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* An address read before the Pathological Society of Philadelphia, April 11, 1907.

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BY LEO LOEB

When I was asked about twelve days ago, to read a paper to-night, I intended to make a small, quite unpretentious communication, giving a few observations and experiments on tumor-inoculation that I have made in the course of the last four months; but when, a few days later, I heard that the paper was to be discussed by some distinguished surgeons and pathologists, and that I was expected to speak somewhat longer than the usual time allotted, I saw that I must change my plans, it being too late to change the program, so, I had to enlarge the scope of my remarks and give a brief outline of some of the work done in the last seven years in the experimental investigation of tumors, instead of reporting a few experiments, I myself have carried out recently. After an interval of several years, I obtained, only six months ago, the opportunity of resuming my work; I will not try to go much into details, but rather to discuss some of the tendencies of cancer-investigation at the present time.

I wish to say in the beginning that I have no startling announcement to make. The "cause of cancer" has not yet been discovered; but I do not, therefore, agree with those that, without much hesitation, condense their final conclusion into the short statement that we know nothing, nothing at all, about cancer. Such a statement is not very encouraging for those that have given their energies to this work for some time; and what is more, I do not believe it is in accordance with the facts. We have learned something about cancer; and, much more than our actual achievements, we see the road clear for future work. We see problems on all sides, problems whose solution can be attempted successfully and that present outlooks into new fields. That is the difference between the conditions now and as they existed eight or ten years ago. There

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is now a feeling of hopefulness among the workers in this field that was not present until quite recently. In Germany, France, England, and Russia, new institutions for the study of cancer have been founded in the last few years. In America which did not lag behind in this respect, Boston, Buffalo, and New York have now special laboratories for the investigation of cancer; and a steadily increasing number of investigators are devoting their energies to this work.

What has brought about the change? The increase in the number of cancer cases, which, as some investigators believe, exists? Hardly. Such an increase is far from being proved. I do not think I shall be far from the truth, if I state that the generally awakened interest in cancer is due to the opening up of a new method of investigation—the experimental method. If I speak of the experimental method as a new one, I, perhaps, do not do full justice to the splendid work done by Hanau and Morau almost twenty years ago. The former transplanted cancer (a squamous epithelioma) in rats; and Morau, a carcinoma in white mice. This work proved that tumors can be transplanted into other animals. Hanau made very careful microscopic examinations of his transplanted tumors, and Morau made very interesting observations on the susceptibility of different strains of mice to the inoculation with carcinomatous material. These efforts, however, remained isolated, for pathologists were not yet prepared for this method of work. I may illustrate this:

About fourteen years ago I had the privilege of studying under Hanau, and the opportunity of speaking freely with him about problems in pathology; but he never so much as mentioned his experimental work on tumors, for he had long since passed to other problems. I did not even know at the time that he had done such excellent work in this field. The possibilities of the extension of the work were certainly not fully realized at that time. On the whole, the investigation of tumors was almost exclusively limited to microscopic studies. Valuable and important as were the results given by these studies, there were noticeable the signs of exhaustion. The principal facts of the histogenesis and structural peculiarities of tumors arising from different types of tissues had been worked out as well as it could be done—in its main outlines, as well as in many of its details.

The similarity between metastatic and original tumor was established. There is now very little doubt that the epithelial

tumors usually arise from a direct downgrowth of the epithelial cells, and that this downgrowth is sometimes at first entirely unaccompanied with changes in the underlying tissue. In carcinoma proper, the changes are primarily in the epithelial cells. The origin of cancer may be unicentric and start from one point, and this seems to apply to the majority of cases; or it may be multicentric, originating simultaneously from several points. The growth of cancer takes place through the multiplication of its own cells, usually without infecting other cells of the body. These are the main results of anatomical and histological studies; and they are, on the whole, well established. There are still a few points about which some doubt is justified. Especially debatable is, for instance, the origin of certain so-called mixed tumors. It is possible that some of these, instead of being of embryonic origin, are due to the influence exerted by one growing tissue upon another, the latter starting to grow secondarily.

So far, purely morphological investigations could go; but they were not able to give us any further information. They could not give us any insight into the conditions of the growth of cancer, and could not bring us any nearer to the understanding of its cause. Attempts to prove the presence of a distinct and specific microörganism in cancer by morphological or cultural methods have, so far, failed. No convincing evidence of their existence could be obtained; although I am by no means ready to say that, among the various structures found in cancer and described by many authors, there may not have been protozoa. The attempt to fill with hypotheses the gaps, where facts were missing has led to the constructing of many theories of the cause of cancer. Either these theories are enlargements upon one single fact, frequently in a purely speculative manner; or they are based upon erroneous observations, as is the case with Ribbert's theory. There is no need to build up hypotheses prematurely, while we see before us a large field for work. First let us find as many new facts as possible and analyze these. There will be no difficulty in drawing our conclusions when we shall have sufficient data. These are what the more recent phase of the investigation of cancer promises to give us.

I refer to the experimental investigations of cancer in animals. That different animals may be afflicted with cancer has been long known, but our knowledge has been markedly increased within

recent years. We are now able to make a certain number of generalizations, which are not without interest. In the first place, it has been established that not only parasitical pseudo tumors but that typical malignant tumors occur in cold-blooded animals.

Secondly, some species of animals are much more frequently afflicted with cancer than others; cattle, more frequently than sheep; dogs, more frequently than either of these; mice and rats, much more frequently than rabbits and guinea pigs.

On looking over the character of different tumors that are found in different animals, I find that in certain species certain distinct types of tumor are prevalent. Eight years ago, I found that by far the most frequent variety of malignant tumors among cattle in America is the squamous-cell carcinoma of the inner canthus of the eye. In dogs, the lymphosarcoma of the genital organs is very prevalent in America and Europe. In white rats, several sarcomata have been found by myself, as well as by Velich, von Eiselsberg, and Firket. Sarcoma seems, therefore, to be a relatively common tumor among white rats. This tumor appears, however, to be rare among white mice; but these animals are liable to another very common tumor, a subcutaneous carcinoma, or adenocarcinoma, which in many cases, at least, seems to take its origin from the mammary gland. This is by far the most frequent tumor in white mice. Among fishes, also, a certain type of tumor is characteristic for certain species; as the carcinoma of the thyroid in trout We occasionally find, of course, other tumors in these animals; but those just named are the most common.

Fourthly, a fact of great importance that has been observed in different animals is that tumors occur in them endemically. This means that tumors are very frequent among them in certain localities. In Wyoming, I found, with Dr. Jobson, a ranch on which for ten years carcinoma of the eye has been endemic among the cattle, although the neighboring ranches are practically free from the disease. Among caged animals, the endemic occurrence of tumors has been found by Hanau, Morau, Borrel, Eberth and Spude, Michaelis, Gaylord and Clowes, and myself in the case of carcinoma; and by myself in the case of sarcoma.

Even among fishes, the endemic occurrence of cancer has been observed during the last few years, having been very carefully described by L. Pick. It is well known that an endemic occurrence of cancer has also been found in man; and especially Behla, Lyon,

and Sticker have investigated the conditions prevailing at such places very carefully. There is, however, one very important difference between the endemic occurrence of carcinoma in man and in animals, to which I called attention three years ago; namely, that while in man different varieties of tumors were observed in the affected area, in animals it was always precisely the same kind of tumor that was observed—namely, squamous carcinoma of the canthus of the eye in cattle, sarcoma of the thyroid in white rats, squamous-cell carcinoma of the vulva in Hanau's rats, adenocarcinoma of the subcutaneous tissue in mice, and carcinoma of the thyroid in fishes.

This is one of the reasons why the endemic occurrence of tumors in animals is so much more favorable for investigation than is the endemic occurrence of cancer in man. Furthermore, in animals we can vary the conditions of life at will much more readily than in man, in whom the number of variable factors is so much greater. In animals, which can be kept in small cages over long periods, the conditions can easily be arranged, according to one's purpose. It is clear that an investigation into the cause of the endemic occurrence of cancer is of the utmost importance.

Three sets of conditions have to be taken into consideration: (1) Hereditary influence, which could cause cancer to appear in certain families of animals: (2) infectious conditions, the transmission of an organism from one animal to another, either directly or by means of a host; and (3) environmental conditions, conditions of the food, water, etc.

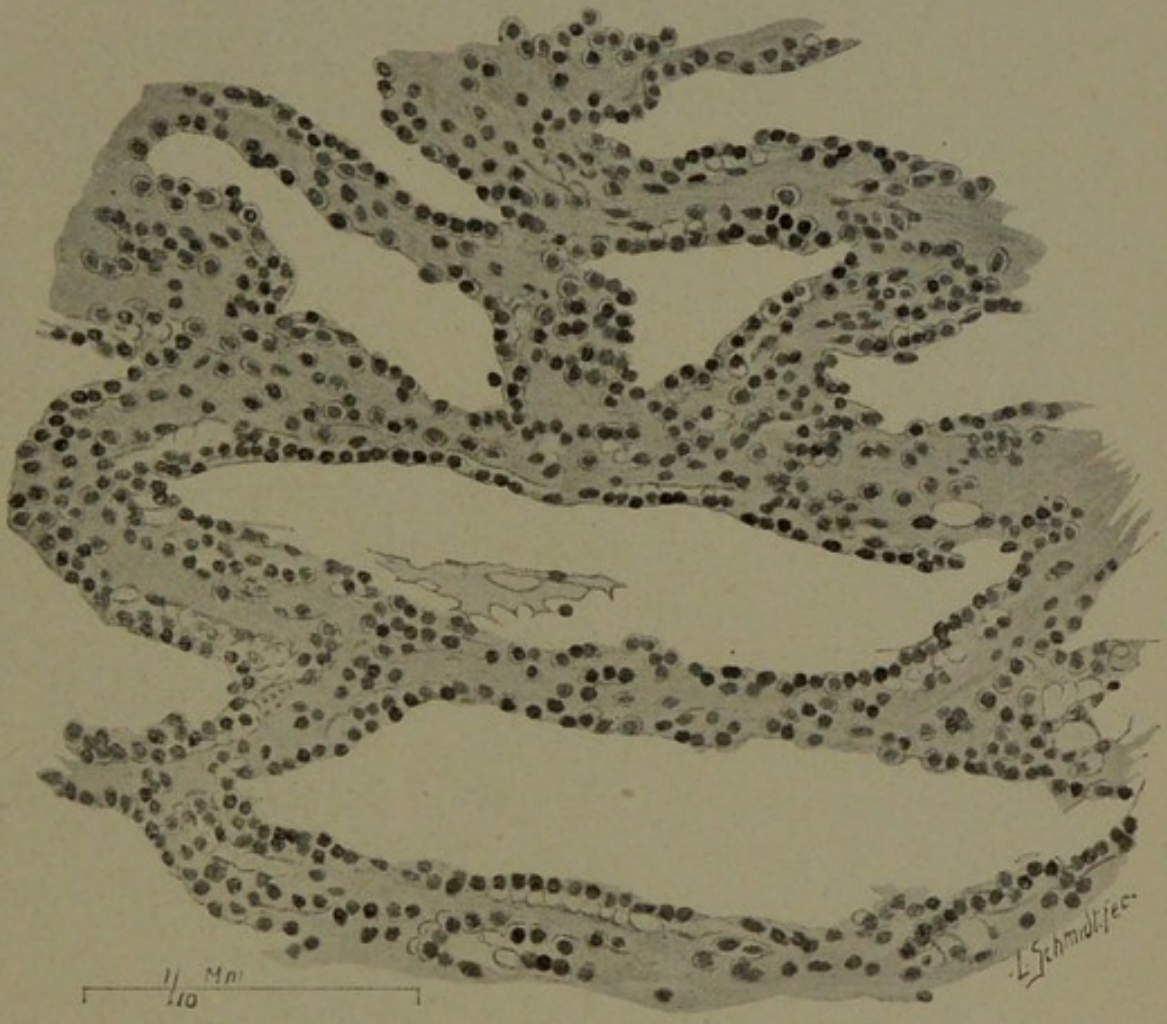
My former observations did not permit me to decide definitely between hereditary and infectious causes. Some recent investigations of another case of the endemic occurrence of cancer in mice have suggested to me the existence of hereditary factors; but some known observations of others seem to point to an infectious cause. I refer especially to those of Haaland, from the Pasteur Institute, and to the recent communications of Gaylord and Clowes. The latter observed three cases of sarcoma in rats confined in cages in which, several years previously, some of my sarcomatous rats had been kept for about five months. The question cannot, as yet, be regarded as absolutely decided. It is quite possible that a combination of factors is responsible for the endemic occurrence, but there is very little doubt that the problem can be decided in an exact way. It is necessary only to have the requisite means and enough time. There is no doubt, also, that such an investigation is of the utmost

importance. It brings us in direct contact with the cause, or with one of the causes, of cancer. Here we see tumors newformed in animals, without inoculation from another tumor. Ordinary tissue-cells, such as the cells of the thyroid of a rat, are transformed, as in my case, into sarcoma-cells, a long time after the animals previously affected with the tumor have been removed from the cage.

The same cannot be said of the second set of investigations to which I should like to call your attention. I mean the production of a tumor in an animal through inoculation with material from another tumor of the same species. In this case we do not convert previously normal cells into tumor-cells, but we make tumor-cells grow in other animals. The metastases of a tumor in the same animal can in this way be regarded as an autotransplantation of tumor-cells. In a similar way as a cell or a multicellular organism can be produced only if there has been previously present another cell, so a tumor can under these conditions be formed only if there has been another tumor present at the start. Notwithstanding this fact, the experimental production of tumors through the inoculation of tumor-material is of the greatest importance, inasmuch as it is likely to give us an insight into the conditions of the growth of tumors that could not be obtained in an exact manner in any other way; and secondly, because it permits us to investigate the conditions under which an immunity against the growth of tumors can be produced in animals.

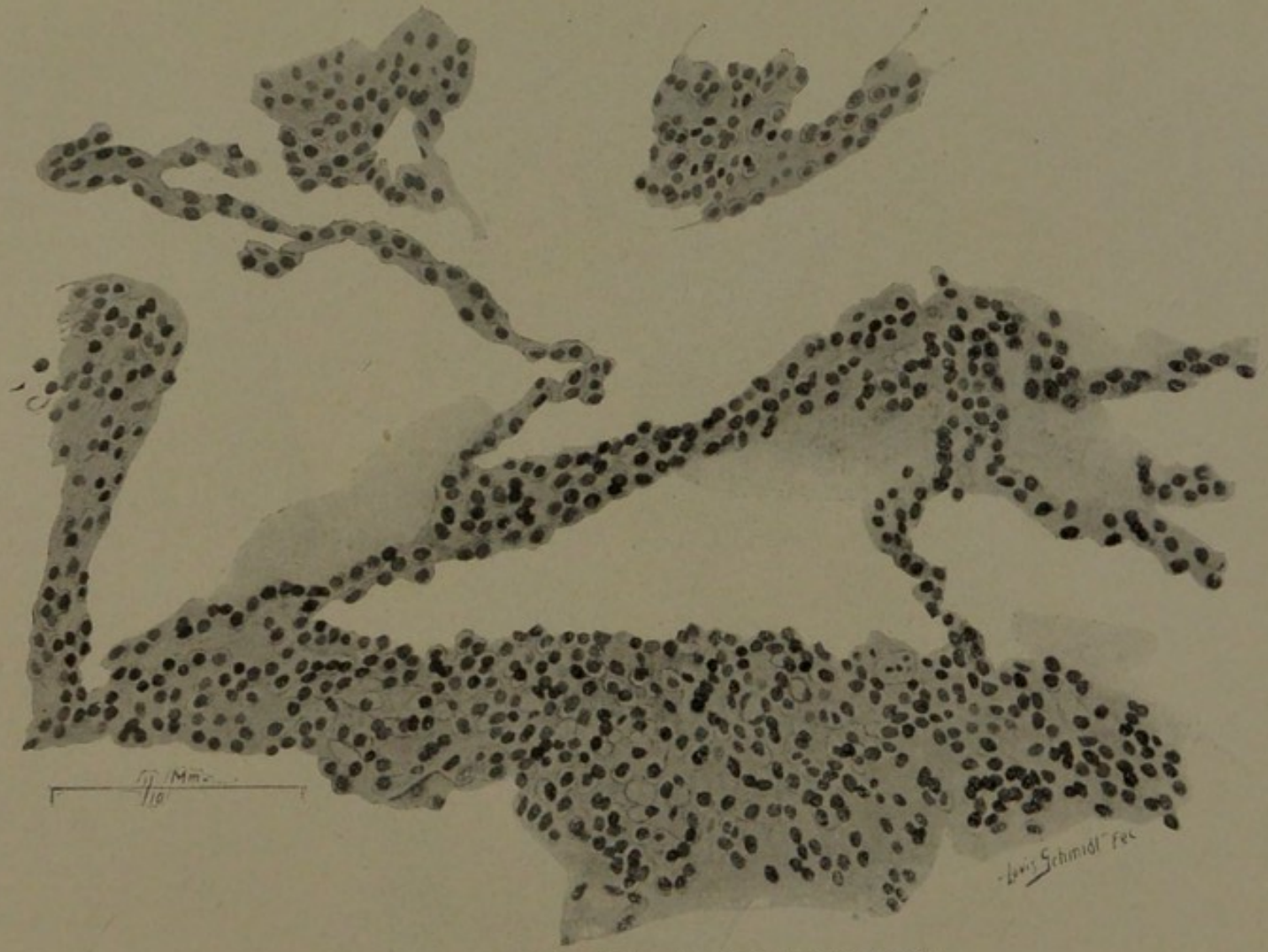
Now it might be argued that while transplantation into other animals can teach us the conditions under which cells grow after they have once been converted into tumor-cells, and can show us the existence of immunity or predisposition to the growth of such tumor-cells; it can show us nothing about how normal cells become converted into tumor-cells. I myself distinguished sharply between these two sets of factors in my earliest investigations on tumor experimentation. Some experiences, however, suggest that there may exist a relation between the inoculability of a tumor and some of the conditions that favor the primary development of such a growth. In experiments on an adenoma of the mammary gland in a white rat, carried out in 1901, I found that the behavior of pieces of tumor when transplanted into the animal affected with the primary tumor, was very different from their behavior when transplanted into other rats. The tumors grew or remained alive in the former; they died in the latter. Similar results were obtained

FIG. 1.



Cystic sarcoma of the thyroid of a white rat. Original tumor.

FIG. 2.

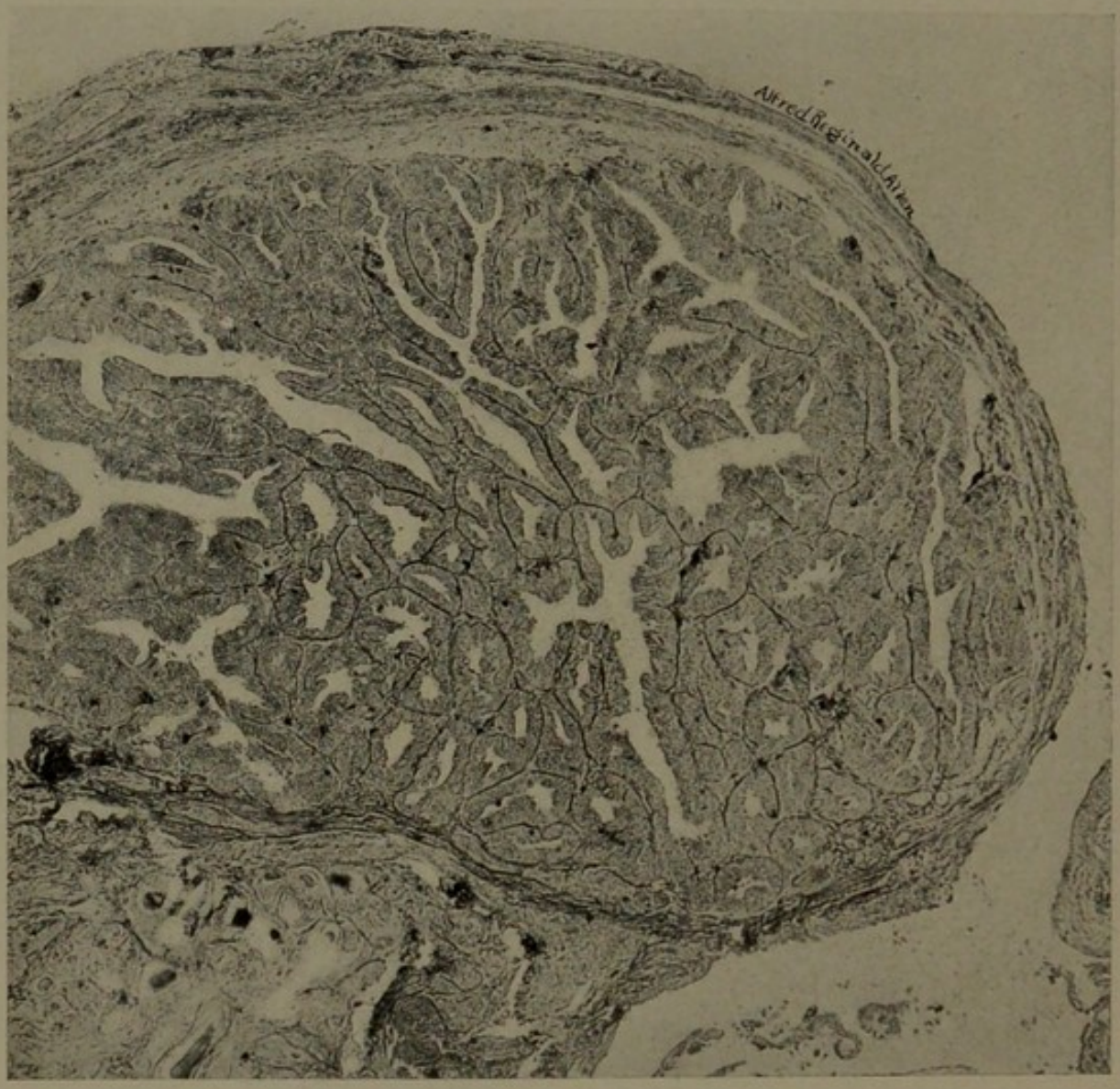


Cystic sarcoma of the white rat. Transplanted tumor.

Fig. 3.

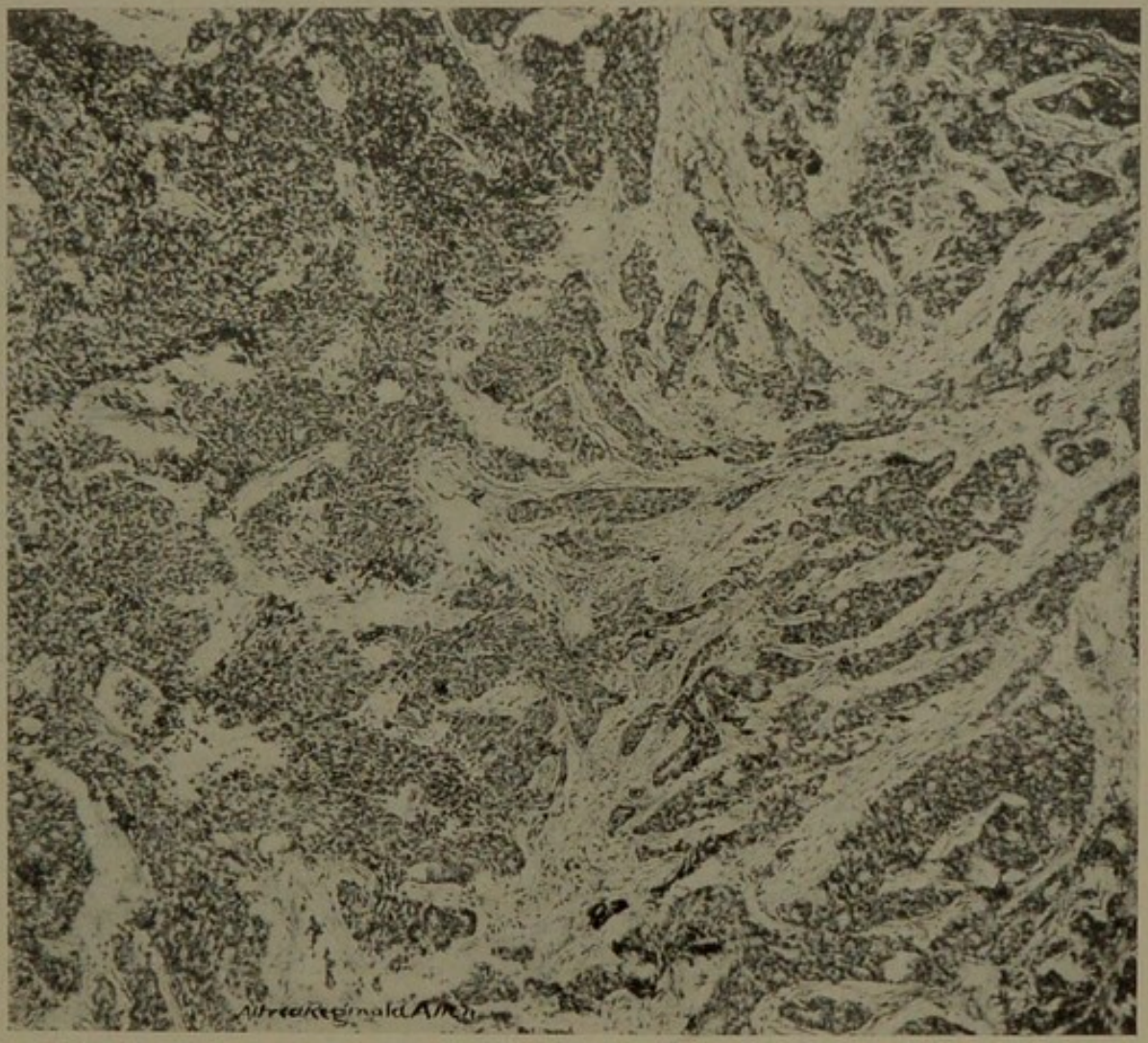
Cystic sarcoma of the thyroid of a white rat.

FIG. 4.



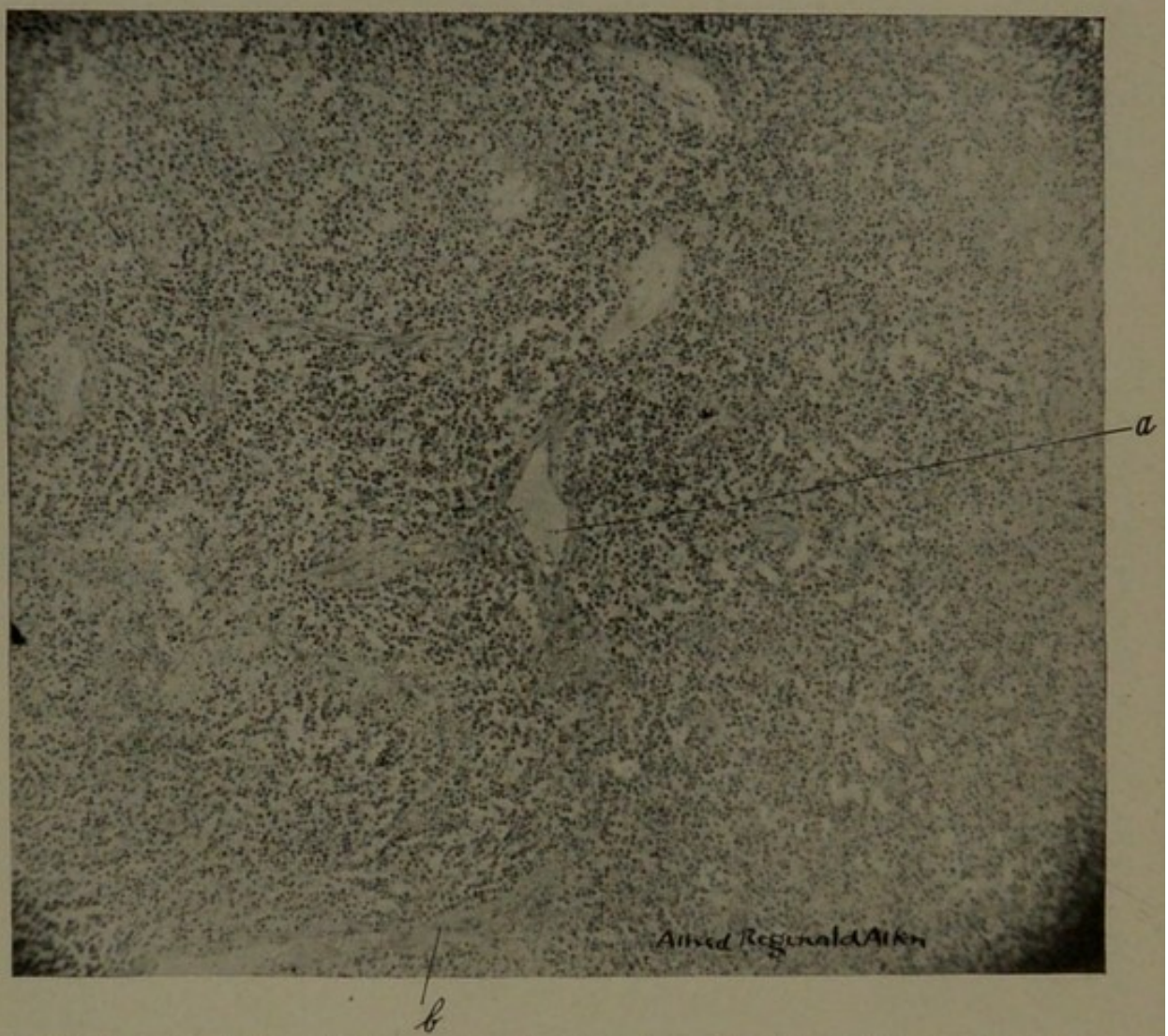
Papillary adenocarcinoma of a white mouse. This was not found to be transplantable.

FIG. 5.



Adenocarcinoma of a white mouse. In all probability originating from the mammary gland.

FIG. 6.



Lymphosarcoma of dog. This tumor was found in the wall of the vagina of a dog; it was readily transplantable. *a*, blood-vessel; *b*, stroma.

in experiments that I carried out last winter with Dr. S. Leopold on a mammary tumor of a dog. In the course of repeated inoculations, it was shown that pieces of tumor transplanted into the bearer of the primary carcinoma remained alive, but that they died, when transplanted into other dogs. In a similar way, in the course of inoculations of tumors into white mice, one experiment showed distinctly that a mouse affected with a spontaneous tumor, similar to the one inoculated, evinced a predisposition to the growth of the inoculated tumor. The conditions that made this animal a favorable soil for the growth of the primary tumor favored the growth of cells that had already been converted into cancer-cells. This is an important point that should be tested in future experiments; and it leads to a further question: Can all tumors be equally well inoculated into other animals?

No, there exist differences. Certain tumors are much more likely to grow in other animals than are other tumors. Carcinoma, as well as sarcomata, have been successfully transplanted; and other sarcomata or carcinoma could not be transplanted. On the whole, however, it seems probable that my prediction that sarcomata will be found more readily amenable to transplantation will be borne out by the facts; at least, our experience so far tends to prove this. A certain percentage of tumors have been transplanted successfully. In the course of sarcoma of the thyroid in the rat, the readiness with which the tumors of the four rats afflicted with primary sarcoma of the thyroid could be transplanted decreased gradually. The sarcoma of the first rat could be transplanted most readily. The last, sarcoma, with which I am now experimenting, gave the smallest number of successes. The others had an intermediate character. This is a remarkable fact which should lead to further investigation. In mice, a large number of subcutaneous adenocarcinomata cannot be transplanted. Others of a similar structure can be readily transplanted, and yield a large number of successful inoculations; while still others give only a very small number of successes. In dogs, the lymphosarcoma found in the genital organs is usually very readily transplanted; although other tumors of the dog show themselves refractory, in most cases, to successful inoculation. The three tumors mentioned are just the ones that have principally been used for inoculation, and I am in a position to-night to show you living animals affected with these three varieties of tumor. Ehrlich has also recently succeeded in a

large percentage of cases in transplanting a chondroma found in a mouse.

If we now inquire into the causes of the difference existing in the inoculability of different tumors, we can mention a number of conditions that are of importance in that respect; but some work still remains to be performed. As I have already stated, I have investigated the differences in the inoculability of the primary cancerous animal and other animals carrying a similar primary tumor, on the one hand, and of other animals of the same species, on the other hand. I found that males and females, young and old animals, can approximately be inoculated to an equal degree; but I also found that certain animals cannot be inoculated, even when repeated attempts are made. Similar observations have been reported by Herzog, Jensen, and Ehrlich. Certain animals are refractory to inoculation with certain tumors. Michaelis, for instance, has made the interesting observation that certain strains of white mice may be more readily inoculated with carcinoma than others. There exists, therefore, a natural immunity in certain individuals against inoculation with tumor-tissue.

I have recently given especial attention to the question whether pregnancy favors inoculation, but I have been unable to find any distinct influence. We see, therefore, that, in the first place, the predisposition or immunity of the animal is of importance; but secondly, the character of the tumor itself has to be considered. Different tumors behave very differently in this respect, even when they have the same structure. I have mentioned the difference of this nature existing in the four sarcomata of the thyroid, which had an almost identical structure. Their inoculability was very different. The same holds good in the case of the carcinoma of mice. Many carcinomata in white mice are practically untransplantable. Three years ago, I transplanted a carcinoma in a Japanese mouse. Its structure did not materially differ from that of the carcinoma of the ordinary white mouse. I was able to transplant this tumor successfully in 100 per cent. of the cases. The lymphosarcoma in dogs can also be transplanted in almost 100 per cent. of the cases; while other tumors of the dog cannot be transplanted at all, or only with difficulty. Perhaps we might be more successful if, for inoculation purposes, we could obtain the same variety of dog as the one in which the original tumor is found.

If we now analyze still further the second set of factors, namely,

FIG. 7.

Mouse with multiple carcinomata.

those dependent upon the peculiarities of the tumor itself, we find that the energy of growth in the primary tumor is not the only factor that determines the inoculability of the tumor; although it is one of the factors to be considered. In the case of the carcinoma of the Japanese mouse, I found that in the original animal and in the first generation of transplanted animals it grew very slowly; nevertheless, it proved to be inoculable in 100 per cent. of the cases. I have recently observed that multiplicity of tumors does not necessarily favor inoculability. I was able to make this observation after having obtained simultaneously from one breeder three mice with multiple carcinoma. One of these animals had as many as nine tumors in different parts of the subcutaneous tissue or near by. We see, therefore, that the inoculability of tumors depends upon a large number of conditions, which offer a fertile field for further investigation.

In this connection I may be permitted to draw attention to certain experiences, which are, perhaps, not without practical interest. I found in the case of my sarcoma in rats that the number of contact-metastases in the animal operated upon, depends upon the readiness with which the tumor can be inoculated into other animals. The first tumor, which could easily be transplanted, made the largest number of contact-metastases. Approximately at the same rate as the inoculability decreased, the contact-metastases decreased *pari passu*. The important point is this: we cannot determine beforehand from the structure of a tumor whether or not it is likely to make contact metastases. The tumors may have a similar structure, yet behave very differently in this regard.

Now let us consider the second phase of the experiment: A tumor has been found to be transplantable; and the next question is: How does it behave during transplantation into further generations? Does the inoculability gradually decrease and does it end after a certain time? This does not need to be the case. My first sarcoma I transplanted into forty generations, and only accidental conditions prevented its further inoculation. Jensen's carcinoma has continually been undergoing propagation in several laboratories for the last five or six years, and there is no sign of diminishing inoculability as yet. I found in my first experiments that the transplantation of a very few cells, in mitotic division, present in the cystic fluid of the sarcoma, suffices to produce the largest tumors. This suggested to me, six years ago, the conclusion that ordinary

somatic cells (ordinary connective tissue cells or epithelial cells) have a much greater propogating power and the possibility of a much longer duration of life than had hitherto been supposed. It appeared to me possible that they might be immortal in the same sense as the germ cells are believed to be immortal. The experiences in tumor inoculation certainly suggest new lines of biological research that will be of great general interest. However, not all tumors can apparently be transplanted indefinitely, even if no accidental infection takes place. Morau noticed a gradual decrease in virulence in his tumors; although, even in this case, we cannot exclude with certainty the idea that accidental weakening influences, such as certain bacteria, had not been gradually inoculated simultaneously with the tumors.

In regard to the energy of tumor growth, some interesting conditions have been discovered to exist. As I pointed out two years ago, it is of frequent occurrence that the original tumor grows more slowly than the transplanted tumors. The maximum rate of growth may be reached in the second generation. This was especially marked in the course of my transplantations of the adenocarcinoma of the Japanese mouse, but I had noticed it in my early transplantations of a sarcoma. Other observers have made some similar observations.

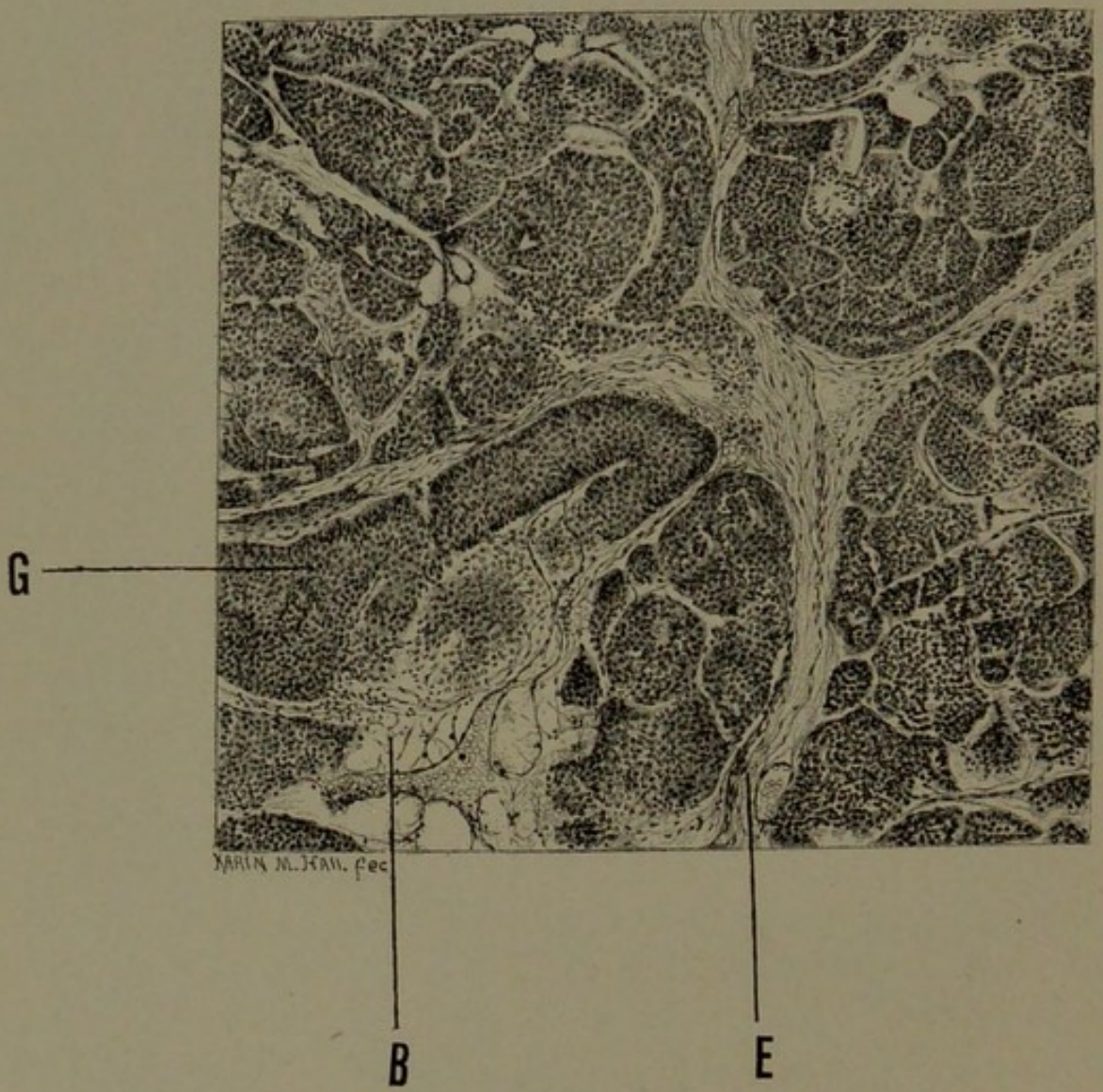
As to the cause of this increase in the energy of tumor-growth, I think it depends mainly upon the operative interference with the tumor, through which it is possible to stimulate its growth. It is possible to obtain a similar stimulation of growth through cutting a piece of tumor or pulling a silk thread through the tissue. In this way, I succeeded in causing tumors that had ceased to grow to start a fresh and vigorous growth. This experiment does not, however, succeed with all kinds of tumors. An adenocarcinoma of the breast of a dog, with which I experimented last winter with Dr. S. Leopold, proved refractory in this respect. The effect of injury upon the tumor does not depend upon the production of a better blood supply; for on microscopical examination this was not found to exist in my specimens. It evidently depends upon a directly stimulating effect of the experimental conditions upon the energy of growth of the cells, and it explains the observations of surgeons that recurrent tumors may grow more rapidly than the original tumors.

It is also possible to diminish the virulence of tumor-cells

FIG. 8.

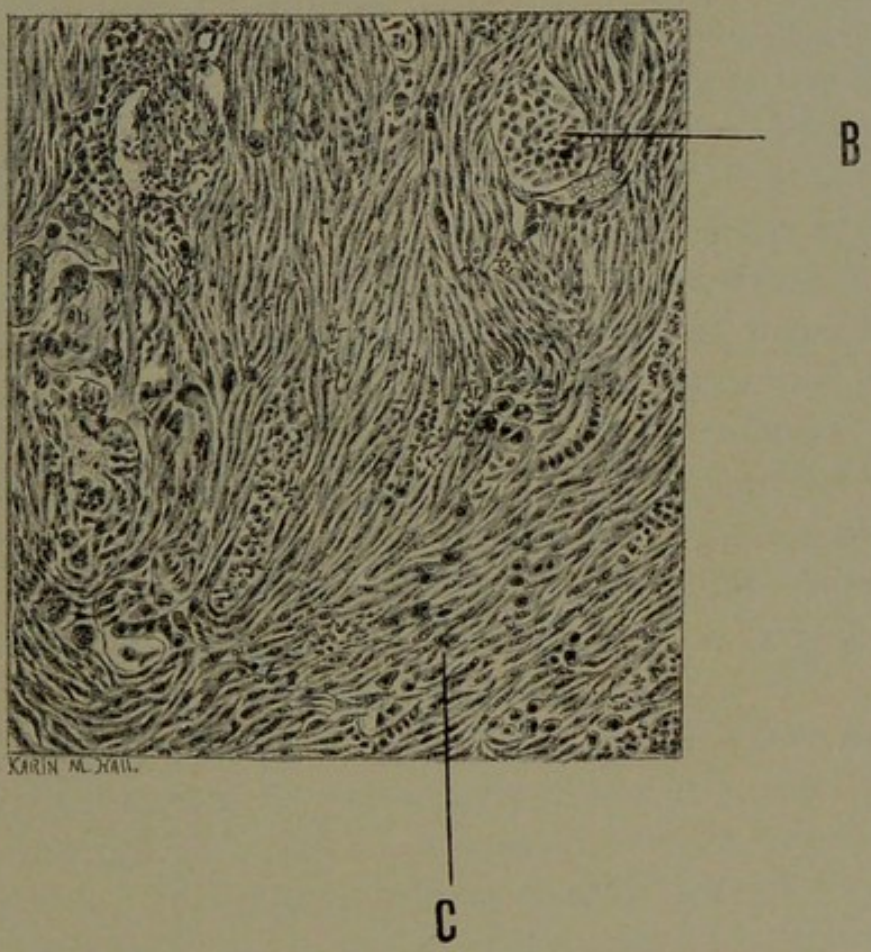
Original carcinoma in Japanese mouse. *i*, *a*, *b*, *c*, *e*, *g*, ramification of ducts. In the inoculated mice carcinomatous and sarcomatous tumors developed.

FIG. 9.



Carcinoma of the Japanese mouse. II inoculated generation. G, carcinomatous cell masses. B, E, stroma.

Fig. 10.



In the II generation inoculated with the carcinoma of a Japanese mouse, spindle cell sarcomata are found besides the carcinomatous tumors.

directly, by subjecting them to certain physical or chemical conditions, *e.g.*, by heating the tumor-cells up to 43° or 44° for half an hour outside the body. Certain chemicals act in a similar way. This decrease in the energy of tumor-growth is caused by a directly depressing effect upon the tumor-cells, or upon the agency included among them that causes the growth. The important bearing of this fact upon some practical problems will soon be discussed. The knowledge that it is possible to decrease the energy of tumor growth experimentally, without killing the cells, came to me quite unexpectedly. The experiments of Sticker, Ehrlich, Apolant, and Michaelis have confirmed my own results. If we increase the strength of the injurious influence but slightly, the tumor-cells are killed. The destructive effect of certain external agencies was determined by me for sarcoma; and independently of me, at about the same time, by Jensen for carcinoma. It is interesting that there is scarcely any difference in this respect between sarcoma and carcinoma. There may, however, be a minor difference of about 2° or 3° in regard to the action of heat on different tumors.

Clowes and Baeslack have recently found that, if the temperature to which the tumor is exposed outside the body before inoculation be still lower, and only slightly higher than the body-temperature, the energy of tumor-growth is increased. It is probable that this stimulus is of a similar kind to the one observed by me in threading a tumor or excising a part of it. Another method of increasing the energy of tumor growth has been used in recent years by Ehrlich. He uses in such series of inoculations the most actively-growing tumor, and believes that in this way he has, by selection, obtained a race of tumors with increased virulence.

A question of great interest is, whether inoculated tumors preserve their morphological characteristics during the course of their many generations of life in other organisms. In general, they do. Sarcomata, as well as carcinomata, occasionally, however, exhibit slight transitory variations as described by me in my first paper on transplantations of tumors. A sarcoma may assume a somewhat endotheliomatous structure, and the type of growth of an adenocarcinoma in mice may undergo slight changes; but, on the whole, the structure remains preserved. Only one very marked exception has been noted; namely, the appearance of a spindle-cell sarcoma in the course of the transplantation of a carcinoma, which I observed three years ago in a Japanese mouse, and which Ehrlich

and Apolant noticed approximately at the same time. In my case, the sarcoma originated as early as the first inoculated generation; in Ehrlich's, it was found only in later generations. A fact of general interest is that in my transplantations, the curve indicating the variations in the energy of growth in different generations applied equally to the sarcomatous and to the carcinomatous components. This suggests that the same factor underlies the growth of the sarcoma and that of the carcinoma. In both cases, the carcinoma and the sarcoma could be mixed or entirely separated in the different animals. Do we have to deal with a transformation of carcinoma into sarcoma? Although there are places that might be interpreted as indicating such a transition, a careful study of the different tumors in very many sections makes it more likely that we have to deal with a conversion of connective-tissue cells into a sarcomatous growth. The epithelium transmits its stimulus to grow to the connective tissue of either the original animal or of the host. As I have mentioned above, these observations may throw some light upon the origin of such tumors as the sarcoma-carcinoma of the thyroid. Instead of assuming that they are due to congenital malformation, we may, with as much justification, hold that primarily one tumor (a carcinoma) was present, and that only secondarily a stimulus emanating from the carcinoma caused the connective tissue to assume a sarcomatous growth.

We now turn to a question that is of theoretical, and promises to be of practical importance, namely, that of immunity. In the foregoing I have already mentioned some facts that have a bearing upon this problem. We see that certain animals of a species are immune, while others are predisposed to the growth of an inoculated tumor. I have not infrequently observed, in the course of my tumor-inoculations, that certain tumors, after a preliminary growth, become stationary, or may even retrogress. Mitoses may be present in these latent nodules for a long time, until mitotic divisions entirely cease to take place.

Animals with merely stationary tumors may still constitute a favorable soil for tumor-growth, as I found during my inoculations of sarcoma. Sticker, however, found, in the lymphosarcoma of dogs, that as soon as an animal has entirely recovered spontaneously from an inoculated tumor, it has become immune against any further tumor-inoculation. Clowes and Baeslack observed the same fact in the case of carcinoma in white mice. They found,

moreover, that the serum of such spontaneously-recovered white mice has a certain, althought only a very slight, immunizing effect against tumor-inoculation upon other mice. Sticker likewise observed a certain curative effect of such serum upon other dogs affected with lymphosarcoma. These observations are probably to be explained in the following way: In a certain number of animals that seem to be predisposed to acquire an active immunity, the latter is acquired as the result of the temporary growth of a tumor. This immunity is an active one, and the serum acquires certain cytocidal properties in vivo. This serum has, however, no agglutinating properties upon a tumor-emulsion; certain antibodies are, therefore, lacking, as Sticker found.

But not all animals in which a tumor has been growing for some time have thereby become immune. Such animals may, as I very early observed in my experiments, be successfully inoculated with another tumor. Here I am able to show you a dog inoculated several months ago with lymphosarcoma, and reinoculated about four weeks ago. The second tumor is growing. Ehrlich has, however, recently found that when a mouse is inoculated with a very rapidly-growing carcinoma, a second inoculation with a carcinoma will not be successful. In this case, the animal has become immune through the first inoculation.

The next step was to find a method by which to immunize animals actively against the tumor-growth. This applies as well to preventive immunity as to curative immunity. The principle that may have to be applied for this purpose is the one announced by me more than three years ago, in a paper before this Society; namely, the use of a virus of decreased virulence. I found especially effective for the production of such a vaccine a graded exposure to higher temperatures. Exactly the same method has been successfully applied by Michaelis [1] in the Berlin Institute für Krebsforschung within the last year. At first he used tumor tissue killed by chloroform for his experiments, but entirely without success. Neither was he able to obtain an active immunity by inoculating the tumors of gray mice into white mice, or vice versa. Ehrlich, however, obtained an active immunity by using for inoculation tumor-material that was originally less virulent; for instance, hæmorrhagic carcinomata in mice.

[1] We have to suspend our definite judgment in regard to his results, until his more detailed report has been published.

Of theoretical interest is the fact that an active immunity against certain tumors of mice can be produced by injecting mice with different varieties of tissues of the mouse; for instance, embryonic tissue and sarcomatous tissue. Conversely the injection of carcinomatous tissue protects against sarcoma. Evidently we have here to deal with an active cytolytic property of the body acquired through the injection of cells of the same species. Practically, however, the inoculation of living tumor-tissue of ordinary virulence cannot be carried out in man; and von Dungern's experiments in the production of an active cytolytic immunity by injecting human milk into man seems to have failed. Probably we shall again have to consider the use of a vaccine prepared by experimentally decreasing the virulence of tumor-material. Very interesting results have been obtained by Sticker, who found in the lymphosarcoma of a dog, that a single intravenous injection of a suspension of tumor-material produces an active immunity in dogs, without ever leading to the new formation of tumors. We see that we shall have to study the conditions under which an active immunity can be produced in different animals, before we can contemplate the use of such means in the case of human tumors; especially as it is quite probable that different varieties of tumors in animals and man behave somewhat differently in that respect.

As to a passive immunity, which means the use of the serum of actively immune animals for the cure of tumors, I can be brief. Since the first experiments of Richet and Héricourt, twelve years ago, many attempts have been made to cure tumors in man by use of a serum. Especially v. Leyden and Blumenthal are making and have been making for the last six years, systematic investigations in this direction, without, however, having produced very marked results. It is said that metastases do not develop under the influence of such serum. In mice, Jensen has used the same principle; but his results have not been of such a character that he could be convinced of the efficacy of the treatment. Other investigators have also tried it, without having reported any definite results so far. Perhaps the future will give better results. It seems to me, however, that active immunity will be the method promising more success than the use of serum.

Time does not permit me to discuss certain recent investigations into the chemical character of malignant tumors. Definite statements in that regard can scarcely be made, as yet; inasmuch as the

cases examined have not been sufficiently numerous to justify definite conclusions. Certain differences seem, however, to exist between the chemical composition of tumors and that of the normal tissues from which they are derived. These differences are especially indicated by certain products found in tumor-tissues undergoing autolysis.

There is, however, one other phase upon which I should like to touch briefly; and that is the difference between the behavior of normal tissue and that of tumor tissue during the process of growth. Normal tissue, when transplanted, if it grows at all, does so for only a limited period; and then the growth ceases. There seems to exist a certain cycle in the response of a normal tissue to a stimulus. I thought it possible that the action of the surrounding host-tissue prevents the further expansive growth of the transplanted epithelium. Therefore, in the course of the last three years, I have carried out a large and varied number of experiments in which, at different stages of its growth, I liberated regenerating tissue from the influence of the surrounding connective tissue by re-transplanting it into other animals. This was repeated a number of times in succession. The result was identical in all the experiments; regenerating epithelium always retained its general properties. It remained regenerating tissue, and did not assume the expansive or infiltrating growth of tumor-tissue. A summation of the stimuli that might lead up to tumor-growth, did not take place.

We may, therefore, conclude that, under the influence of localized stimuli, of whatever character they may be, a malignant growth of cells cannot be initiated. Such cells, under the influence of localized stimuli, grow as long as the stimulus exists; and then they return to their former state of equilibrium. Transplanted into another animal, in which the same stimulus would no longer be present, they behave like ordinary regenerating epithelium. We are forced to conclude, from all the experiments that have so far been carried out on normal tissues, that an hereditary transmission of the changes produced by such stimuli upon certain cells cannot take place. Whether or not such an hereditary transmission does exist, was one of the questions that I have tried to answer by the experiments in the successive transplantation of tissues. As we have seen, there is no indication that such an hereditary transmission can ever take place. Until this is proved we have to assume, in order to explain the growth of the malignant tumors, that can

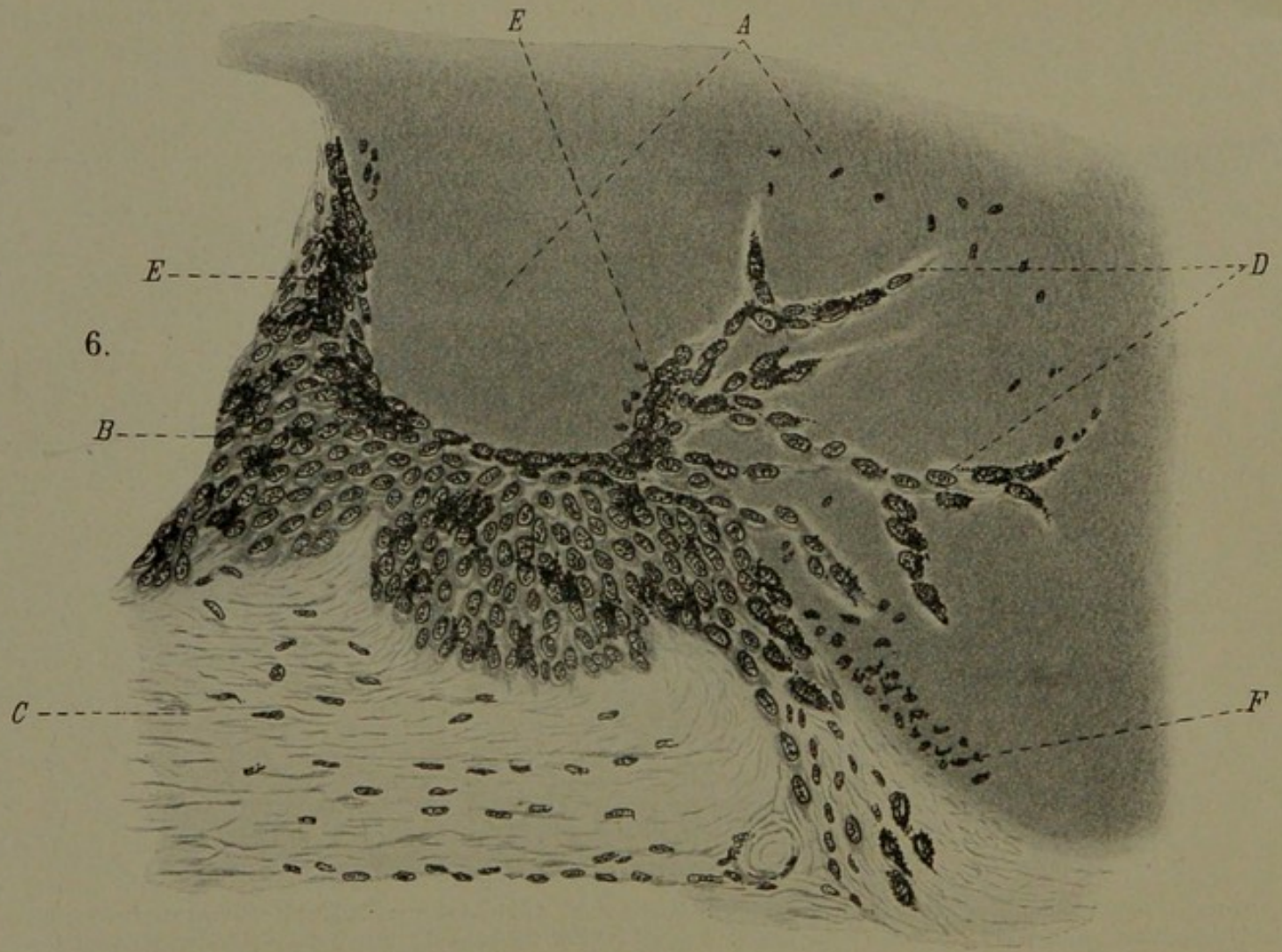
be inoculated into other animals, the constant presence of a certain stimulus in or around the tumor-cells themselves, a stimulus that remains connected with the tumor-cells into whatever animal these cells may be transplanted.

What I have just now said in regard to localized stimuli holds good of stimuli originating at points of the body farther distant. I may illustrate this with an observation that I have made in recent years. Towards the end of pregnancy, the atresia of follicles in the ovaries of young guinea-pigs can assume a specific character, distinguished by a marked hypertrophy of certain cells. Such changes may be multiple. We have a right to believe, in this case, that a stimulus not unlikely of a chemical character is produced outside the ovaries, leading to this hypertrophic change in the follicles of the ovary. Transplanted into other animals, however, such changes would not progress in the follicles; because the stimulus that had initiated them would no longer be at work.

Localized stimuli, and those coming from more distant parts of the body, may lead to what might be called transitory tumors, tumor-like, new formations that show a definite cycle in their development. They grow up to a certain point, so long as a certain stimulus is present; then they gradually retrograde. The corpus leutum may be regarded as the prototype of a transitory tumor. The small syncytiomata in the ovaries of very young guinea-pigs, which I found to be present in about 10 per cent. of the animals, also belong to that class. They reach a certain development, and then retrogressive changes take place. In a wider sense teratomata may likewise be placed in this class if they remain dormant; as well as other tumors that would cease to exist if transplanted into other animals in which a stimulus calling forth their proliferation would no longer be present. The course of such typical malignant tumors that seem to grow indefinitely in other animals can, however, be explained only if we assume that the tumor-cells carry with them the stimulus that causes their proliferation.

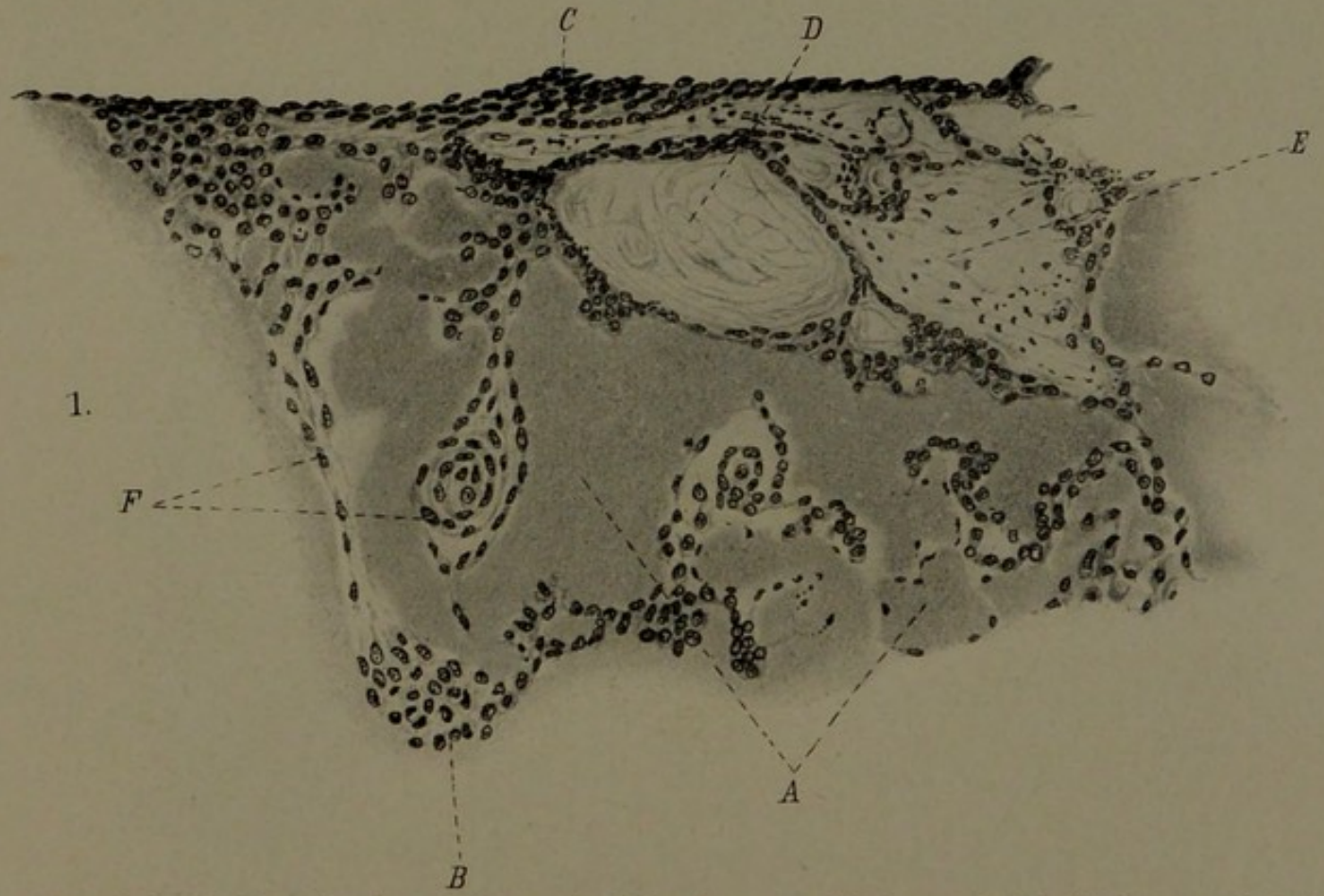
In conclusion, I wish to say that I believe that the tumor problem must at first be regarded as one of biology, and must be dissociated from any considerations of practical medicine. We have to analyze this problem as a part of the problem of growth in general; although any insight into the application of the knowledge we may gain through purely theoretical studies will certainly, in the end, benefit medicine.

FIG. 11.



Epithelium growing into Agar. A number of branches are formed (D) (E), A, Agar. C, connective tissue. Regenerative growth is quite distinct from tumorous growth.

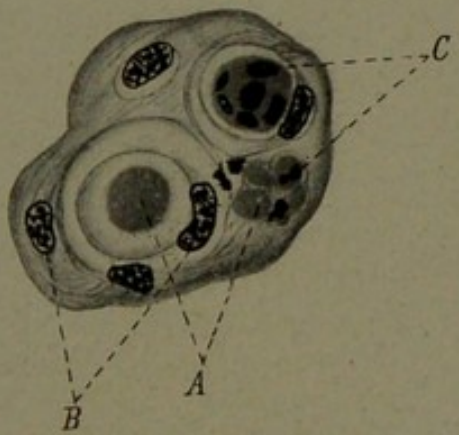
FIG. 12.



Growth of epithelium of a guinea pig in coagulated blood-serum. A, blood-serum. B,F, epithelium growing into the blood-serum. D, Keratin. E, connective tissue. The growth of the epithelium may take place without connective tissue. The growth ceases after some time. Carcinoma does not develop from transplanted cells.

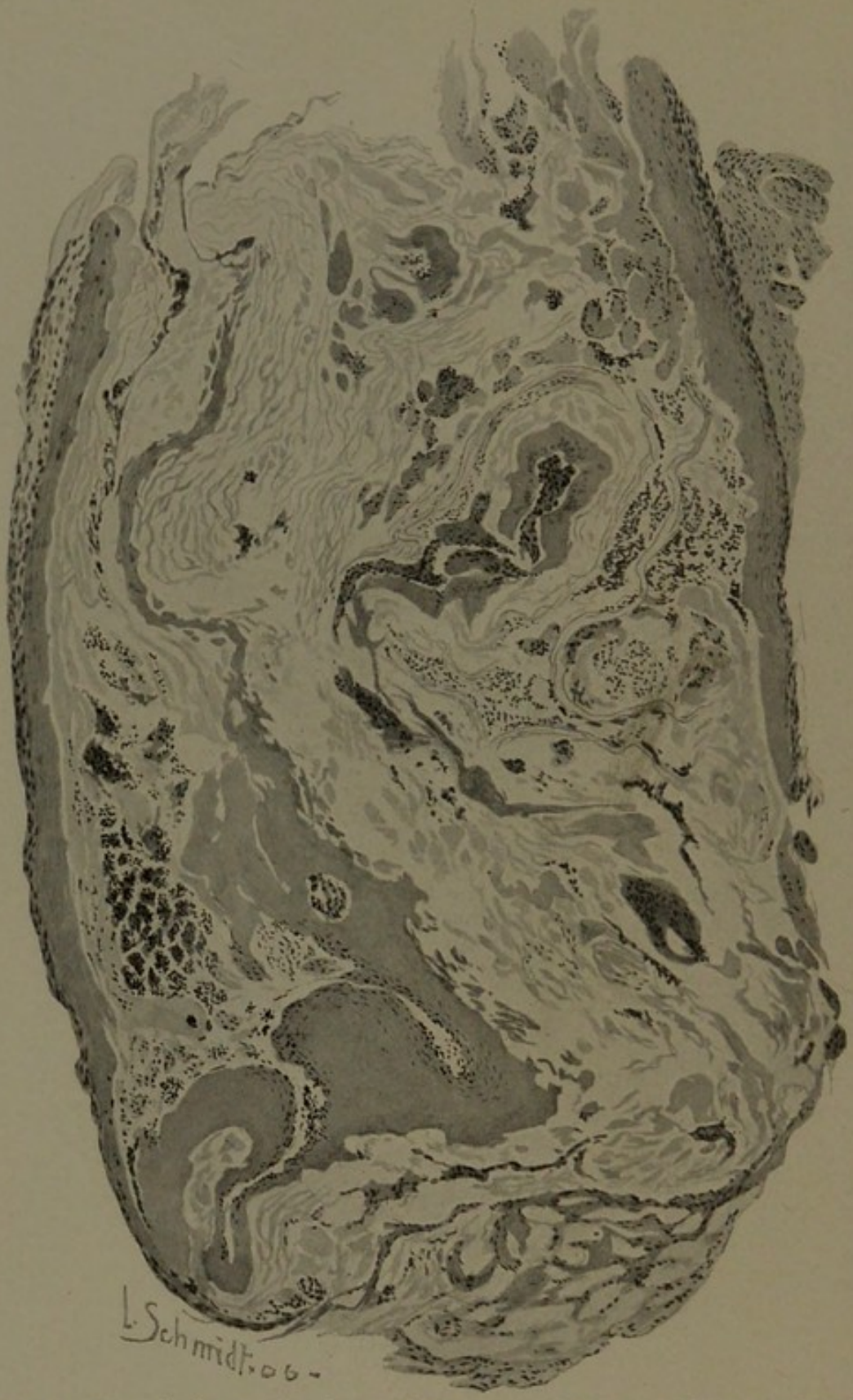
FIG. 13.

5.



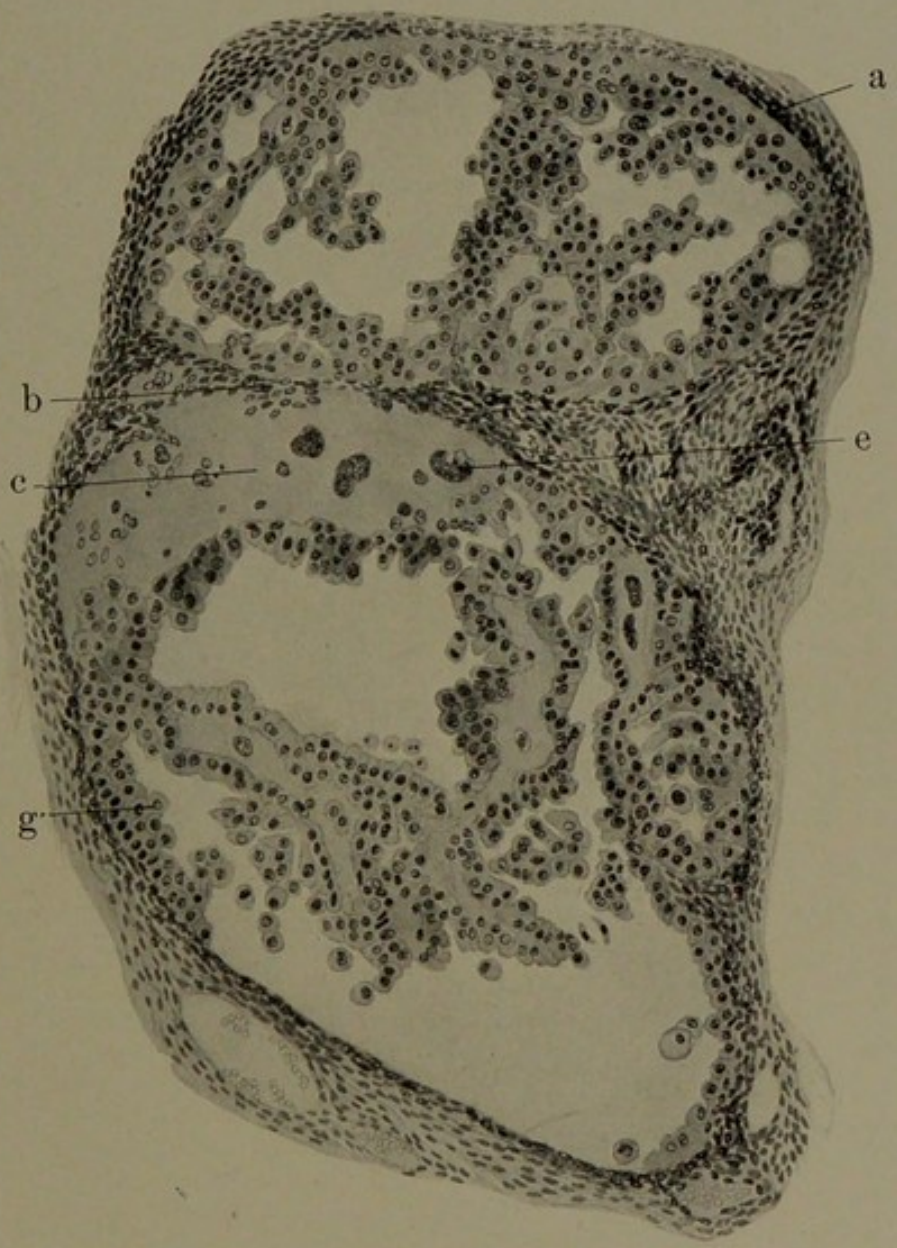
Epithelial pearl developing in epithelium in coagulated blood-serum.
See explanations of Fig. 12.

FIG. 14.



Skin of a guinea pig after a series of retransplantations. Large masses of horn are formed. In the periphery there is a layer of living epithelium and connective tissue. No tumor-like growth has taken place.

Fig. 15.



Small transitory tumor in the ovary of a young guinea pig. Such tumors are found in about ten per cent of all young guinea pigs and have frequently the character of a syncytioma.