THE EFFECT OF OPERATIVE INTERFERENCE WITH THE
CERVICAL SYMPATHETIC NERVOUS SYSTEM
UPON THE GROWTH AND MALIGNANCY
OF A TRANSPLANTABLE NEOPLASM
OF THE RABBIT.

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Previous papers dealing with a transplantable neoplasm of the
rabbit have emphasized the conception that variations in the character
of the disease are largely due to variations in the mechanisms of
reaction and resistance of the host and, furthermore, that this mecha-
nism is an expression of animal metabolism or economy. It has been
found, for instance, that the clinical course of the malignant disease
may be correlated with the state of the glands of internal secretion as
measured by the mass relationships of these organs (1). From our
observations upon normal rabbits (2) as well as those infected with
Treponema pallidum (3) it would appear that the alterations in mass
relationship in the endocrine glands of tumor animals possess a func-
tional significance and, furthermore, that as one of the factors in the
constitutional organization of the animal, this system of organs occu-
pies an important position in the mechanism of animal resistance.
This view was submitted to direct investigation by means of various
operative procedures with these organs and it was found that the
growth and malignancy of the tumor could be affected in certain in-
stances, notably by complete extirpation of the thyroid, a procedure
markedly increasing the severity of the disease (4). It was felt, how-
ever, that the relative value of individual endocrine organs was of less
importance than the integrity and balance of the system as a whole.

The possibility of a direct or indirect participation by the sympa-
thetic nervous system in the reaction and resistance to the tumor has been
considered with regard to the growth of the primary tumor and the
subsequent course of the disease. In order to investigate it, various
parts of the sympathetic nervous system were removed before inoculation with the tumor. The cervical portion of the sympathetic system was selected because of its probable connection with the thyroid as well as its surgical accessibility.

Material and Methods.

Description of the Cervical Sympathetic Nervous System.—The cervical sympathetic nerve system in the rabbit comprises the upper two ganglia of the sympathetic chain on either side, together with the connecting trunk and rami of distribution. The superior ganglion lies at the base of the skull just medial to the internal carotid artery and vagus; the inferior ganglion is situated at the base of the neck directly above the origin of the subclavian artery; the trunk follows the course of the vagus through the neck. By analogy with human anatomy it is assumed that each ganglion is connected to the central nervous system by centripetal fibers (grey rami) and by centrifugal fibers (white rami). The grey rami join the corresponding cord segments in the case of each ganglion but the white rami for both ganglia enter the sympathetic trunk from the upper thoracic segments. Each ganglion, also, distributes fibers peripherally to blood vessels, glands, etc. It is not certain which of them, in the rabbit, is chiefly concerned in supplying the thyroid gland.

Operative Procedures.—Four types of operations were performed: (1) extirpation of both superior ganglia ("superior sympathectomy"), (2) extirpation of both inferior ganglia ("inferior sympathectomy"), (3) extirpation of both superior and both inferior ganglia and of both cervical sympathetic nerve trunks ("complete sympathectomy"), (4) division of the sympathetic trunk ("sympathotomy"). Ether anesthesia was used for each operation. No especial preparation was employed except the omission of the morning feeding on the day of operation. The hair over the ventral cervical region was clipped and shaved and the skin washed with 50 per cent alcohol. A midline incision was made, and by careful dissection in a bloodless field, the sympathetic trunk was isolated at a point just below the thyroid with retraction of the sternomastoid muscle medially. The trunk was then followed upwards or downwards to the ganglion to be removed. Extirpation of the superior ganglion was easily accomplished because of ready approach and clear identification. It was avulsed, together with such of its fibers of distribution as came with it. Removal of the inferior ganglion, on the other hand, was much more difficult, principally because of its close relation to the subclavian artery and to a fine blood vessel plexus, and the approach to it was difficult also. Manipulation of the ganglion during a dissection was found to set up cardiodepressor reflexes occasionally resulting in sudden death. The operation of sympathectomy consisted in division of the sympathetic trunk in a midposition opposite the lower pole of the thyroid, by excising a small section between ligatures.

Our entire group of complete cervical sympathectomy operations numbers
thirty-two rabbits with an operative mortality of 18.8 per cent; however, among
the last twenty animals there was but one death. Twenty-four rabbits have been
operated upon for double inferior sympathectomy with an operative mortality of
16.7 per cent and but one death in the last fifteen animals. There were no deaths
in the observation period between these operations and inoculation with the tumor,
and we have had no fatalities with the superior cervical sympathectomy or
sympathotomy operations.

The criteria of complete removal of the superior or inferior ganglia, or of the
sympathetic nerve, were entirely objective, since the conditions of the work
precluded the use of physiological tests. The dissections were so carried out that
we could be reasonably certain during the operation of removing the entire
ganglion, and its absence was verified by careful search at the postmortem examina-
tion of each rabbit. Extirpation of the cervical nerve or a portion of it was con-
trolled by following the nerve to the superior cervical ganglion before removal or
section of it.

**Animals.**—The animals employed were young adult or adult male rabbits
selected and matched according to breed, age, and length of caging. They were
separately caged and fed the ordinary diet of oats, hay, and cabbage used in these
laboratories.

**Tumor.**—The tumor has been described in detail in previous papers (5, 6).
It belongs to the class of epithelial tumors, is easily transplanted by intratesticular
inoculation, and gives rise to a primary growth and metastatic growths in prac-
tically every tissue and organ of the body. The course of the disease in individual
animals or in different series of animals is variable both as regards the actual
outcome of the disease and as regards the course of the primary tumor and the
incidence and distribution of metastases. Some rabbits die within 3 to 4 weeks
after inoculation with extensive tumor involvement while others which may have
shown a similar primary tumor growth ultimately recover and at postmortem
examination show few or no foci of tumor. All gradations between these extremes
are to be found.

**Method of Inoculation.**—At various intervals after operation inoculations were
made with a salt solution suspension of an actively growing primary tumor; 0.3
cc. of the tissue emulsion was injected into one testicle. A suitable number of
normal rabbits were inoculated at the same time to serve as controls.

**Conduct of Experiments and Method of Analysis of Results.**—Each rabbit was
examined at frequent intervals with special reference to the following points:
the rate, type of growth, and eventual fate of the primary tumor, the appearance
of metastases in superficial parts of the body, and the general physical condition
of the animal. Twice a week the animals were weighed and the primary tumor was
measured. Rabbits which developed a paralysis of the legs or a physical deteriora-
tion with emaciation and weakness were killed with ether. The experiment was
terminated 2 months after inoculation, at which time all surviving animals were
killed. In each instance a complete postmortem examination was made with
special attention to the distribution, amount, and character of tumor tissue. In
addition, all the principal organs were weighed.

The data obtained were used as a basis for estimating the character of the
disease. The total probable mortality rate of a group includes those animals
which died or were killed during the experimental period of 2 months and those
which showed, at the end of this period, such metastatic growths as would probably
have caused death at some future time as, for instance, tumors of both suprarenal
glands. The incidence and distribution of secondary growths have been con-
sidered upon a relative and actual basis, the former including all animals of a
group, while the latter takes into account only those in which metastases were
found. The percentage estimations of the distribution of metastases have been
calculated upon the basis of the number of foci theoretically possible as shown
by the actual location of metastases in the first twenty generations of tumor
animals (6).

The figures refer to the number of organs or tissues involved, not to the actual
numbers of secondary growths, and, consequently, the expressions “foci of metas-
tases,” “distribution of metastases,” or “metastatic rate” are used rather than
“number of metastases.” By contrast the figure for the number of clinical
metastases detected during the life of the animal refers to the actual number of
individual secondary tumors found.

There are certain obvious objections to the above method of estimation. For
instance, such organs as the liver and kidneys may be markedly involved with
numerous tumors or by only a few which destroy little of the organ. However, the
general character of the disease process, whether of high, moderate, or low malig-
nancy, is shown by a grouping of the percentage estimations of metastatic distri-
bution according to the following four subdivisions (Text-figs. 2 and 3): (1) exten-
sions and implantations including those to the retroperitoneal and mediastinal
lymph nodes, (2) those to the lungs and pleura, liver, kidneys, and pancreas, (3)
to the skin and subcutaneous tissue, superficial lymph nodes, muscles, bones and
bone marrow, heart and pericardium, glands of internal secretion with the excep-
tion of the suprarenals, spleen, and the central nervous system, (4) to the supra-
renals and eyes. This system of grouping was selected for the following reasons.

It has been found, from the study of several hundred rabbits inoculated with
this tumor, that in those animals in which the most malignant disease develops
and in which death occurs within 3 to 5 weeks after inoculation there is usually a
widespread distribution of metastases to the skin, the superficial lymph nodes, the
muscles, the bones and bone marrow, the heart, the spleen, and the endocrine
glands as well as to the parenchymatous viscera, the retroperitoneal and mediast-
inal tissues, and the serous membranes of the abdominal cavity. In instances
of a somewhat less malignant disease, the most conspicuous and frequent second-
ary growths are found in the liver, kidneys, lungs, and pancreas. A level of still
lower malignancy is chiefly characterized by the predominance of extensions to
the retroperitoneal and mediastinal tissues and by implantations upon the omen-
tum, mesentery, and parietal peritoneum. If death occurs in animals so affected during the first 2 months after inoculation, the extensions and implantations referred to are found to be of an extreme grade or else, and more often, some organ such as the kidneys or hypophysis is also involved. Finally, in those animals in which the disease is very mild, metastases may be found only in such sites as the eyes or suprarenal glands which do not appear to share, to an equal extent, the resistance to tumor growth possessed or developed by other tissues and organs in the body. However, secondary growths in the eyes and suprarenals also occur in cases of extreme malignancy with a widespread distribution of metastases, so that with reference to the character of the disease it is necessary to separate the instances of a mild disease from those of a severe malignancy. In addition, it should be emphasized that metastases to the skin, muscles, bones, and endocrine gland group practically never occur in cases of low malignancy.

Number and Time of Experiments.—Our first experiments served to emphasize the necessity of a larger number of animals and the desirability of a uniform time interval between operation and inoculation. We have chosen as the basis for this report the third experiment in which such factors and that of the operative technique have been satisfactorily controlled. The series was inoculated on November 14, 1924, with the thirty-ninth generation of the tumor and consisted of 10 rabbits submitted to double superior sympathectomy (14 and 15 days between operation and inoculation), 9 with double inferior sympathectomy (16, 17, and 18 days between operation and inoculation), 10 with double complete sympathectomy (9, 11, 14, and 18 days between operation and inoculation), 9 with double sympathotomy (8 and 9 days between operation and inoculation), and 10 controls.

RESULTS.

The results of the experiment have been considered upon the basis of the general character of the disease developing in the various groups of animals rather than that of individual rabbits. The principal points are summarized in Tables I and II and Text-figs. 1 to 3. The disease of the normal or control rabbits will first be described as a means of comparison with that of the operated groups.

The primary tumor in the control rabbits grew in each instance; in two animals it was comparatively small, in two others it developed very rapidly and to extreme proportions during the first 3 weeks, while in the remainder it grew somewhat less rapidly but eventually attained a large size. The curves in Text-fig. 1 record the average calculated volume of the primary tumors of all the various groups of rabbits during the 1st month of the experiment, and it is seen that the volume in the control rabbits was somewhat greater than in the
### Table I: Analysis of Results

<table>
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<th>Group No.</th>
<th>No. of rabbits</th>
<th>Mortality</th>
<th>Clinical metastases</th>
<th>Total foci of metastases</th>
<th>Surviving rabbits</th>
<th>Character of disease</th>
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<td></td>
<td></td>
<td>Actual</td>
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<td>Negative or probable recovery</td>
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<td>Probable total</td>
<td>%</td>
<td>%</td>
<td>No. rabbits</td>
<td>Condition of primary tumor</td>
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<td></td>
<td></td>
<td>Time of death</td>
<td>No. per animal</td>
<td>Relative rate</td>
<td>Actual rate</td>
<td>No. of probable deaths</td>
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<td>11</td>
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**Notes:**
- Table represents the results of a study on transplantable neoplasms in rabbits.
- The table details various metrics such as incidence of paralysis, time of death, and condition of primary tumor.
- Data includes the number of rabbits, actual and probable total, time of death, incidence of paralysis, total No., No. per animal, relative rate, actual rate, no. of probable deaths, and condition of primary tumor.
- The character of disease includes negative or probable recovery, condition of primary tumor, and metastatic foci.

**Source:** Published October 1, 1925.
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Group 1, superior; Group 2, inferior; Group 3, complete; Group 4, sympathectomy; Group 5, control.
operated animals with the exception of the sympathotomy group. Among the seven rabbits surviving at the conclusion of the experiment, the primary tumor was healed in one, largely necrotic in five, and mostly of living tissue in one instance. Three metastases were detected clinically in two rabbits. The actual mortality rate for this group was 30 per cent, the deaths occurring 4½, 5, and 7½ weeks after inoculation. However, it was felt, from postmortem examination at the end of the experiment, that two other animals would have eventually died from the effects of secondary tumor growths, thus making the total probable mortality 50 per cent. At autopsy one or more secondary tumors were present in each rabbit, an animal incidence of 100 per cent (Table I). The total number of metastatic foci in the group was 66, or a relative and an actual distribution rate of 6.6 per animal. A conception of the general distribution of these growths may be obtained by reference to Text-fig. 2 in which it is seen that the highest proportion of metastases occurred in the suprarenals and the eyes, while the smallest number were in the group comprising the skin, muscles, bones, and endocrine glands. As has been previously mentioned, metastases of the suprarenals and eyes usually occur either in cases of high malignancy with a widespread distribution of tumor or in instances of low malignancy in which such foci are frequently the only tumors found. There were six animals in the control group with metastases to these organs; in four the disease was mild while in two it was severe. Taking into consideration the mortality rate, the animal incidence of metastases, and the general distribution of the growths, the malignancy in the controls may be classed as of moderate or average severity.

In the four operated groups the general severity of the disease or the level of malignancy was definitely higher than in the controls. The primary tumor always grew, but only in the sympathotomy group was its average volume comparable with that of the controls. In the case of the superior and complete sympathectomies the smaller size of the primary tumor was apparent 17 days after inoculation (Text-fig. 1), while by the 3rd week the tumors of the inferior group

1 The health and condition of the rabbits did not appear to be impaired as a result of the operations. The interval prior to inoculation was sufficient for recovery from any immediate ill effects.
were also definitely smaller than those of the controls and sympathotomy groups and continued to be so. At the conclusion of the experiment there were six surviving rabbits in the superior, inferior, and complete groups and three in the sympathotomy group. There was little difference in the character of the residual primary tumor among these groups except possibly in the case of the sympathotomy animals in which two were healed and one was practically entirely necrotic. There was one instance in each of the other three groups of a primary tumor which contained a considerable amount of living tissue. The relation of the character of the primary tumor growth to the general disease picture will be considered later.

There were more superficial metastases evident during life in all the operated groups than among the controls. Thus, after sympathotomy there were 12 in 5 rabbits (2.5 per animal), 10 in 4 after complete sympathectomy (2.5 per animal), 10 in 5 after superior sympathectomy (2.0 per animal), 11 in 6 after inferior sympathectomy (1.8 per animal), and 3 in 2 controls (1.5 per animal). As will be seen later, the most malignant disease developed in the sympathotomy and complete and superior sympathectomy groups, while the series with inferior sympathectomy fell between these and the controls. It so happens that the figures for metastases observed during life follow the same order.

The actual mortality rate (Table I) for the superior and complete sympathectomy groups, 40 per cent, was slightly higher than that for the controls, 30 per cent, while that for the inferior sympathectomies was the same, whereas the rate for the sympathotomies was more than double that of the controls, being 67 per cent. The greatest number of early deaths occurring, that is to say in the 4th and 5th weeks, occurred in the sympathotomy and complete sympathectomy groups. There was one instance in the complete, superior, and inferior sympathectomy groups and three in the sympathotomy group, of metastases to the spine causing paralysis of the hind quarters on which account the animals were killed. Among the controls there was one instance of deposits of tumor in the floor of the middle fossa of the skull beneath the dura. The total mortality rates of the several groups, which include those animals surviving throughout the experiment but which probably would have died from the effects of the tumor, approximate
each other more closely, but in the case of the sympathectomy rabbits the actual and total rates are the same, 67 per cent. There are slight differences, however, in the complete and superior sympathectomy groups which may be significant. Thus, there was an estimated mortality of six deaths in the complete sympathectomy group of which four actually occurred, and five in the superior sympathectomy groups with four actual deaths. On the other hand, among the five probable deaths in the inferior sympathectomy group and control animals, only three actually occurred.

With regard to the character of the disease as revealed by post-mortem examination, it is seen by reference to Table I that the highest animal incidence of metastases occurred in the controls. One or more foci of tumor tissue besides the primary tumor were found in each control animal, that is to say there was an animal incidence of 100 per cent, while the figures of the operated groups are as follows: inferior sympathectomy 89 per cent, sympathectomy 78 per cent, complete sympathectomy 70 per cent, superior sympathectomy 70 per cent. Here again, the inferior sympathectomy and control series approximate each other, while the other three operated groups fall closer together. The greatest distribution of metastases occurred in the complete sympathectomy and sympathectomy groups, the
numbers of metastatic foci being 97 and 91 respectively, while there were 88 in the superior sympathectomy, 81 in the inferior sympathectomy, with 66 in the control groups. In the sympathotomy series this distribution value may be considered as deceivingly low because of the number of what might be termed accidental deaths due to spinal metastases early in the course of the disease. Had these animals lived longer the metastatic rate would undoubtedly have been much higher and the actual amount of organ and tissue involvement considerably greater. The average number of metastatic foci per rabbit in which secondary growths occurred is as follows: complete 13.9, sympathotomy 13.0, superior 12.6, inferior 10.1, controls 6.6. The figures clearly show that upon a basis of distribution and growth of metastatic tumors the disease developing in the operated animals was considerably more malignant than among the controls, and, furthermore, that there were outspoken differences among the various operated groups which are of the same order as the mortality rate, the average number of clinical metastases per rabbit, and the total number of metastatic foci.

A more adequate conception of the general character or type of disease which developed in the several series of animals may be obtained by considering the distribution of metastatic tumors in various groups of organs according to the plan already described in the method of analysis of results.

The curves in Text-fig. 2 have been drawn upon the basis of organ and tissue grouping, the figures for the relative curves being based upon all the animals in a group, while those for the actual curves include only those animals in which metastases were found. The actual curves parallel the relative except at one point and, in general, merely emphasize the different types of disease which actually developed. At every point in both sets of curves, except in the relative curve in the case of the eyes and suprarenals of the superior sympathectomy group, the incidence and distribution of metastases are seen to be greater in the operated than in the control animals. The sympathotomy and inferior sympathectomy curves are similar in form, but the former is consistently higher and is considerably higher in the last column which records the involvement of the skin, muscles, bones,
TEXT-FIG. 2. Distribution of metastatic foci.
The curve representing metastases in the complete sympathectomy rabbits is almost the same as that of the inferior sympathectomy group in the first two columns (suprarenals and eyes; lungs, liver, kidneys, pancreas), but is much higher as regards extensions and implantations and definitely higher as regards skin, muscles, bones, and endocrine glands. The curve for the superior sympathectomy group resembles that of the complete sympathectomy animals, except in the case of suprarenal and eye metastases, in which it approaches the control curve.\(^2\)

Upon the basis of these two sets of curves, one would conclude that the disease which developed in the four operated groups was on a much higher plane of malignancy than that of the control animals and, further, that the disease of greatest severity occurred in the sympathectomy and complete sympathectomy rabbits. In order to classify the inferior and superior sympathectomy series, however, an additional analysis is needed of the type of disease in which metastases occurred to the suprarenals and eyes. Relatively little importance has been attached to the incidence of extensions and implantations, but the fact that the figures for the superior sympathetic series are definitely greater than those for the inferior sympathetic animals in the groups of parenchymatous organs and the skin, muscles, bone, etc., indicates that the much greater value of the inferior sympathetic series for suprarenal and eye metastases is indicative of a mild or chronic disease rather than of greatly increased malignancy.

\(^2\) Differences in the figures for the skin, muscle, bone, and endocrine gland group which appear comparatively small are actually of much greater significance than in the case of the other subdivisions because of the larger number of organs and tissues making up the group, the total figure for which is used in arriving at the percentage estimation values (6).

\(^3\) While the level of malignancy of this superior sympathectomy group was much higher than that of the control animals, one of our preliminary experiments suggests that such may not always be the case. In this experiment there were only five superior sympathectomized rabbits, but the general character of the disease for the group was only slightly more severe than that of the controls. A possible explanation of this result may lie in the much longer interval between operation and inoculation—6 weeks—which may have been sufficient for such a readjustment of the animal organism that its resistance capacity reached the level for normal animals prevailing at that time.
The significance of the growth in the suprarenals and eyes is brought out in Table II which summarizes the principal points regarding the relation of these metastases to the total number of metastatic foci occurring in these rabbits as well as in all the animals of each group. The highest animal incidence and the largest number of suprarenal and eye tumors occurred in the inferior and sympathectomy series, but the inferior and control groups showed the greatest proportion of these growths as compared with the total number of metastatic foci of these rabbits (22.5 per cent), with the sympathectomy, complete, and superior groups following in the order named (18.8, 15.6, 14.7 per cent). Furthermore, when one classifies the type of disease which developed in the rabbits in which suprarenal and eye tumors were found, it is seen that the largest number of mild cases occurred in the control and inferior sympathectomy animals, 67 and 43 per cent respectively, while there were only 17 and 14 per cent of mild cases in the complete sympathectomy and sympathectomy groups, and none in the superior sympathectomy group. These points are graphically illustrated by a second set of curves from which the metastases to the suprarenals and eyes occurring in cases of low malignancy have
Text-Fig. 3. Distribution of metastatic foci omitting those to the suprarenals and eyes occurring in mild cases.
been omitted (Text-fig. 3), giving a more adequate conception of the precise character of the disease of the various groups. The curves representing the operated series are seen to be markedly higher than that of the controls. There is not a great deal of difference between the curves for the superior and complete sympathectomy groups, the former being slightly higher, except in the case of metastases to the eyes and suprarenals, but the disease of the inferior sympathectomy group is now clearly shown to be the least malignant of any occurring in the operated series. The order of malignancy of the several groups, as shown by these curves, is therefore as follows: sympathotomy, superior and complete sympathectomy, inferior sympathectomy, controls.

Finally, the condition of those rabbits surviving the experiment and not considered as probable ultimate deaths should be mentioned. The number of such animals is practically the same for all groups, four or five (Table I), except in the case of the sympathotomy series, in which there were three. A few foci of metastases were found at autopsy, from one to seven per group, and the relative animal incidence of these growths again brings out the resemblance of the inferior sympathectomy group to the controls (1.75 and 1.4 foci per animal), while the sympathotomy, the superior and complete sympathectomy groups are associated together on a plane of higher malignancy (1.0, 0.6, and 0.25 per animal).

DISCUSSION.

It is evident from this brief analysis that the various operations performed upon the cervical sympathetic ganglia and nerves brought about a condition of the rabbit host which permitted the development in the several groups of animals of a disease considerably more malignant than that prevailing among controls inoculated at the same time. Furthermore, there were differences in the malignancy level among the groups themselves. Upon a basis of actual and total probable mortality, the time of actual deaths, the number and animal incidence rate of clinical metastases, the total number of metastatic foci, and finally the general character of the disease as revealed by the distribution of these metastases, the order of malignancy in the operated groups beginning with that manifesting the most severe disease was as follows: sympathotomy, complete sympathectomy, superior sympathectomy, inferior sympathectomy, controls.
There were two points in which the disease of the controls might be considered as more malignant than in the operated animals. The average volume of the primary tumor was greater for the control group during the 1st month than that of any of the operated groups except the sympathotomy. It has been pointed out, however, that in a disease of a fairly high malignant level animals with the largest primary tumors are likely to show a less severe metastatic involvement than those with smaller primary growths (7). This generalization does not hold for a disease of a more severe character and consequently cannot be applied to the operated groups.

The rate for the animal incidence of metastases in the controls was 100 per cent, while that of the operated groups ranged from 70 to 89 per cent. In other words, tumor tissue in addition to the primary tumor was found in all the control animals, while two or three rabbits in each operated group had been able completely to prevent or suppress any metastatic growths. Although there was only a single focus of secondary tumor in four control rabbits, consisting of a cord nodule or a metastasis to one suprarenal gland, neither of which would have caused the death of the animal, still such a finding indicates that in certain rabbits or under certain conditions the surgical procedures employed did not invariably induce a state of decreased resistance to the tumor.

We have drawn attention to the fact that in any group of five or ten normal rabbits the proportion of those with high, low, and intermediate grades of resistance to this tumor, and to infections with Treponema pallidum as well, is roughly 1:1:3. The operative procedures employed in this experiment have not disturbed this ratio as regards the proportion of animals with high resistance, but apparently has done so in the case of the intermediate or low grades, since instances of moderate and severe malignancy of each group were considerably more numerous than in similar cases in the controls.

The interpretation of the facts that have been presented with regard to the general character of this malignant disease in rabbits after operative removal of various portions of the cervical sympathetic nerves can be only tentative, since our knowledge of the anatomy and physiology of these structures in the rabbit is slight. In particular there is no definite information available upon the connection between
the cervical sympathetic and the thyroid gland, though from what is known in the case of man and certain of the lower animals, it is probable that a relation of some sort exists. Our results furnish some evidence that both the superior and inferior ganglia are important structures in the mechanism of animal resistance to an induced malignant disease, the superior ganglia appearing to be the more essential in this relation. Whether it operates through the thyroid or by some other means is not certain, but the effects of complete thyroidectomy and of removal of the superior cervical ganglia, or of a portion of the sympathetic nerves, are, on the whole, strikingly similar in terms of general malignancy. There is in both cases a clear-cut increase in the severity of the disease. But, while removal of the thyroid practically always induces this effect, there are certain rabbits in which superior sympathectomy or sympathotomy did not. Furthermore, the rapid and very extensive growth of the primary tumors characteristic of completely thyroidectomized rabbits is not seen in superior sympathectomized animals nor is it equalled in the sympathotomized animals.

Removal of the inferior cervical ganglia resulted in a less malignant disease than that which developed in the superior and completely sympathectomized and the sympathotomized groups but one more severe than in the controls.

If the superior ganglia are the more important or essential elements in the cervical sympathetic system, then their removal alone or as a part of a complete cervical sympathectomy should bring about analogous effects. Such was apparently the case in this experiment. On the other hand, removal of a small portion of the cervical sympathetic nerve alone, without surgical interference of the superior or inferior ganglia, brought about a similar but even greater effect than removal of the superior ganglia or of the entire system. One might presume that extirpation of the inferior ganglia, in which the nerve is necessarily sectioned as in the sympathotomy operation, might bring about a similar effect. This did not occur, however.

The reasons for these various states of malignancy, or conversely, of animal resistance are not clear. The results of the experiment suggest several explanations as possible. The character of the malignant disease may be considered as a result of two major factors, (1) the
growth of the inoculated tumor cells and (2) the defensive forces which the animal host brings to play against these cells. There was a good initial growth of the primary tumor in every animal and we can assume that the operative procedures themselves did not interfere with or favor, to any material extent, the initial stage of the disease. On the other hand, since the eventual character of the disease as a whole was more malignant in the operated than in the normal animals, it is evident that the natural or acquired defensive forces of the host were in some way rendered less effective in the former.

When the superior ganglia were removed, either alone or as a part of a complete extirpation of the cervical system, or a medial portion of the nerves was removed, the mechanism of resistance was less efficient than when the inferior ganglia alone were extirpated. In both ganglion operations the nerve was necessarily cut, but one set of ganglia was not disturbed. It would seem, therefore, that these structures are associated with more than a single functional effect. There is probably a coordinating function of some kind between the two ganglia; yet, in addition, it would seem that both a favorable and a deleterious influence is associated with them. Thus, when the superior ganglia alone are extirpated a markedly unfavorable effect predominates; when the inferior ganglia alone are removed a much less deleterious effect is observed; whereas when both superior and inferior ganglia and the connecting nerves are extirpated the unfavorable effect is similar to that observed after removal of the superior ganglia. In other words, the absence of the inferiors does not increase or decrease the deleterious effect produced by the removal of the superior ganglia, so that it would seem that whatever unfavorable effect is produced by an inferior sympathectomy is mainly caused by an interruption of the path and hence of the coordinating function existing between the superior and inferior ganglia and that the additional removal of the inferior ganglia permits of the development of a favorable influence. Such an influence is not appreciable when the path between the ganglia is simply interrupted and the inferior as well as the superior ganglia are undisturbed. When this is the case, an outspoken deleterious effect upon resistance is to be seen, as witness, the severe character of the neoplastic disease. Under these conditions, the presence of either the superior or the inferior ganglia would appear to be a disadvantage.
If the effect of the various surgical procedures is obtained through the thyroid gland, the experiments would suggest that the absence of the superior cervical ganglia is associated with a condition of lowered or abolished thyroid function, as in the case of completely thyroidectomized rabbits in which there is a relatively ineffective resistance to the tumor. Furthermore, it would appear that since the absence of the inferior ganglia alone is associated with a less pronounced decrease in animal resistance the intact superior ganglia are still capable of exerting a favorable influence or of counteracting the unfavorable one brought about by the removal of the inferiors. However, since a distinct deleterious effect upon animal resistance followed an interruption of the direct nerve pathway between the undisturbed sets of ganglia, it is obvious that other factors are involved than are apparently associated with a simple extirpation of the ganglia.

Whatever may be the ultimate explanation of these apparently paradoxical results, it is clear, from this experiment, that removal of the cervical sympathetic system or certain of its component parts is, in the rabbit, followed in many instances by a less effective resistance to a transplantable neoplasm. In consequence, the character of the disease which develops in such animals is highly malignant.

**SUMMARY AND CONCLUSION.**

The effect of the removal of the complete cervical sympathetic nervous system, of both superior and of both inferior cervical ganglia, and of a small portion of the cervical sympathetic nerve in the rabbit was studied in relation to the character of a malignant disease induced by a transplantable neoplasm.

It was found that the general character of the disease which developed in the operated groups of animals was more severe than that of a similar sized control group. Comparisons of the mortality rate in the several groups, of the animal incidence of metastases, the number of metastatic foci, and the distribution of these secondary growths all showed this to be the case. There appeared, furthermore, to be differences in malignancy among the operated groups themselves. The most severe disease occurred in the group in which a portion of the sympathetic nerve only was removed (sympathectomy); that in the
complete sympathectomy and superior sympathectomy groups was slightly less malignant; and that in the inferior group was much less so.

These results have been interpreted as due to a less effective animal resistance, the mechanism of which has been interfered with in some way by the interference with the sympathetic nerves. The reasons for the difference in malignancy exhibited by the several operated groups are undetermined. A tentative explanation is suggested upon the basis of coordinating, favorable or deleterious functions subserved by the cervical sympathetic nervous system.

BIBLIOGRAPHY.