STUDIES BASED ON A MALIGNANT TUMOR OF THE
RABBIT.

II. PRIMARY TRANSPLANTATION AND ELIMINATION OF A COEXISTING
SYPHILITIC INFECTION.

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PLATES 41 TO 43.

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The report (1) dealing with the spontaneous tumor upon which this
series of investigations is based, contained a brief reference to attempts
which were made to transfer the tumor to other rabbits, indicating that
these attempts had proved successful and that the tumor had been
propagated for a number of generations. In view of the difficulties
which others have experienced in the transplantation of tumors of the
rabbit and as a means of conveying a general conception of the be-
havior of the tumor when transplantation was first accomplished, a
more detailed account of these phases of our work will be given in the
present paper.

Primary Transplantation.

An early diagnosis of a malignant growth simplified the problem of
primary transplantation to the extent of permitting several attempts
to be made before the animal succumbed. There was a complicating
factor, however, in the coexistence of a syphilitic infection, the signifi-
cance of which was not known at that time. It was not known whether
the tumor was inseparably bound up with a local infection or to what
extent the systemic infection might have influenced its development.
At any rate, there were two possibilities to be considered; first, the
transmission of syphilis by the inoculation of normal animals, and, second, the influence which an established syphilitic infection might
exert upon the growth of the transplanted tumor.
First Series.—While a tentative diagnosis of a malignant tumor was made from the nodule excised in October, 1920, it was several months before the growth recurred and developed sufficiently to provide material for transplantation. The first attempt to transplant the tumor was made on January 27, 1921. The material used came from a metastatic growth in a lymph node of the left inguinal region. Inoculations were made according to the conventional method of subcutaneous implantation of small pieces of tumor tissue. A transplant was made in the right groin of the original animal, and six male rabbits, three normal and three syphilitic, were inoculated in the scrotum; one female was inoculated at the base of the right ear.

The homograft grew fairly actively and was subsequently used in the inoculation of other animals. The transplants in the normal animals and one of the syphilitics with a comparatively recent and still active infection appeared to grow for upwards of 2 to 3 weeks, but the nodules remained small and indurated and eventually regressed, so that for practical purposes, growth results in these animals may be regarded as negative. They were valuable, however, in that they served as a warning against placing too much reliance upon subcutaneous transplantation and in this way aided in the orientation of the next series of inoculations.

Second Series.—The second attempt to transplant the tumor was made on March 3, 1921. In this instance, material was taken from several different sources, including a portion of the cutaneous recurrence, the homograft in the right groin, and parts of metastases in both the right and the left groins. This series contained fourteen male rabbits, ten normal and four syphilitic, all of which were inoculated subcutaneously, either in the groins or scrotum, with small bits of tissue as in the preceding experiment. In addition, however, three of the normal rabbits were inoculated in the right testicle with 0.3 cc. of a cell emulsion from the transplant of the original animal.

The results of the subcutaneous inoculations were much the same as before. Of the ten normal animals, two died soon after inoculation, five showed a suggestion of growth, in two there was slight but definite growth, while the tenth animal was definitely negative. Of the four syphilitic animals, one showed a definite growth, and while the nodule remained small, it persisted for at least 2 months before final regres-
sion set in. It may be noted that this animal was one that had exhibited an unusually severe syphilitic infection as regards both the extent and the duration of the lesions.

The results of the testicular inoculations were somewhat better. Small but transient tumor nodules developed in two of the three animals, while in the third, the growth measured approximately 1 cm. in diameter at the end of a month and was still increasing actively when it was removed to supply material for another series of inoculations and was the source from which the existing line of stock transfers was started (used for second generation).

From this experiment, it was also found that the transmission of syphilis had to be reckoned with. Of the eight normal rabbits that survived, five developed definite syphilitic lesions at the site of inoculation and it appeared not unlikely that the infection was more general.

Third Series.—Soon after the second series of transplants was made, the condition of the original animal became such that it had to be killed and a third series of rabbits was inoculated as a safeguard against the loss of the tumor. By this time, we were convinced that little was to be hoped for from subcutaneous inoculations. It had been found that the pieces of tissue introduced beneath the skin stimulated a vigorous granulomatous reaction much the same as any foreign body and that the initial efforts at growth were almost immediately suppressed by the formation of a dense fibrous capsule, the tumor cells being incarcerated and smothered out, as it were. For the same reasons, it appeared that the opportunities for growth might be improved by the introduction of the cells into some organ in which connective tissue was less abundant or in which nutritive conditions were better than those afforded by the subcutaneous tissues. The indications were that the testicles might meet these requirements; hence, the third series of inoculations was carried out by this route. The material used was taken from metastatic nodules in the liver. The tissue was finely minced and carefully rubbed up in a mortar, an emulsion being prepared by the addition of a small amount of normal salt solution. 0.5 cc. of this emulsion was injected into each testicle of four normal rabbits by means of a syringe and an 18 gauge needle.

Three of these animals developed tumors which grew slowly at first and then more actively and eventually metastasized to various
parts of the body. One animal in particular showed extensive tumor
growths in the abdominal viscera with metastases in the ciliary body
of one eye and in the upper jaw.

None of the animals in this group developed syphilitic lesions, and
while there is no assurance that they were not infected, the contrast in
this respect with animals inoculated with material from lymph node
metastases is worthy of note, especially in view of the more vigorous
growth of the tumor in the absence of outspoken lesions of syphilis.

Solution of the Problem of Transplantation and Elimination of the
Syphilitic Infection.

The success obtained by the use of intratesticular inoculations
gave promise of a satisfactory solution of the problem of transplanta-
tion, but the advantages of this method as a means of propagating the
tumor and the behavior of the transplanted growth were still to be
determined upon a larger series of animals; there was also the ques-
tion of a syphilitic contamination to be disposed of, and these prob-
lems were taken up with the second generation of transfers.

Second Generation.—The inoculations of the second generation were
made on April 7, 1921, from the testicular growth of the animal pre-
viously indicated in Series 2. In this instance, the tissue was finely
minced with scissors so that, when salt solution was added, it could
be drawn into a syringe through an 18 gauge needle which was used
for making the inoculations. The animals inoculated included
four syphilitics, seven rabbits previously inoculated with tumor tissue,
and twenty-two normal animals, only the last of which need be
considered at this time. The normal rabbits were divided into three
groups: ten of them were inoculated in the right testicle, nine were
given an intracutaneous inoculation on the ventral surface of the
sheath, and three were inoculated in both the testicle and the sheath.

The results of this series of inoculations were very striking and may
be described in greater detail than the preceding experiments as a
means of illustrating the important part which intratesticular inocu-
lation has played in the transplantation of the tumor and the behavior
of the growth at the beginning of transplantation. For convenience
of analysis, the essential data of this experiment are assembled in
Table I.
By reference to Table I, it will be seen that only one animal of the nine inoculated on the sheath (Group A) developed a tumor of any considerable size. The growth in this instance was essentially the same as that illustrated in Figs. 1 to 4. The primary tumor grew actively for a period of approximately 8 weeks, during which time a small metastatic nodule developed in the right inguinal lymph node. Regression then took place with apparently complete recovery, and at autopsy, there was no evidence of healed metastases in other parts of the body.

A second animal (No. 2) developed a small nodule at the site of inoculation which appeared to be something more than the usual granulomatous reaction but was not sufficiently definite to warrant a positive diagnosis of tumor growth. As will be seen, three animals of this group were kept under observation for 6 to 7 months; the others were reinoculated in the right testicle at the end of 7 weeks with a rather anomalous result in that all but one of them developed testicular tumors from the second inoculation.

This fact is mentioned because a growth subsequently appeared in one of these animals (No. 3) at the site of the original inoculation. The growth did not appear until long after the second inoculation, but there is no way of determining whether it represented a delayed development from the first inoculation or a metastasis from the testicular tumor, the location of which might have been determined by the previous trauma. At any rate, the lesion on the sheath was still active when the animal died 4½ months after the second inoculation. Death was due to the development of widespread and extensive metastases which were accompanied by gradual emaciation, weakness, and anemia, the loss in weight amounting to 550 gm., or more than 25 per cent of the normal body weight. The extent of the growth and the emaciation at the time of death are illustrated in Fig. 5.

The part played by the sheath lesion in the production of this condition is uncertain, but it appears that metastases such as those in the inguinal lymph nodes (Fig. 5) may have originated from this source. In all probability, however, this animal illustrates a condition of affairs essentially the same as that of the second group of animals (Group B) in which there was a simultaneous inoculation of testicle and sheath. This opinion is based upon the fact that in no
TABLE I.

Results of Tumor Inoculations in the Second Generation.

| Animal No. | Result of inoculation | Incubation period | Extent of primary growth | Duration of growth | Length of observation | Presence of metastases | Disposition of animal | Remarks |
|------------|-----------------------|-------------------|--------------------------|-------------------|----------------------|-----------------------|----------------------|---------|
|            |                       |                   |                          |                   |                      |                       |                      |         |
| Group A. Intracutaneous inoculation. | | | | | | | | |
| 1          | +                     | 9                 | +++                      | 8                 | 29                   | +                     | Killed.              | Spontaneous recovery. |
| 2          | ±                     | ?                 | ?                        | ?                 | 7                    | -                     | Reinoculated.         | Reinoculation +.      |
| 3          | -?                    | -                 | -                        | -                 | 7                    | -?                    | "                    | See text for results on this animal. |
| 4          | -                     | -                 | -                        | 24                | -                    | -                     | Killed.              | No tumor growth.      |
| 5          | -                     | -                 | -                        | -                 | 25                   | -                     | "                    | "        |
| 6          | -                     | -                 | -                        | -                 | 7                    | -                     | Reinoculated.         | Reinoculation +.      |
| 7          | -                     | -                 | -                        | -                 | 7                    | -                     | "                    | "        |
| 8          | -                     | -                 | -                        | 7                 | -                    | -                     | "                    | "        |
| 9          | -                     | -                 | -                        | 7                 | -                    | -                     | "                    |         |
| Group B. Intracutaneous and intratesticular inoculation. | | | | | | | | |
| 1          | + +                   | 9 9               | +++ +++                  | 10 10             | 10                   | +++                   | Killed.              | Encapsulated tumor in right testicle. |
| 2          | + +                   | 10 6              | +++ ++                  | 29 5              | 29                   | -                     | "                    | "        |
| 3          | + ±                   | 9 ?               | +++ ?                   | 24 24             | -                    | -                     | "                    | "        |

MALIGNANT TUMOR OF THE RABBIT. II
### Group C. Intratesticular inoculation.

|   |   |   |   |   |   |
|---|---|---|---|---|---|
| 1 | + | 14 | ++++ | 4 | 4 | Killed.  
| 2 | + | 9  | ++++ | 4 | 9 | “  
| 3 | + | 9  | ++++ | 9 | 9 | “  
| 4 | + | 9  | ++++ | 8 | 8 | “  
| 5 | + | 6  | ++++ | 7 | 7 | “  
| 6 | + | 6  | ++++ | 10| 10| “  
| 7 | + | 9  | ++++ | 24| 24| “  
| 8 | + | 9  | ++++ | 11| 11| Died.  
| 9 | + | 9  | ++++ | 12| 24| Kiled.  
| 10| + | 9  | ++++ | 29| 29| “  

Growth still active when killed.
Castrated 4 wks. after inoculation.
“ 4 “ “ “
“ 4 “ “ “
Growth still active when killed.
Castrated 7 wks. after inoculation.
Intercurrent infection.
Spontaneous recovery.
Extremely weak when killed.

? indicates result uncertain; -, negative; ±, suggestive positive; +, positive, slight primary growth or metastases; ++, moderate primary growth or metastases; ++++, large primary growth or numerous metastases; and ++++, extremely large primary growth or extensive metastases.

In Group B, the double columns of figures refer to testicle and sheath respectively.
other instance has an intracutaneous inoculation led to the death of the animal.

Of the three animals in the second group (Group B, Table I), two developed large tumors at both sites of inoculation, while in the third, there was a good growth in the testicle but the result of the sheath inoculation was uncertain.

The first animal of the group may be taken as an example of the height of activity attained by the tumor at this time and under these conditions. The growth of the primary tumors from the 5th to the 10th week is shown in Figs. 1 to 4. It will be seen that when the animal was killed at the end of the 10th week, there were well-developed metastases in the inguinal lymph nodes of both sides. The animal was in good physical condition. The weight had fluctuated between 1,825 and 2,025 gm., the initial weight being 1,850 and the final weight 2,000 gm., giving a net gain of 150 gm. At autopsy, metastases were found in the inguinal and flank nodes, the omentum, the mesentery, the perirenal fat, the kidneys, and the wall of the right ventricle.

The course of the tumor growth in the two other animals of this group was somewhat different. In one animal, both tumors grew actively for a period of about 5 weeks, at which time the lesion on the sheath began to regress and completely disappeared. The testicular growth persisted and at the time the animal was killed (29 weeks after inoculation) formed a mass about 5 to 6 by 2.5 to 3 cm. in diameter which was necrotic at the center and enclosed in a thick fibrous capsule. The animal was in good physical condition and no active or healed metastases were found.

The third animal showed no definite growth on the sheath but the course of the testicular tumor and the autopsy findings were much the same as those of the second.

The ten animals of Group C need not be considered individually, except in a few instances. By reference to Table I, it will be seen that all the animals inoculated in the testicles developed large primary tumors with an incubation period of from 6 to 14 days. These animals were used in various ways for further transplantation experiments and for studying the progress of the tumor growth. Three (Nos. 1, 5, and 6) were killed for pathological examination 4, 7, and
10 weeks respectively after inoculation; three animals (Nos. 2, 3, and 4) were castrated at the end of 4 weeks and later killed (8 to 9 weeks) and one other animal (No. 7) was castrated after 7 weeks. This left three rabbits in which there had been no operative interference with the progress of the tumor and one of these (No. 8) died from an intercurrent infection (11 weeks). The two remaining animals (Nos. 9 and 10) together with the one castrated at 7 weeks (No. 7) were held under observation for 24 to 29 weeks before being killed for final examination.

The first animal killed (4 weeks) showed no recognizable metastases, but two of the three animals castrated at the same time showed recurrence of the tumor in the scrotum and cord with metastases to internal organs when killed 4 and 5 weeks later (Nos. 3 and 4). At the end of 7 weeks (No. 5), the growth was found to have extended to the abdominal cavity with metastases to numerous organs, and a similar but more marked picture was presented by the animal killed after 10 weeks (No. 6). Metastases were also present in the animal that died from an intercurrent infection (11 weeks).

The picture presented by all these animals was much the same in character. There was an active growth of the primary tumor which, if undisturbed, filled the entire testicle and usually extended up the cord in the form of isolated nodules situated in the cord itself or in the serous membranes of the inguinal canal and adjacent parts of the abdominal cavity. In addition, metastases were present in the mesentery and omentum, in the retroperitoneal tissues, and in various internal organs. The appearance presented by the primary tumor and the extension of the growth along the inguinal canal may be illustrated by Figs. 6 and 7, taken from Animal 5, killed 7 weeks after inoculation. The histology of the early growth is shown in Fig. 8, which represents a section from the testicle of Animal 3, 4 weeks after inoculation.

Only three animals of this group were held beyond the 11th week. One of these (No. 9) showed an apparently complete recovery, and when killed (24 weeks), there was no evidence of metastases. The second animal (No. 7) had been castrated, but local recurrence had taken place, followed by encapsulation and partial regression. At autopsy, however, large metastatic growths were found in the pelvis, the mediastinum, and the right suprarenal.
The other animal of the group showed a slowly progressive tumor growth with palpable metastases in the abdominal organs and gradual development of cachexia. When the animal was killed after 29 weeks, he had become extremely emaciated and weak. At autopsy, extensive metastases were found in the abdominal and thoracic organs, the condition presented being much the same as that shown in Fig. 5, with an especially marked involvement of the kidneys, one of which is shown in Fig. 9.

The results obtained in this series of animals will serve to indicate the general characteristics of the growth and the potentialities of malignancy as they appeared at this time under conditions of transplantation which were favorable to the growth of the tumor. These results also convinced us of the superiority of intratesticular inoculation over subcutaneous or intracutaneous inoculations as a means of propagating the tumor, and this type of inoculation has since been employed as the routine method for stock transplantations. The only respect in which the method used in this experiment has been changed is in the substitution of a homogeneous cell emulsion, prepared by mincing and grinding the tumor tissue, for the more tedious process of preparing a finely minced suspension of tumor fragments.

**Elimination of Syphilitic Infection.**—None of the animals of the second tumor generation showed outspoken lesions of syphilis, but since the infection was known to be widely disseminated among those of the first generation, steps were taken to remove the possibility of transmitting this infection through tumor inoculations. For this purpose, several animals with actively growing tumors were subjected to vigorous treatment with arsphenamine. The treatment given to different animals varied from a single intravenous injection of 20 mg. of arsphenamine per kilo of body weight to two or three doses of 15 mg. per kilo given at weekly intervals. This gradation in treatment was adopted as a precaution against any harmful effects which the drug might exert upon the tumor itself and to secure at the same time the necessary degree of treatment. Among the animals treated, there were some known to be infected with *Treponema pallidum*, and the ultimate effects upon the transmissibility of the infection were controlled by subsequent inoculation of normal animals with emulsions prepared from the popliteal nodes of the treated animals.
The treatment with arsphenamine produced no harmful effects upon the tumor growth which were immediately demonstrable. On the contrary, the tumors in these animals grew much more rapidly than those of untreated animals of the same series. Eventually, however, there was a suggestion that spontaneous recovery might have been facilitated by this treatment, but the number of animals was too small and the period of observation too short to permit of any definite conclusion upon this point, and as yet the experiment has not been repeated.

Test inoculations were not made from the lymph nodes of treated animals for several months after treatment in order to allow sufficient time for any surviving organisms to recover. The results of these inoculations were negative in all cases. This in itself furnishes no assurance that the infection had been completely eradicated, but as a further provision of control, the test animals were reinoculated with *Treponema pallidum* at the end of 3 months and developed syphilitic lesions in the testicles.

While awaiting the outcome of tests as to the efficacy of the treatment which had been given, transfers were made from an animal that had received two doses of 15 mg. of arsphenamine per kilo of body weight. This line has been perpetuated as our stock strain and no further evidence of syphilitic infection has been seen in animals inoculated with material derived from this source.

**Method of Transplantation.**—As a result of the experiments reported, intratesticular inoculation was adopted as the routine method of transplantation, and the details of the method now used differ very little from those described above. Care is exercised in the selection of a tumor which is actively progressing, and, as a rule, transplantations are made at intervals of from 2 to 4 weeks, depending upon the rate of growth and the general behavior of the tumors which are to be used for inoculation.

The animal is anesthetized and castrated with aseptic precautions. The tumor is then sectioned and the most actively growing parts are placed in a dish or mortar and finely minced with scissors. Occasionally a suspension of this material is made by the addition of 0.85 per cent sodium chloride solution, but, as a rule, the minced tissue is rubbed up in a mortar and a homogeneous cell emulsion is prepared.
In either case, the inoculation is made by the injection of 0.1 to 0.3 cc. of this material with a syringe fitted with an 18 or 20 gauge needle.

The preparation of material is carried out aseptically but no antisepctic precautions are used in making inoculations other than to sponge off the surface of the scrotum with a 50 per cent solution of alcohol in some instances. For routine purposes, animals are inoculated in only one testicle. The dose used in different series of animals is largely a matter of judgment as to the quality of the material and the thickness of the suspension. A cell emulsion is used in preference to a suspension of tissue fragments purely as a matter of convenience, as thus far no material difference in results has been observed. The method as described is extremely simple and has given an almost uniform series of takes with a high percentage of malignant tumor growths.

DISCUSSION.

The ease with which this tumor was transplanted and has been maintained for more than twenty generations will doubtless be apparent. Success is attributed in part to good fortune and in part to the recognition of the true significance and importance of simple pathological processes as factors in the growth of the transplanted tumor. We were fortunate in discovering the tumor before the condition of the animal became critical and more fortunate in being able to recognize the cause for the failure of subcutaneous transplantations and to devise methods which obviated these difficulties. The chief element of success in the transplantation of the tumor was the interpretation of the reaction in the skin and subcutaneous tissues as an ordinary process of repair or of encapsulation which was capable in itself of determining the fate of the tumor cells, and the correctness of this interpretation was amply sustained by the success which followed the use of methods based upon this assumption.

It is also of interest to note that while the tumor was first transplanted from a graft in the original animal, transplantation was accomplished with equal facility from metastases in the liver, and the growth in these animals was more malignant than that in animals inoculated from the graft.
In regard to the syphilitic infection which was transmitted to some of the earlier animals, attention may be called to the fact that so far as is known, these infections all originated from inoculations made with material from lymph nodes; that is, no instance of outspoken syphilitic infection developed among the animals which were inoculated only from the skin, the graft, or liver metastases. A further feature of interest is the fact that in no instance was there a simultaneous activity of both processes. There were only a few animals in which a tumor growth was obtained, but none of them developed syphilitic lesions, and with one exception, the tumor failed to grow in animals with an established syphilitic infection or in those in which syphilitic lesions developed following tumor inoculation.

The percentage of active tumor growths obtained by testicular inoculation and the malignancy displayed by the tumor in the first and second generations are somewhat unusual, and while these conditions were due in part to the method of inoculation, they are also indicative of a high degree of proliferative activity or resistance on the part of the tumor cells. No accurate forecast of the course of the tumor during the first and second generations can be given, since so few of these animals were held for any considerable period of time. The occurrence of metastases was determined in the great majority of animals, and in several instances, it was shown that they must have occurred as early as the 4th to the 7th week. It seems safe to assume that eventually the majority of the animals with metastases to internal organs would have died as a result of the tumor growth, but probably not all of them.

Some indication of the probable course of the disease at this period in its history may be obtained from a group of two animals of the first generation and five of the second which were held for 6 to 7 months after inoculation. These animals were inoculated in the testicles, but two of them received an intracutaneous inoculation in addition. Two animals virtually succumbed to the tumor growth, being killed when it was apparent that they could survive for only a short time, but both of them lived approximately 7 months after inoculation. There were two other animals in which active metastatic lesions were found at autopsy, and these probably would have succumbed in time. Two animals showed what may be termed a partial recovery or an arrested growth in that encapsulated and partially necrotic primary growths
were still present but no metastases were found. Both of these received a cutaneous as well as a testicular inoculation. Finally, there was one animal in which an apparently complete recovery had taken place.

Upon this basis, one might forecast a prolonged course of disease with a mortality of more than 50 per cent. These figures may be somewhat misleading, however, in that the animals of the second generation were hardly representative of their group in respect to age and activity of growth of the primary tumors, and as we know, these factors are of some importance. Discounting the results upon this basis, it is not unlikely that the mortality would have been increased somewhat and the length of survival materially shortened. Nevertheless, a slowly progressive course appears to have been a characteristic feature of the disease at this time as compared with later generations. It is obvious, however, that the transplanted tumor possessed highly malignant characteristics in even the earliest generations. Since this time, the tumor has exhibited some rather striking variations in its behavior which will be made the subject of a future communication.

**SUMMARY.**

Several attempts were made to transplant a spontaneous malignant tumor in a syphilitic rabbit before a method was devised which proved successful. Subcutaneous and intracutaneous inoculations were unsuccessful on account of the vigorous granulomatous reaction which was aroused by the introduction of tumor fragments into these tissues. This difficulty was overcome by the use of intratesticular inoculations. With this method, a good growth was obtained in practically all animals. It appeared possible, however, that a syphilitic infection had been transmitted along with the tumor, and hence treatment with arsphenamine was instituted as a means of eliminating this infection. A study of the transplanted tumor in the first and second generations showed that it possessed a high degree of malignancy. Metastases occurred at an early period in the majority of animals, and while some of them appeared to recover, the indications were that more than 50 per cent might be expected to succumb to the effects of the tumor growth within a period of 6 to 7 months.

The method of intratesticular inoculation now in use is described in detail.
BIBLIOGRAPHY.

1. Brown, W. H., and Pearce, L., *J. Exp. Med.*, 1923, xxxvii, 601.

EXPLANATION OF PLATES.

The illustrations are all from photographs which have not been retouched.

**PLATE 41.**

Figs. 1 to 4. Rabbit 1, Group B. Primary tumors in the right testicle and sheath showing stages in development between the 5th and 10th weeks after inoculation. Fig. 4 shows metastases in the inguinal lymph nodes. $\times 1$.

**PLATE 42.**

Fig. 5. Rabbit 3, Group A. Primary and metastatic tumor growths with emaciation. $\times \frac{1}{2}$.

**PLATE 43.**

Figs. 6 and 7. Rabbit 5, Group C. Primary growth in the testicle with metastases along the inguinal canal 7 weeks after inoculation. $\times 1$.

Fig. 8. Microscopic appearance of the transplanted tumor 4 weeks after inoculation. $\times 150$.

Fig. 9. Kidney of Rabbit 10, Group C. $\times 1$. 
(Pearce and Brown: Malignant tumor of the rabbit. II.)
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