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ON SOME CONDITIONS DETERMINING VARIATIONS IN THE ENERGY OF TUMOR GROWTH.

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In the following, I intend to communicate certain of the observations on the energy of tumor growth, and especially on experimentally produced variations, of the rate of growth which were made in the course of four series of consecutive transplantations of tumors, three of which have already been discussed mainly in regard to other problems. The fourth series, a fuller report on which shall be published soon, concerned the transplantation of a mixed tumor of the submaxillary gland found in a Japanese (waltzing) mouse.

In a provisional way, it may be stated that two variable factors determine the rate of tumor growth: 1. Certain conditions present in the organism and probably in part, at least, in the lymph and blood of the animal in which the tumor is growing. 2. The energy of growth of the tumor, either inherent in the tumor cells or modified by certain environmental conditions other than those named under No. 1. These two sets of factors being both variable, only a long series of observations will enable us to analyze the sphere of influence of each of them. At present, the analysis must of necessity be still very incomplete.

In regard to the first of these two factors, a number of interesting facts has been established by different investigators. The transplanted tumors will not grow in animals of different species. The salivary tumor of the Japanese mouse did not grow in a white mouse. I succeeded, however, in inoculating a sarcoma of a white rat into a hybrid between a white and gray rat. Yensen succeeded in a restricted number of cases in transplanting

a tumor found in a white mouse into the common gray mouse, not, however, into other species of animals. Sticker succeeded recently in making a lymphosarcoma, found in a dog, grow in a fox.

In my first and second series of transplantations, I have noticed that occasionally repeated inoculations of the tumor material into the same animal were unsuccessful, and furthermore, that if two pieces were transplanted simultaneously into one animal, either both pieces grew or none. Similar observations were made by Maximilian Herzog with the cystic sarcoma of the third series.

On the other hand, it was possible to obtain tumor growth in all kinds of animals of the same species, in male and female, in young and old, in healthy and in weak individuals. These facts led me to consider the possibility that individual variations in the organism might exist, favorable or injurious to the growth of the inoculated tumor. The complication with the second set of factors permitted, however, such a statement to be made only in a tentative way, especially as in the early stages of transplantation, frequently in all inoculated animals, tumors developed.

Yensen found that about a half of his inoculated mice did not show tumor growth, and concluded that these were naturally immune animals, especially because repeated inoculations into the same mouse were without success in such cases. He suggests that the blood-serum of such naturally immune mice might contain substances detrimental to the tumor growth, a question which he intended to investigate further. In a certain number of cases he found the blood-serum of animals inoculated with tumor juices to possess immune substances, inhibiting the growth of his tumors in mice.

Michaelis also found an immunity of certain individuals against the growth of Yensen's mouse tumor, which could be successfully transplanted into mice obtained from Copenhagen, but not into mice raised in Berlin.

Sticker, in his transplantations of a lymphosarcoma of a dog, did not find that any marked predisposition or natural immunity was present in certain varieties of dogs, although some differences existed between individual dogs.

From these observations we may conclude that certain tumors are more independent in their growth from predisposing conditions in individuals of the same

species than others, and that perhaps the individual predisposition becomes of more importance in tumors in which the energy of growth is declining.

Sticker found during his transplantations of a lymphosarcoma of a dog the interesting fact that animals in which a transplanted tumor was growing had acquired an active immunity against a new inoculation. He also, like Yensen, investigated the question whether this active immunity was due to the presence of immune substances in the blood of the animal.

Gaylord, Clowes and Baeslak working with Yensen's mouse tumor found that those mice which were not susceptible to tumor growth contained in their blood, substances inhibiting the growth of the tumors.

That, however, an active immunity is not in all tumors as easily obtained as in Sticker's experiments can be concluded from the following observations: In my first series of tumor transplantations I described an experiment carried out with a rat, in which a transplanted sarcoma had grown for some time; a piece was excised from the tumor, after its growth had ceased, and this cut out piece was retransplanted into another part of the same animal. After reinoculation, this piece began to grow actively. This animal had therefore not become immune against the growth of inoculated tumors through the first inoculation. In a similar way did Bashford, in his recent transplantations of tumors find that animals inoculated once with tumors had not become immune against a second inoculatian.

It is therefore likely that the facility with which active immunity against tumor growth can be produced varies according to the variety of tumors used, or according to the differences in the species or in the individuals which are inoculated with the tumor.

It can, therefore, be stated that the rate of tumor growth is not only influenced by the species into which the tumor is transplanted, but also by variations which exist among individuals or families, of the same species, but that certain tumors are more selective than others. A condition of active immunity can, under certain conditions, be experimentally produced, and this active immunity is accompanied by or due to the presence of certain substances inhibiting the growth of the tumor. Whether in the blood-serum of animals naturally immune against the growth of inoculated tumors such substances are likewise present remains yet to be determined, the serum apparently having been tested so far only in ani-

mals which had been previously inoculated with tumor material.

We now shall consider the second set of factors determining the rate of growth of inoculated tumors. It is known that tumors of different character vary in their energy of growth. It is, however, possible to produce variations in the energy of growth of a certain tumor. Recently I had an opportunity to make some observations, not without interest, in regard to this question.

In the beginning of March, 1904, I obtained a Japanese waltzing mouse with a tumor in the upper part of the neck, which I used for further inoculations. I shall report here the results of these transplantations only insofar as they have some connection with the problem under discussion. The tumor was, by microscopic examination found to be a tumor of the submaxillary gland, and of a similar type as the salivary tumors found in man.[1] By some investigators the main constituents of such tumors are held to be of endothelial, by others to be of epithelial character.

The mouse was, when I received it, 6 to 8 months old. The tumor became noticeable when the animal was 2 months old. It was excised in the beginning of its growth, but recurred soon, and was from then on slowly but steadily growing. At the time I received it, it was not quite the size of an almond, and was nodular in outline.

March 12, 1904, the tumor was transplanted into 11 Japanese mice. A number of them either died soon after operation or a few weeks later, or were lost by an accident in the course of the next month. May 9, about two months after the first operation, two mice were alive, and they both showed very small nodules at the places of inoculation. One of these nodules was cut out May 14, 1904. It began to recur in about six days, and grew rapidly. May 26, 12 days after the excision it was four to five times greater than the first nodule had been after a growth extending during two months. During this time also the other tumor nodules were gradually growing in both animals. One of these two mice died June 9 or June 10, 90 days after it had been inoculated and 26 days after the small nodule had been excised. The other mouse was killed June 13, 93 days after the inoculation. A part of its tumors was used for further transplantations. Of the inoculated mice of the second generation several died soon after the operation. Six remained alive. One of these died June 24, 11 days after inoculation. The beginning of the growth of the inoculated tumor had been noticeable five days after the operation. In the six days preceding death a marked increase in the size of this tumor had taken place.

The second rat had been inoculated intraperitoneally. She died in the night from June 27 to June 28. Fourteen days after

[1] The finding in a mouse of a salivary tumor of a similar character as the salivary tumors found in man, is a further demonstration of the great resemblance or identity existing between tumors found in men and in lower animals.

inoculation, the abdominal cavity was found to be filled with two large and many smaller tumors. Tumor tissue was penetrating into the liver, into one kidney, and into the pancreas.

By this time, 14 days after inoculation, tumors were likewise present in three of the four remaining mice. In the fourth mouse very soon a tumor also began to develop, and soon reached large proportions.

July 15, 32 days after inoculation, the third mouse died; she had a large nodular tumor which had begun to develop five or six days after operation, and had grown progressively since then.

July 19, 36 days after inoculation, the fourth mouse died with a very large tumor. The latter was situated on the back of the animal.

July 24, 41 days after inoculation, the fifth mouse died with a very large tumor, and July 25, 42 days after inoculation, the sixth mouse died with a very large tumor, covering almost the whole back of the animal.

Further inoculation could not be made because of the difficulty which existed in procuring a sufficient number of Japanese mice.

We see, therefore, that the tumor in the original mouse was growing slowly during a number of months. Even the early excision of this tumor did not cause the tumor to grow rapidly. We furthermore see that only after about two months, the growth of the tumors became, in the first generation, sufficiently large to be noticeable to the naked eye, from which time on the tumors grew almost steadily, but rather slowly.

The six mice of the second generation, however, developed tumors inside of one to two weeks after inoculation, with the exception of one, in which the development of the tumor began soon afterward and progressed rapidly. The energy of growth of the tumors of the second generation was considerably greater, and the development a much more rapid one than in the first generation or in the original tumor. The period of latency (the period during which no growth as yet appeared to the naked eye) was shorter.

An identical variation in the energy of tumor growth was present in one of my former series of tumor inoculations of a sarcoma of the thyroid in rats, although in this case the difference in the rate of growth in the first and second generations was not as marked as in the series of transplantations of the submaxillary tumors. In the case of the sarcoma of the thyroid the growth in the first generation became visible in the third week. The growth in the second generation became visible toward the end of the second week. In the two other series of transplantations of a sarcoma the rapidity of growth in the successfully transplanted pieces was much greater

than in the original animal. The record of the individual transplantations has since been lost, so that it is not certain whether the same difference between the growth in the first and second generations existed, but, as far as I can remember, it did exist, at least in the first series. The same curve of growth (maximum of growth in the second generation) appears in the record of Sticker's inoculations of a lymphosarcoma in dogs. In all of these series of transplantations the inoculations were in each generation made in a number of different animals, and the result was identical in all animals inoculated in each generation, so that this occurrence cannot be explained by individual differences in the susceptibility of the inoculated animals. The only other series of tumor inoculations in which the growth in the succeeding generations is recorded is that of Morau. This investigator also finds the growth of the transplanted tumors more extensive than the growth of the original tumor; in his case, however, the lengthening of the period of latency took place after the first transplantation.

It is, however, not essential that the same curve of growth should be present in each series of inoculations. It should be present frequently enough so as to exclude all possibilities of an accidental happening. These facts certainly permit the conclusion that transplantation of a tumor has a tendency at first to increase the energy of tumor growth, and that this increase may be cumulative. In all instances in which a larger series of tumor inoculations were made, a further shortening of the latent period or an increase in the rapidity of tumor growth did not take place in the following generations. Duration of the latent period and rapidity of growth either remained stationary through many generations or the energy of tumor growth even declined somewhat. This fact may perhaps be explained by the presence of counteracting influences, the actual existence of which can be demonstrated, as shall be shown later.

One more conclusion can be drawn from these facts: The animals of the first and second generations offer less resistance to the expansive growth of the tumor cells than the animal originally affected with the tumor.

What is the cause of this increase in the energy of tumor growth? The first explanation which suggested itself was that the injury to the connective-tissue capsule surrounding the tumor removes the tension which inhibited a further growth of the tumor. Certain observations in my earlier transplantations had suggested

such an explanation. In a number of former experiments I had repeatedly found that it was possible to make a stationary or retrogressing tumor resume its growth by excising a piece and by retransplanting it either into the same or into another animal. Under these conditions it was possible for the retransplanted piece and also for the retrogressive and stationary piece to grow again. In such cases a capsule had existed around the stationary piece, the tension of which was removed by the excision of a part of the tumor. In the second series of transplantations of the sarcomatous part of a tumor of the thyroid, a tumor was likewise made to grow again after excision of a piece and retransplantation into another animal.

In the first series of transplantations of a sarcoma of the thyroid the following experiment was made: A piece from a large infected tumor was transplanted November 26, 1900. The piece did not show any marked growth. December 20, 1900, a piece of the stationary tumor was cut out; after this operation the piece which had been left back grew a little; the growth, however, ceased soon, the piece became surrounded by a connective-tissue capsule, and it decreased in size. January 24, 1901, a piece of this tumor was transplanted into the peritoneal cavity of another rat. In the succeeding 15 days a larger tumor developed out of the transplanted piece, which was afterward used for further transplantations, which were also successful. In the meantime the original tumor from which the piece was excised January 24 became converted into a number of small pearls, which gradually decreased in size.

In another case not only the transplanted piece began to grow, but also the rest of the tumor, which some time previously had ceased to grow; the piece which had been excised from the tumor began to grow, although it had not been transplanted into a different but into the same animal, in which no tumor growth had taken place before the excision was performed. In such cases it is not unlikely that the removal of the tension of the connective-tissue capsule is of some importance.

In the last series of tumor inoculations (inoculations of a mixed tumor of the submaxillary gland) we observed a similar phenomenon, namely, the increase in the energy of tumor growth after transplantation into the first, and especially after the inoculation into the second generation had taken place. In this case increase in the rate of growth after the inoculation into the second

generation as compared with the rate of growth after the inoculation into the first generation speaks against the importance of the removal of the connective-tissue capsule, because the tension of the surrounding connective tissue was removed as much in the first inoculation as in the second. Moreover, it could be shown that in the transplanted tumor of the submaxillary gland no capsule existed around the sarcomatous part of the tumor during the relatively slow growth of the first generation, and that it behaved in this respect like the rapidly growing sarcoma which recurred in the first generation after excision May 14, and also like the quickly growing sarcoma of the second generation. In a similar way the influence of the removal of a surrounding connective-tissue capsule could not explain the difference in the growth of gland-like structures of the tumor in the first and second generations, the connective tissue being arranged in both cases in a similar way. A further experimental proof can be found in the fact that during the series of transplantations of the first sarcoma of the thyroid a small tumor or nodule included in its uninjured capsule was transplanted into a different animal and that it began to grow after some time. The tense connective-tissue capsule became dilated by the inner pressure of the growing tumor. After the initial growth the tumor remained unchanged for a long period and no further growth took place, until a piece was cut out, when the remaining piece again started to grow rapidly. It can therefore be definitely stated that the excision of a piece of a tumor does not increase the energy of tumor growth merely by the removal of the tension of the capsule. A tumor which is growing is able to overcome such a resistance, as shown in the case last mentioned; it is more likely that the formation of a tense capsule is rather an indication of an already existing limitation of the expansive power of the tumor cells than the cause of it. Nevertheless it is possible, and even likely, that the existence of such a capsule exerts a restraining influence. This is the most probable interpretation of the last mentioned case. After transplantation the tumor was able to grow in its capsule. This growth, however, began soon to cease. After excising a piece a much more extensive growth set in.

A second possible explanation of the increased energy of growth after reinoculation is that a better vascularization of the inoculated material supplied more material for growth. There is, however, no reason why the

vascular supply should be better in the second generation than in the first; moreover, the microscopic examination permitted to exclude this factor, insofar as some rapidly developing tumor nodules in the second generation had no better blood supply than the very slowly growing little nodule of the first generation which had been excised May 14. We have therefore to assume that experimental conditions other than the aforementioned ones cause the increase in the energy of tumor growth and that this change may be a cumulative one.

The energy of tumor growth can be increased directly, and not only indirectly merely, by the removal of the tension of the surrounding capsule or by a better vascular supply. Such a direct stimulating effect of a wound upon the cell growth explains probably a phenomenon not infrequently observed by surgeons, namely, the increase of malignancy in recurrent tumors. The observation that tumor growth becomes sometimes apparent after a trauma, is probably to be interpreted in a similar way.

Another question which might be raised is whether this energy of tumor growth is caused by the transfer of the tumor into a different animal or whether the trauma or wound would have the same effect without any change of soil. Our present experience permits us to state that the trauma or wound itself is an important factor, sufficient to cause an increase in the tumor growth. We saw, for instance, that the nodule which recurred in the first generation of the animals inoculated with the mixed tumor of the submaxillary gland, after the primary nodule had been excised, had a much more rapid growth than the primary nodule, in a similar way as the tumors of the second generation grew more rapidly than those of the first one.

It is, however, probable that under certain conditions the transfer of tumor cells into a new organism stimulates its growth specifically in a way different from the mere effect of a trauma. It may happen that after excision of a tumor piece, and after its retransplantation into another animal, only the excised piece grows, but not the piece left back, although it was likewise subjected to the influence of a trauma.

Another fact is the following: In those cases in which, after the extirpation of the original tumor, the animal survived, multiple recurrences of the tumor were found to develop. These, however, did not have the same rapid rate of growth which was found in the other ani-

mals which were inoculated with the same tumor, although a trauma existed in each case. We mentioned already, above, that the growth of the primary tumor is a slow one. In this case, the transfer of the tumor cells into a different animal seems to favor the increase in the energy of growth. We may, therefore, conclude that the stimulating effect of the wound is a factor leading to an increase in the rate of the tumor growth, and that the transfer into a different animal is perhaps an aiding factor, which may, under certain conditions, become of some importance.

If we further ask by what means does the wound stimulate the cell growth, we have no way to answer this question, because we do not know the factor or the factors ultimately determining regenerative cell growth. We might rather conclude from the facts stated above that the break in the tissue is not the factor which stimulates growth directly, insofar as the tumors, the growth of which we just considered, did not have a well-defined border, comparable to that of a normal organ. The stimulating effect of the wound must therefore in this case be brought about in a different way.

It is also possible to diminish the energy of tumor growth. In the course of tumor inoculations it not rarely happens that certain tumors remain stationary or retrogress even spontaneously. This is especially found in the course of later inoculations, and it probably indicates that after many inoculations one or several of the factors determining a vigorous tumor growth become gradually weakened. We may also find it in cases in which a part of the tumor had been infected with bacteria. It sometimes happened in my former transplantations of a sarcoma of the thyroid that the infected part of the tumor became separated from the rest of the tumor by a connective-tissue capsule. Under such conditions the encapsulated, not infected part, had been so much weakened, probably by the effect of bacterial toxins, that it soon ceased to grow.

In such tumor nodules one can observe that even a long time after the expansive growth of such a tumor piece has ceased, many mitoses are present in the cells of stationary or retrogressive tumor. I have found this to be the case in several tumors which had ceased to expand a considerable time ago, and which were even shrinking. At a still later stage mitoses may, however, be absent in such nodules. These observations have been recently confirmed by Sticker, in his transplantations of

a lymphosarcoma of a dog. We may therefore conclude that the number of mitoses present in a tumor is not a quantitative measure of the actual growth taking place. On the other hand, this fact shows, in combination with the observations recorded above, that a retrogressive, very small tumor nodule may be the source of a rapidly growing tumor, if an external stimulus of growth is transmitted to it.

Another factor of a similar character is the following: Microscopic examinations in the period of latency show that the growth as evidenced by the presence of mitoses is going on during a considerable period before any growth is apparent to the naked eye. In the former inoculations of a sarcoma of the thyroid, mitoses were present in the peripheral part of the tumor, already on the first or on the second day after transplantation. In the first generation of the tumor of the submaxillary gland, the growth became apparent to the naked eye after about two months. Microscopic examination, however, showed signs of growth in a small inoculated piece which was excised 16 days after, at a time, therefore, when no development of the tumor was apparent to the naked eye. It is as yet doubtful whether microscopically a period of latency of any length does exist.

It is possible to diminish the virulence of tumor cells directly by subjecting them to certain physical or chemical conditions. By heating tumor cells up to 43° or 44° for a half hour outside the body in a sterile way, or by leaving them before inoculation in glycerin for 12 to 24 hours, and washing them afterward in 0.85% sodium chlorid solution, or by keeping them one to two days in $\frac{N}{700}$ KCN solution before transplantation, we are able to diminish the energy of the following growth, and to increase the period of latency. This applies especially to tumors previously heated for a half hour to 43°. Frequently such tumors remain stationary after a short preceding period of growth, or they may even retrogress. In the first experiments of this kind I found that a temperature of 45° during a half hour kills the tumor cells. Yensen found a similar sensitiveness of his mouse tumors. Sticker's lymphosarcoma could be heated up to 45° without being killed. The power of resistance of different varieties of tumor cells varies therefore somewhat, and the means to be adopted to obtain a diminished virulence in the growth of an inoculated tumor will vary accordingly.

Less apparent is the lengthening of the period of latency and the following diminished energy of growth in those tumors which before inoculation had been subjected to the influence of KCN or of glycerin, although it may be present in such tumors. Frequently pieces which had been kept for some time in glycerin did not grow at all afterward.

In my last series of tumor inoculations, in all the animals inoculated with fresh tumor pieces, well-growing tumors developed. Of three mice which had been inoculated with pieces which had been previously kept in glycerin for about 20 hours, and had then been washed in sterile 0.85% NaCl solution, one died after 11 days, without any growth. Of the two remaining mice, one developed a tumor about six weeks after inoculation. We see, therefore, that a very marked increase in the duration of the latent period had taken place in the piece kept in glycerin before inoculation, insofar as the control pieces began to grow after two weeks.

In this connection it may be mentioned that these facts can possibly find a practical application insofar as pieces of tumors previously subjected to such treatment might be used to procure an active immunity against tumor growth. Especially pieces which have been subjected to heating, promise to be favorable. That active immunity is possible, at least in the case of certain tumors is, as I mentioned before, especially indicated through the observations of Sticker. I had intended to use the submaxillary tumor for experiments of this character. The difficulty, however, of obtaining Japanese mice in a quantity sufficient for this purpose made it impossible to carry out these plans.

If we now wish to analyze the cause of this decrease in the rate of growth of tumor cells, we have to consider several possibilities. It might be that the physical or chemical means employed kill most of the cells and leave only a few cells alive able to give origin to the developing tumor. Two facts speak against such an interpretation: 1. In the case of any tumor transplantation, the growth starts from a relatively small number of cells, insofar as the central part of the transplanted piece becomes necrotic. 2. I succeeded in my first series of tumor transplantations in obtaining well-growing tumors, after injection of cystic tumor fluid into the peritoneal cavity of rats. In such cases one or very few cells must have given rise to the tumor growth, and these tumors developed in a few cases quite rapidly. Such an expla-

nation is therefore improbable. Further, we would have to consider the possibility that some of the means employed to decrease the virulence of tumor cells are favorable to the growth of bacteria, and that they inhibit in this way the development of tumors. Bacterial toxins certainly act frequently unfavorably upon the growth of tumors. Against this explanation, however, the objection can be raised that tumors with experimentally diminished virulence did not show any sign of putrefaction, nor did they, after inoculation, cause a formation of abscesses, occurrences which are frequent after transplantation of infected material. It is, therefore, most likely that the cause of this decrease in virulence is the result of the direct decrease of the vitality of the tumor cells as expressed in their energy of growth. It is, however, desirable to analyze further these facts in future experimental work on tumors, especially as the character of such work limits of necessity the number of experiments a single observer can make.

With this restriction we might state that the observations here recorded point to the conclusion that *it is possible to cause an experimental increase and decrease in the energy of tumor growth and that these variations are caused by a direct stimulating or depressing effect upon the tumor cells, and that such a stimulating effect may be cumulative.*

Another question might be mentioned, although it is only indirectly connected with the problem under discussion. In recent years it has been frequently discussed by surgeons whether or not, contact inoculation of tumors takes place, especially in cases in which a tumor is removed in the course of an operation and touches the wound or parts of serous cavities. Such inoculation by contact might, however, also take place, if a tumor rests for any length of time upon a certain tissue. By some surgeons such contact metastases were explained as really due to cells which were carried away by the lymph and only secondarily broke through the mucous membrane or through the serosa covering the lymph vessels, and afterward presented an appearance of having primarily been deposited on the mucous or serous covering itself.

Our experiments permit us to state with certainty that such contact metastases may occur in introducing a tumor piece through a wound of the abdominal wall into the peritoneum. It happened several times that tumors developed not only in the peritoneal cavity, but also in

the muscular or subcutaneous layer of the abdominal wound, or that if a piece was introduced into a deep pocket of the subcutaneous tissue, not only the inserted piece gave origin to a tumor, but that also near by, in the subcutaneous tissue, small isolated nodules began to grow, due in all probability to the fact that the inoculated tumor piece touched the wound at such places. In other cases in which the tumor had been inoculated intraperitoneally, little nodules developed at such places where large tumors rested against the peritoneal wall.

These facts, observed in the course of experimental inoculation of tumors, permit us to state with certainty that inoculation by contact may occur, and that it is probably not a rare occurrence. We may, however, go even further, and state that different tumors which are morphologically similar or identical behave differently in this respect. Thus it was observed that the sarcoma of the thyroid used in the first series of transplantations gave rise more frequently to such contact inoculations than the sarcoma used in the second series, although both tumors had an almost identical structure. It is, therefore, impossible to foretell whether or not a tumor during extirpation is liable to cause the formation of contact metastases, and the greatest care ought to be taken in avoiding a tumor touching the wound during extirpation.

In order that such contact metastases should occur certain conditions must be present. In our experiments contact inoculations were found only in such cases in which the implanted cells had favorable conditions for growth, as, for instance, in the peritoneal cavity or in subcutaneous or muscle wounds which were carefully closed after operation. Under such circumstances the tumor cells could develop undisturbed.

Contact inoculations were, however, never observed on the skin of an animal or in the intestinal canal after the animals had been fed with freshly extirpated tumors, although we may assume that the skin or mucous membrane showed slight abrasions, which came into contact with tumor cells. In the surface of the skin, the cells are probably exposed to many injurious influences, as light, drying out, mechanical removal. The same applies to the skin of operating surgeons. Here, inoculated tumor cells do not find a favorable place where they could grow, especially if we consider that the surgeon's skin, especially after having been wounded, is during or immediately after operation, bathed in anti-

septic solutions, which kill tumor cells rapidly. It is, therefore, not astonishing that no cases are known in which surgeons have been inoculated with a tumor during an operation.

Another factor has to be considered in this connection. To judge from the rather limited number of experiments which have been made so far, it is possible that tumor inoculation is more difficult in certain species of animals than in others. Successful transplantations seem, for instance, to be more difficult in dogs than in some other species, although they have been successfully done in dogs. The reason for such apparent differences is not yet clear. Recently I tried to transplant into other dogs a sarcoma from the neck of a Boston terrier, which had recurred after operation, however, without success. In order to determine whether the difference of the soil caused this failure to grow, I transplanted several pieces into the Boston terrier itself, but they did not grow any more than the pieces transplanted into other dogs. The cause for this failure to grow lies, therefore, probably in the tumor tissue itself. How human tumors behave in this respect, we are, of course, unable to say, because experiments of this kind are excluded in men, especially if we consider that a simultaneous inoculation into a number of individuals would be necessary.

One more conclusion resulting from experimental tumor inoculation might be stated: At the bottom of all tumor growth must lie an increased energy of growth of those cells from which the tumor took its origin. The growth of tumors cannot be due to a lowered resistance of the organism in which the cells carry on their apparently unlimited growth. This follows from the fact that in a sufficiently large number of cases it has been possible to so make tumor cells continue their destructive growth in a very large number of animals of the same species, and we find frequently that such inoculated tumors grow more rapidly than the original one. If, on the other hand, we transplant ordinary tissues as epithelium or cartilage, they have only a very limited growth, which never leads to the formation of a tumor.

The experimental analysis of tumor growth is a relatively new field of investigation. Although no proof has been found for the existence of parasites as the cause of tumors, nor has it been possible to exclude entirely the possibility of the causal connection of microorganisms with the origin of tumors, a number of facts have been

established in recent years which are not without interest, and which give us reason to hope that by a patient continuation of these experimental researches our knowledge of the conditions of tumor growth will more and more enlarge.