transplantation of the tumor in one of these cases had given positive results.

But these transplantation experiments not being quite finished on publication of the said paper, I have since then subjected the mouse to a thorough examination and completed the investigations, — and — in view of the great interest which attaches to the observation I shall here supply my previous brief remarks with a detailed report.

Albinotical male mouse 6—8 months old is fed on February 16. 1916 on muscles of 5 cockroaches (P. americana), infected with the Spiroptera. January 3. 1917 typical Spiroptera eggs are found in the excrements of the mouse. The mouse dies June 12th 1917, 482 days after the transmission of the Spiropterae. The weight on death is 24 gr.

[1] Det Kgl. Danske Videnskabernes Selskab. Biologiske Meddelelser I, 11. 1918.

The abdominal cavity is widely distended by a rough tumor mass of the size of a large hazel nut, taking up the place of the stomach and in the most lateral left portion adherent to the left lobe of the liver, to the left side of the diaphragm and to the upper pole of the spleen. Tumor measures $2\frac{1}{2} \times 2 \times 1\frac{1}{2}$ ctm. It seems due to an enormous new growth partly in the stomach wall itself, partly perforating the latter, tumor masses being visible on the outer side of the stomach wall as well. The pyloric portion is apparently undamaged. The mouth cavity, tongue and gullet are normal. In the mesenterium, the omentum and the peritoneal cavity, especially in the dorsal wall of the latter, numerous isolated, greyish-white, firm, roundish tumor nodules as large as the head of a pin up to the size of a pea, are found. The liver, spleen, kidneys, genitalia, lungs and heart are normal, no metastases. Columna normal. The brain presents no pathological changes. No cutaneous or subcutaneous nodules.

The stomach. (Natural size).

On opening of the stomach the wall of the fundus proves to be about ½—1 ctm. thick and consisting of a homogenous greyishwhite tumor tissue, in which pronounced necrosis has taken place on the cavity side. The mucous membrane of the pyloric portion seems to exhibit no special changes, the line of demarcation towards the fundus is, however, hardly discernible. The stomach contains neither concrements nor hairballs. The intestines after opening present no abnormities.

On microscopical examination the greatly thickened part of the stomach wall is found to be the seat of a typical — to a great extent strongly necrotical — squamous celled carcinoma with numerous areas of keratinisation. In most places the carcinoma extends itself to all the membranes of the wall, lining the cavity with a strongly necrotic tumor tissue and reaching not only into the serosa, but penetrating this membrane and in several areas invading the most superficial parts of the liver, the spleen and diaphragm, the muscular bundles of which are split up by carcinomatous tissue.

In other places the carcinomatous growth is less violently pronounced, the mucous membrane, set with papillomatous excrescences and often containing numerous lymphocytes, — being here lined with a strongly hyperplastical epithelium, which in several areas is the seat of carcinomatous transformation and sends out carcinomatous streaks penetrating invasively into the deeper layers of the wall. On the pyloric border the carcinoma invades the glandular portion of the stomach and grows invasively into the basal layers of the wall, lifting

up the mucosa. The glandular lining in this area only here and there contains a few carcinomatous elements, built up by squamous epithelium. For the rest the pyloric portion is normal. In a few places the mucous membrane of the cardiac portion presents no carcinomatous changes but only pronounced hyperplasia of the epithelium and more or less pronounced papillary changes. On the other hand, the deeper layers of the wall may here contain several carcinomatous areas, due to an invasive growth of adjacent cancerous elements into submucosa and muscularis.

The carcinoma is of a somewhat heterogeneous type (s. Plate II figg. 5—6). In some areas it is built as a malignant epithelioma with epithelial pearls and horny globes, — in other areas it presents itself as an alveolar carcinoma, built up by cubical cells or squamous epithelium without — or with but a slightly pronounced keratinisation, and containing numerous mitoses. More frequently alveoli are found, the central part of which contains concentrical layers of keratinised squamous-celled epithelium containing nuclei, — and finally areas may occur with violent keratinisation and in which the tumor tissue consists of large cyst-like alveoli and cavities filled with stratified keratinised masses, and interspersed with thin streaks of connective tissue, lined with a single or some few layers of cubical or flat cells, in which sometimes eleidin granules are found. The stroma is highly developed throughout the tumor and often infiltrated with lymphocytes.

As mentioned in the previous preliminary report of this case no Spiropterae were found at the post-mortem examination of the fundus of the stomach. Nor did the microscopical examination of several areas of the strongly carcinomatous parts show any parasites, and I did not succeed in finding Spiroptera eggs in the contents of the intestines (direct microscopical examination and examination by means of TELEMANN's method). At a later thorough examination of areas from all parts of the wall of the fundus a single fully developed Spiroptera was found in the strongly hyperplastical epithelium of a part of the mucous membrane which exhibited no carcinomatous changes. Microscopical examination of the epithelium of the gullet and of the tongue showed no pathological changes and no Spiropterae.

The metastases in the mesenterium, in the omentum and in the peritoneum at the microscopical examination prove to be built entirely as a typical, more or less keratinising carcinoma of the same structure as that of the cardiac portion (s. Plate II figg. 7—8). They grow invasively into the subperitoneal muscles, — in a single nodule invasion of the lymphatic space of a nerve is seen. They contain neither Spiropterae nor their eggs. Carcinomatous lymphatic glands are not met with; on the other hand some peritoneal lymphatic glands prove to be non-cancerous.

The heart, lungs, kidneys and brain present no special changes. The liver and spleen contain no pathological changes besides the slight

invasion of the carcinoma mentioned above. No amyloid degeneration of the spleen. Gl. thyreoidea, the tongue, trachea and a salivary gland normal. Transverse sections of a lumbal vertebra show no changes of the osseous tissue or of the medulla.

As will be seen from the above report the stomach of a Spiroptera-infected albinotical mouse, which died 482 days after the transmission of the Spiropterae, proved to be the seat of an extremely extensive, in some places strongly keratinising squamous-celled carcinoma, arising from the hyperplastical epithelium of the fundus and invading from here adjacent parts of the pyloric portion.

All the layers of the wall of the cardiac portion were the seat of carcinomatous changes, propagating even from several parts of serosa into adherent parts of the diaphragm, the liver and the spleen. In peritoneum, furthermore, numerous metastases of the same structure as that of the mother tumor were found.

This carcinoma, thus, both in extension and production of metastases surpassed not only all the cases of Spiroptera carcinoma in rats and mice hitherto observed by me, — but also — as far as may be judged from the reports in hand — all carcinomata of unknown origin observed in the cardiac portion of the stomach of the mouse by other investigators. Altogether 6[1] observations of this kind have been made (MURRAY[2], ITAMI[3], SLYE, HOLMES and WELLS[4]). In none of the recorded cases was there any evidence of the presence of animal parasites in the stomach (SLYE, HOLMES and WELLS, MURRAY).

[1] In a 7th case observed by LITTLE and TYZZER (s. the report by SLYE, HOLMES and WELLS) it cannot be quite precluded that the carcinoma found in the fundus of the stomach, has originally arisen in another organ.

[2] Third Scientific Report of the Imperial Cancer Research Fund 1908.

[3] quoted by SLYE.

[4] Journal of Cancer Research 1917.

While the etiological factors of these carcinomata must remain unexplained, no doubt exists that the carcinoma in the case here recorded as well as those of the 2 other cases previously briefly mentioned[1] by me were due to the fact that the epithelium of the cardiac portion had housed the *Spiroptera neoplastica (Gongylonema neoplasticum)* for a very considerable space of time.

In all these 3 cases carcinoma had developed in mice which on transmission of the Spiroptera were healthy, and the fundus of whose stomach harboured the parasite as late as on death. In the 2 cases previously briefly recorded it did not cause any difficulty to point out the Spiroptera. In the above case, on the contrary, neither post-mortem examination nor microscopical examination of several areas of the fundus of the stomach revealed any specimen of the parasite. Not till numerous parts of the cardiac portion had been subjected to microscopical examination, did I succeed in finding a single fully-developed Spiroptera. That this stomach contained only one parasite perfectly corresponds to the common findings in Spiroptera-infected non-carcinomatous and carcinomatous rats, where the number of Spiropterae, as mentioned in a previous paper[1], very frequently already 3 months after the transmission of the nematode may be so considerably reduced that the fundus only contains a single or a few specimens, although several hundreds have been transmitted. The corresponding disappearance of the parasite from the tongue as well has been mentioned in previous papers[2].

Thus, it perfectly harmonizes with these observations that the fundus of the stomach of this mouse, which had survived the transmission of the Spiroptera for 16 months contained likewise but a single parasite. That the fundus must actually

[1] Det Kgl. Danske Videnskabernes Selskab. Biologiske Meddelelser. I, 11. 1918.

[2] loc. cit. I, 10 and I, 11.

have harboured Spiropterae formerly and for a longer time, — at least c. 11 months — was evidenced by the fact that the excrements of the live mouse had contained typical Spiroptera eggs 322 days after the transmission. There is no possibility of stating exactly the length of the time passed, before the reduction of the number of parasites took place, — but it hardly admits of any doubt that this reduction is mainly due to the pronounced necrosis of the carcinoma, which has again caused the desquamation of the superficial layers of the epithelium. — Also, in non-carcinomatous mice, which had survived the transmission of the Spiroptera for a long time, I have often found the cardiac portion of the stomach to contain only a single or a very few Spiropterae. Thus, the behaviour of the worms in the stomach of mice and in the stomach of rats may correspond.

That also the effects of the Spiroptera invasion quite correspond in the stomachs of these different rodents, except that the carcinoma develops with a far greater frequency (above 50 %) in the stomach of black and white rats, has been mentioned in preceding papers. According to my investigations previously finished — out of the 211 mice, altogether examined, 59 had survived the transmission of the Spiroptera for 45 days or more; and in 52 of these animals the fundus of the stomach exhibited not only inflammatory changes but also considerable hyperplasia and downgrowth of the epithelium; in numerous cases, furthermore, heterotopic downgrowth, and in several cases papillary transformation of the mucous membrane and of the connective tissue of submucosa. Finally the 3 mice above-named, showed, besides, a typical carcinoma. Thus, cancer of the fundus of the stomach has been found altogether in 3 out of 59 mice, infected with the Spiroptera and which had survived the transmission for 45 days or more. To what extent the frequency of the carcinoma of the fundus of the stomach in spiroptera-infected mice — however little

it may be — surpasses its frequency amongst other mice according to investigations hitherto performed, will be seen from the fact that the 3 cases recorded by Slye, Holmes and Wells were the entire result after examination of no less than 16 500 mice. And from the laboratory of the Cancer Imperial Research Fund only 2 cases have been recorded (Murray).

As mentioned above, I have never in the fundus of the rat's stomach found any Spiroptera carcinoma, the extension of which surpassed or even reached that of the one here recorded. Not even in advanced and metastases producing cases in rats did the carcinoma though penetrating submucosa invade muscularis, while both in the case in question and in another of the cases observed in mice[1] the carcinoma had infiltrated all the membranes of the wall of the fundus of the stomach. Nor did I ever meet with carcinomata in rats extending from the cardiac into the pyloric portion.

It may be that this difference is plainly accounted for by the circumstance that the Spiroptera infected carcinomatous black and white rats had not harboured the nematode for so long a time as had the two mice mentioned above. That this explanation is right in all cases where the rats died soon (1½—2—3 months) after the transmission of the Spiroptera and in which the carcinomata were of very slight dimensions is beyond doubt. But even the longest lived carcinomatous rats hitherto observed by me, had survived the transmission of the nematode for 9—10 months only while, on the other hand the two mice in the stomach of which the carcinoma had reached a great extension did not die till about 16 and 13 months resp. after the transmission.

The possibility, thus, exists that the greater extension of

[1] Det Kgl. Danske Videnskabernes Selskab. Biologiske Meddelelser. I, II. 1918 pag. 23. In one case more (pag. 22) the cancer of the fundus of the stomach was only slightly developed.

the carcinoma in these mice, and the smaller extension in the rats might be ascribed solely to the tumors having had longer time for further propagation in the mice, while the black and white rats — being less resistent to the infection on the whole — have probably succumbed to the influence of the Spiropterae or to complicating diseases more rapidly, and, thus, may not have lived sufficiently long for the carcinoma to undergo such violent development in these animals as in the mice.

But also other factors may possibly have played a part. The difference of the frequency of the Spiroptera carcinoma in rats and mice, pointed out in my preceding paper gives indication that not only differences according to individuals but also differences according to species and — probably according to race too — exist in the susceptibility to the cancer producing power of the Spiroptera infection. Whether or not similar differences may also exist in the resistance to the invasive growth of the carcinoma into the deepest muscular layers of the wall of the fundus of the stomach, is a problem which cannot yet be definitely solved.

In both the cases in which a far developed Spiroptera carcinoma occurred in the fundus of the stomach of a mouse, transplantation of a metastasis has been effected, but only with success in the case here copiously recorded. In this case transplantation met with no difficulty whatever.

The I Transplantation of the tumor was established in immediate continuation of the post-mortem examination on June 12th 1917. Fragments of a peritoneal non-necrotical metastasis were used for the implantation. All the mice of this and of all subsequent transplantations were inoculated with about 10 to about 25 milligr. of tumor tissue. The inoculation was effected by means of a hollow needle like the one employed in the Imperial Cancer Research Fund's laboratories. At the 1st transplantation altogether 12 white mice, weighing 10—15 gr. were inoculated, 7 subcutaneously (in the axillary region by introducing the needle in the groin), and 5 intraperitoneally.

In 4 out of the 7 mice inoculated subcutaneously small sub-

cutaneous nodules were soon palpable, and in 3 cases on death of the mouse (resp. 65, 82 and 93 days after implantation) had attained the size of the kernel of a hazel nut (2 mice) or of a hazel nut (1 mouse). In the 4th mouse an enormous nodule developed, which little by little became fluctuating and on the death of the mouse, 84 days after transplantation, presented itself as a colossal subcutaneous cystic tumor (4 × 4½ × 3½ ctm.) filled with a limpid, slightly fluffy, yellowish fluid, and adjoining the thorax and the abdominal muscles by rugged greyish-white tumor masses measuring 1—2 ctm. in thickness (see Plate I, fig. 1). The mouse weighed 38 gr. before the opening of the tumor.

In the remaining 3 mice, 2 of which died 137—164 days, and 1 was killed 378 days after transplantation, — the result of inoculation was entirely negative.

In all the 5 mice inoculated intraperitoneally, the peritoneal cavity on death of the animals was found to contain rugged tumor masses, more or less adherent to peritoneum or to the intestines or to other organs. In 1 mouse (which died 41 days after transplantation) the tumor was as large as a pea, in 2 mice (which died 84 days after transplantation) it was as large as the kernel of a hazel nut and in 2 mice (which died 63 and 64 days after transplantation) as large as a walnut. In one of these mice (see Plate I fig. 2) the weight of the mouse was 22 gr., 10 of which represented that of the tumor.

For the II transplantation, which took place on September 4th 1917, fragments of a tumor were employed originating from one of the above mice, inoculated intraperitoneally on June 12th, and in the peritoneal cavity of which (on death September 4th) a tumor as large as the kernel of a hazel nut had developed. Transplantation was effected intraperitoneally into 20 younger mice. 5 mice died from Sept. 5th to Sept. 8th. In 3 out of the remaining 15 mice intraperitoneal nodules were palpable as early as October 20th.

Intraperitoneal tumors developed in altogether 10 mice, in 7 of which (surviving the transplantation for 44—87 days) they had attained the size of a pea or the kernel of a hazel nut, in 3 (which died resp. 64, 98 and 109 days after transplantation) somewhat more than the size of a hazel nut. In several of the animals strong necrosis had taken place in the tumor.

In 5 mice which died or were killed 3—12 months after the transplantation only small nodules of granulative tissue or no signs of the inoculation at all were found.

For the III transplantation (on November 7th 1917) portions of a tumor were employed, which had developed in one of the mice of the transplantation II. In this mouse, which died November 7th a nodule as large as a hazel nut was found in the peritoneal cavity.

Transplantation was made intraperitoneally into 8 youn-

ger mice. In 3 of these (which died within 50—62 days after transplantation) nodules developed somewhat larger than a pea or the kernel of a hazel nut, — in a 4th mouse (see Plate I, fig. 4) which survived transplantation for 57 days, the tumor had nearly attained the size of a walnut.

In the remainder (1 of which died 4 months, while 3 were killed about 7½ month after inoculation) no tumors developed.

For the IV transplantation made on January 3rd 1918, portions of a tumor were used, which had developed in one of the mice from transplantation III, which died 57 days after inoculation (January 3rd 1918).

Transplantation was made intraperitoneally into 10 adult mice (weighing 15—20 gr.). In 2 out of these mice (which died 84 and 164 days after transplantation) intraperitoneal nodules somewhat larger than a pea were found, in 2 mice (surviving the inoculation for 92 and 119 days) the tumors had attained the size of a plum and a walnut resp. The weight of one of these 2 mice (which died 92 days after inoculation) was 28 gr., 9 of which represented the weight of the tumor.

In one mouse, (which died 107 days after transplantation) enormous tumor masses had developed, larger than a plum and penetrating through the lower part of the abdominal wall. Pronounced necrosis had taken place in these tumors (see Plate I, fig. 3). This mouse weighed 25 gr., 11 of which represented the tumor alone.

No tumors developed in the remaining 5 mice, 3 of which were killed about 6 months, 1 died about 9 months, after transplantation.

For the V transplantation made on March 26th 1918 fragments of a tumor were employed which had developed in one of the above mice of transplantation IV, which died March 26th 1918 and whose peritoneal cavity contained a nodule nearly as large as a pea.

Transplantation was made intraperitoneally into 10 younger mice, 5 of which died within 4 to 8 months, and 5 were killed about 9 months after inoculation.

No tumors developed in any of these mice.

Thus, altogether in 28 mice transplantation had been successful; all the tumors developed were subjected to microscopical examination in all these cases. Neither Spiropterae, nor eggs nor parts of the parasite were met with.

Besides, microscopical examination was effected in all cases, where microscopical inspection presented no definite hold whether a nodule were carcinomatous or merely built up by granulation tissue.

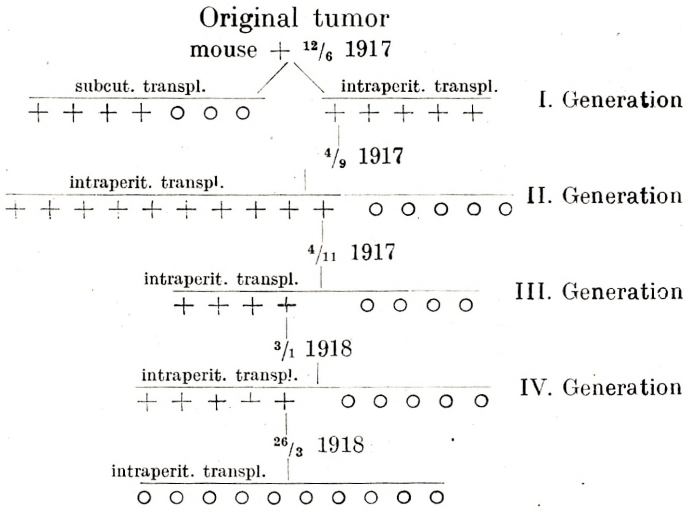
In all 28 cases the nodules, like the original tumor, exhibited the structure of a typical keratinising squamous-celled carcinoma, (see Plate III) which kept its histological features unaltered through all 4 generations, — in as far as deviations within the transplanted tumors might consist merely in quantitative differences as to the degree and extension of the keratinisation. On the whole, the tendency to keratinisation seemed to be more pronounced in the propagated tumors than in the mother tumor, and might even in some cases be extraordinarily strong (see Plate III Figg. 11—12). Perfect alveolar structure without keratinisation was only found here and there and only in smaller areas of the tumor. Adenomatous structure was not met with at all. All tumors presented signs of necrosis, most advanced in the largest tumors and in the longest lived mice.

In several mice, into which transplantation was made intraperitoneally, there was found invasive growth into the abdominal muscles, and into organs adjacent to the tumor (as f. inst. a lymphatic gland, the renal capsule, the kidneys, the stomach wall and the intestines).

Unquestionable metastases in the lungs were not discernible, and a complete microscopical examination of the lungs of 5 mice gave negative results. The spleen of 3 mice was subjected to examination for amyloid changes, but only one gave a slightly positive reaction.

The schematic table below, in which the mice inoculated successfully are marked with +, the mice inoculated unsuccessfully with ○ gives a summary view of all the experiments.

As may be seen the tumor proved transplantable during half a year for 4 generations. It must be noted that the inoculation material employed for the fifth generation on a later microscopical examination presented the appearance of



an extensive necrosis, which most probably accounts for the negative result of the last transplantation.

Taken together the transplantations gave positive results in 28 out of 55 inoculated mice, which did not die immediately after implantation. Tumor was preserved living by means of transplantation for altogether about 12 months (from June 12th 1917 to June 16th 1918).

Most successful was the result of the 1st transplantation, in which tumors developed in all mice intraperitoneally inoculated, and in 4 out of 7 mice subcutaneously inoculated. In the 2nd transplantation made intraperitoneally (as in all the subsequent transplantations) tumors developed in 10 out of 15 animals, while in the 3rd and 4th transplantations tumor growth was only noticed in half of the transplanted animals.

For comparison be it noted that transplantation of the tumor, described by MURRAY[1] and extirpated from the axillar region of a mouse, and consisting of adenomatous alveolar and keratinised areas, was only successful in 4 out of 156

mice, which had survived transplantation for more than 4 weeks. A recurrent tumor, developed after the extirpation of the original tumor, was not transplantable at all, though inoculated into 52 mice surviving for at least four weeks.

That, as a rule, keratinising tumors will present far greater difficulties with regard to transplantability than did the tumor here recorded, is furthermore seen from the above-mentioned report by HAALAND (1911). Out of 11 keratinising tumors (typical adeno-cancroids) 8 showed themselves transplantable, tumors developing only in 49 out of 1116 mice, into which these 8 tumors had been inoculated (and 838 of which survived for at least 4 weeks). 3 tumors were transplanted without success into 170 mice (152 surviving for at least 4 weeks).

But as far as strongly keratinising tumors were concerned, the difficulties turned out to be still greater, as, by transplantation of 4 such tumors HAALAND did not succeed in getting positive results in any of the cases, although these 4 tumors were transplanted into 1594 mice, 1159 of which survived the transplantation for at least 4 weeks.

It is, thus, justifiable to ascribe to the Spiroptera carcinoma here recorded a transplantability which must not only be regarded as extraordinary when compared with the transplantability of the tumors generally found in mice, but even as quite remarkably great, in consideration of the tumor's being a carcinoma with a strong tendency to keratinisation. The rapid and infiltrative growth of the transplanted tumor tissue further illustrates the considerable malignancy of this carcinoma. But the greatest importance of the results of these experiments lies in their establishing the transplantability of the Spiroptera carcinoma.

Taken together the investigations here and previously

[1] Third Scientific Report of the Imperial Cancer Research Fund 1918 pag, 159.

published will manifest the fact that this experimentally produced carcinoma possesses the structure of keratinising typical squamous-celled carcinomata, grows invasively into various tissues and organs, gives rise to metastasis formation and is transplantable. As to the development of the carcinoma the influence of the Spiropterae is limited to production of the primary tumor; the growth and further expansion in the fundus of the stomach and in the tongue continues itself no matter, whether the Spiropterae remain in these organs or partly or completely (as seen in the tongue) disappear. In the development and growth of the metastases and the transplanted tumors the parasites have no share.

I desire to acknowledge my indebtedness to the W. Bendix Legacy for its support of these investigations.

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PLATES

Plate I.

Fig. 1. Mouse with subcutaneous, transplanted Spiroptera carcinoma. 84 days after the transplantation. First generation.

- 2. Mouse with intraperitoneal, transplanted Spiroptera carcinoma. 63 days after the transplantation. First generation.

- 3. Mouse vith intraperitoneal, transplanted Spiroptera carcinoma. 107 days after the transplantation. Fourth generation.

- 4. Mouse with intraperitoneal, transplanted Spiroptera carcinoma. 57 days after the transplantation. Third generation.

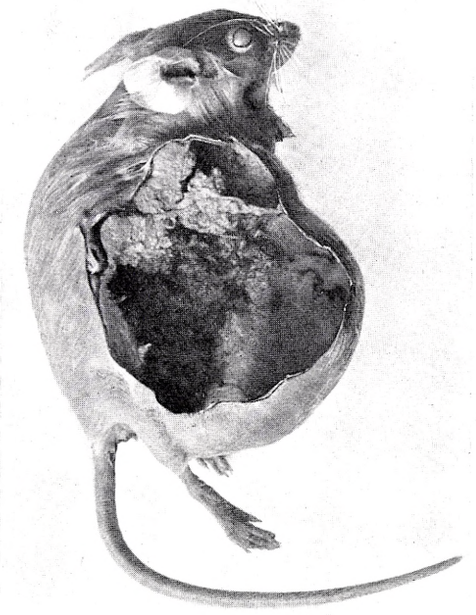

Fig. 1.

Fig. 3.

Fig. 2.

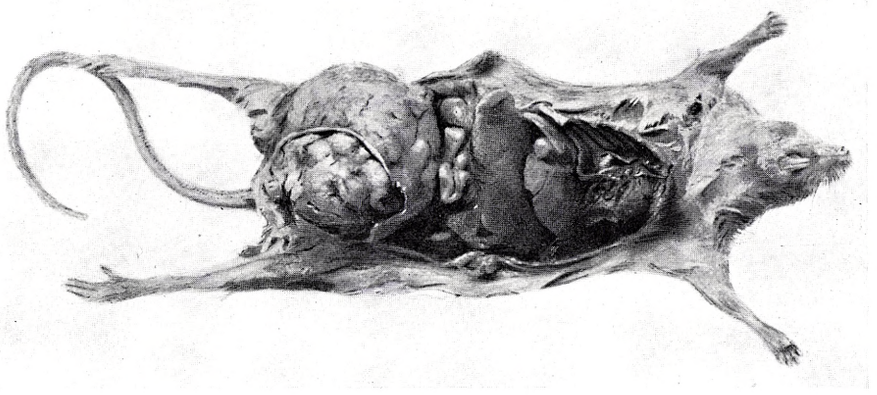

Fig. 4.

Plate II.

Fig. 5. Primary Spiroptera carcinoma in the fundus of the stomach of an albinotical mouse. Alveolar squamous-celled carcinoma. 50 ×.

- 6. The same tumor. Areas of keratinisation. 50 ×.
- 7. Peritoneal metastasis of the same tumor. 50 ×.
- 8. Peritoneal metastasis of the same tumor. Great areas of keratinisation. 50 ×.

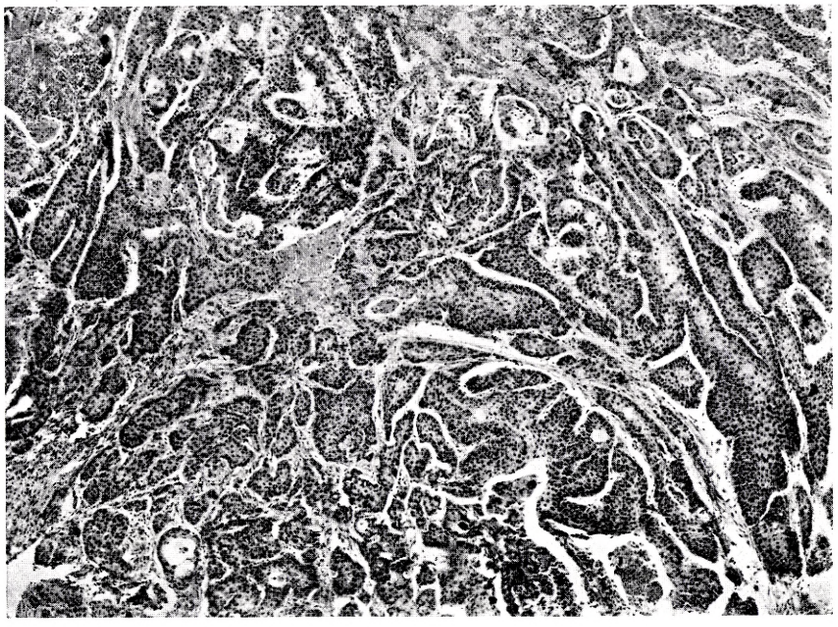

Fig 5.

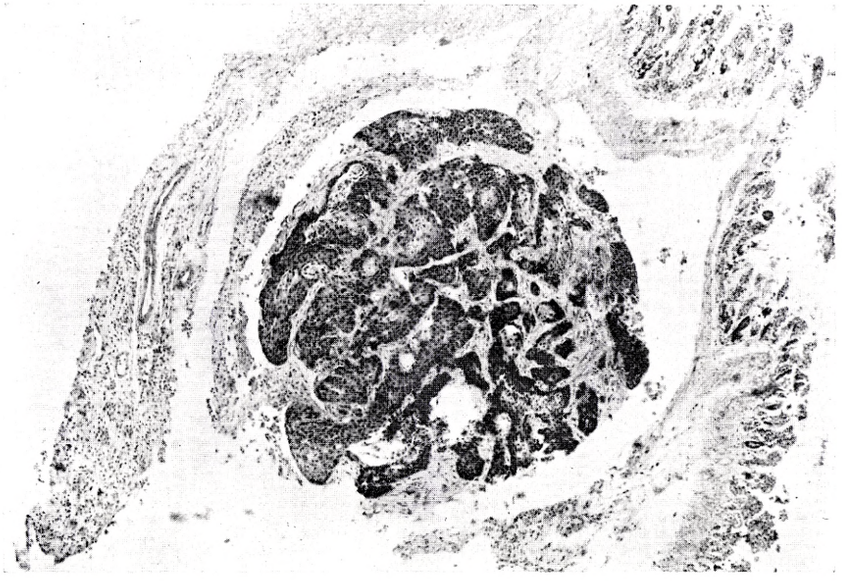

Fig. 7.

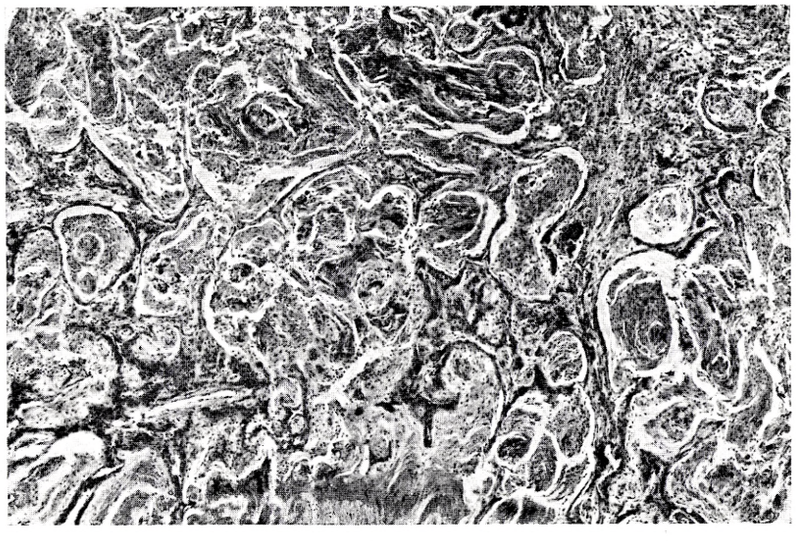

Fig. 6.

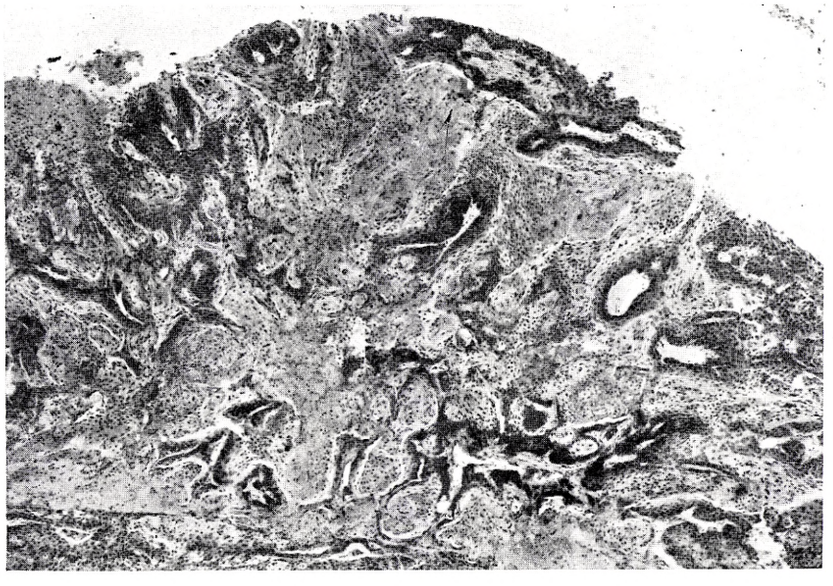

Fig. 8.

Plate III.

Fig. 9. Transplanted keratinising Spiroptera carcinoma of the second generation. 50 ×.

- 10. Transplanted keratinising Spiroptera carcinoma of the third generation. 50 ×.

- 11. Transplanted strongly keratinising Spiroptera carcinoma of the fourth generation. 48 ×.

- 12. Transplanted Spiroptera carcinoma of the fourth generation. Very extensive keratinisation. 50 ×.

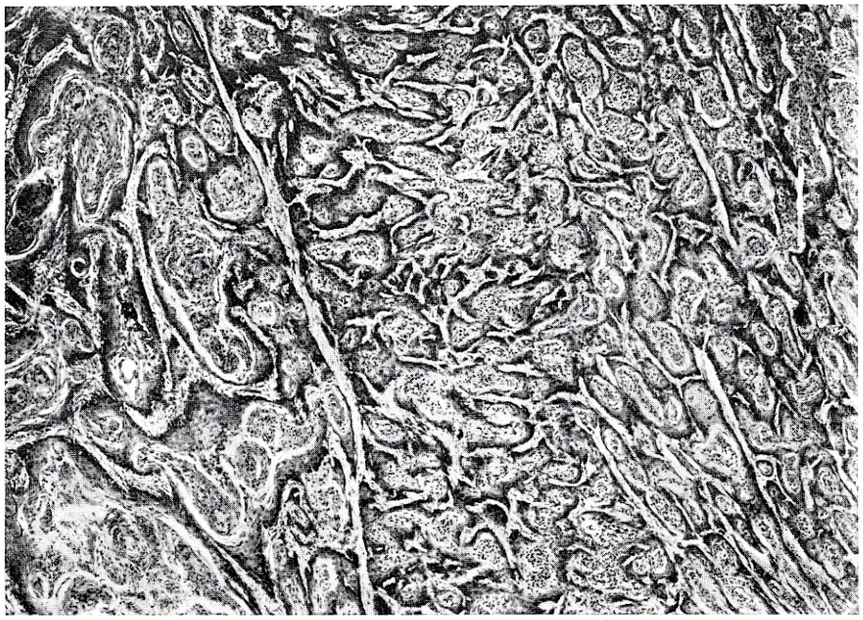

Fig. 9.

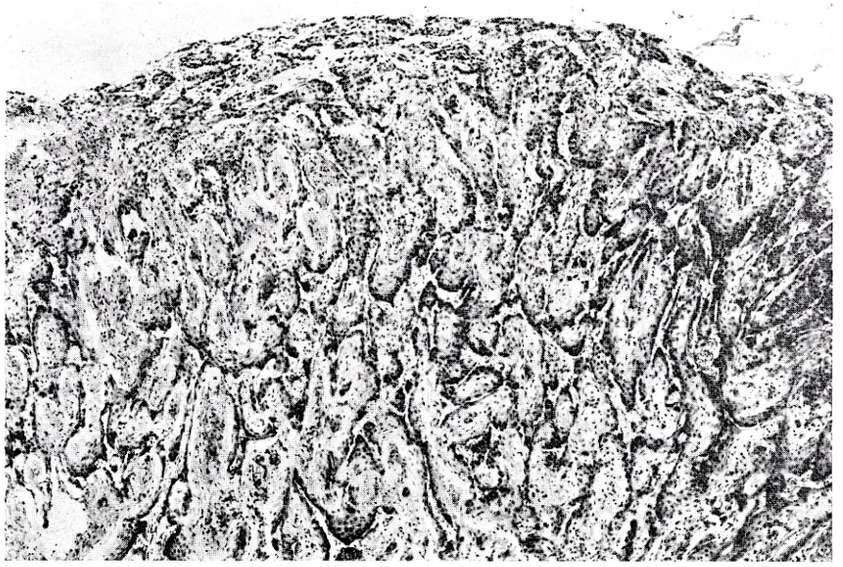

Fig. 11.

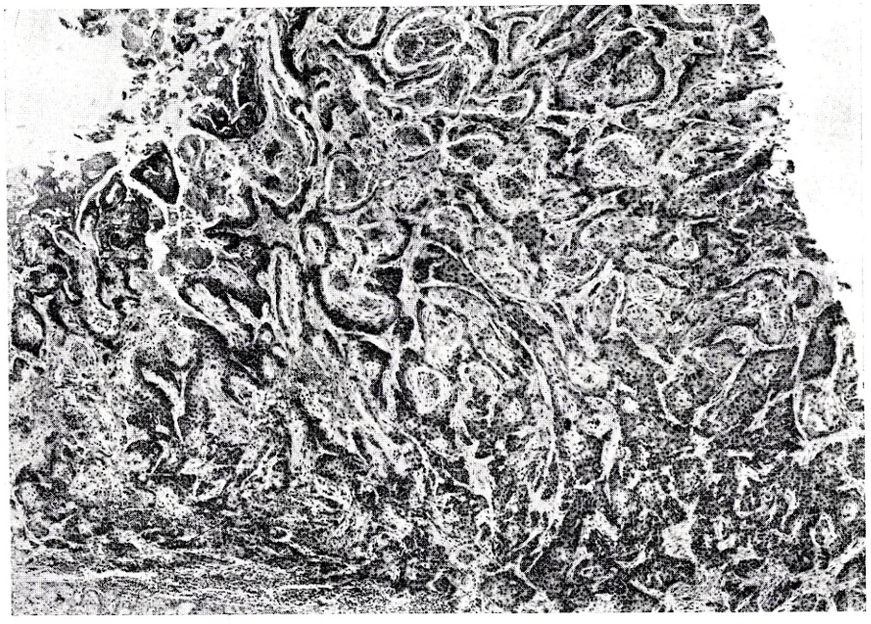

Fig. 10.

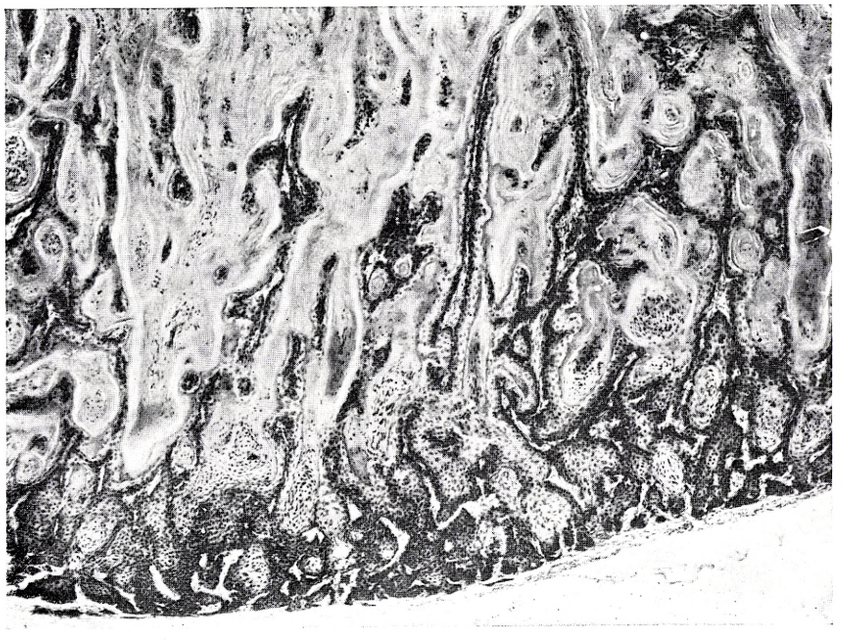

Fig. 12.

DET KGL. DANSKE VIDENSKABERNES SELSKABS SKRIFTER

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5. ZEUTHEN, H. G.: Hvorledes Mathematiken i Tiden fra Platon til Euklid blev en rationel Videnskab. Avec un résumé en français. 1917 8,00

II., 1916—1918 (med 4 Tavler) 11,50

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5. JUEL, C.: Die gewundenen Kurven vom Maximalindex auf einer Regelfläche zweiter Ordnung. 1917 0,75
6. WARMING, EUG.: Om Jordudløbere. With a Résumé in English. 1918 3,65

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V., (under Pressen).

1. BJERRUM, NIELS u. KIRSCHNER, AAGE: Die Rhodanide des Goldes und das freie Rhodan. Mit einem Anhang über das Goldchlorid. 1918 3,50

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