

Figure 2 is iodoform dermatitis 72 hours after an only application of iodoform to an infected laceration marked A. A large bleb is seen at B and surrounding this are the small vesicles C. The case was as follows:

J. W. G. came with slight laceration on dorsum of left hand, July 18, 1901. This was cleansed antiseptically and was treated with no application, except bichlorid dressing for four days, when a little pus appeared. It was then dressed with sparing applications of iodoform of the very best quality from a box, out of which I had used half the contents on other cases with no harmful result. He returned after forty-eight hours for another dressing, at which time the peculiar form of local iodoform poisoning shown in the cut was apparent. The blisters were clipped and carbolated vaselin applied every day.

Figure 3 shows an advanced stage of the process, eight days after the application was made (March 4, 1901) to the infected laceration of the fourth and fifth fingers and of the dorsum near the base of the index finger shown at points A—A. The first succeeding dressing was March 6, 1901, when the patient complained of considerable itching of the parts. On examination, several blisters, which surrounded lesions and contained a yellowish serum, were noticed. The iodoform was thoroughly washed off, but too late to prevent the dermatitis. The process continued until at its worst the hand appeared as this picture shows it. The points B—B are the dead but as yet unseparated epithelium; C—C are red inflamed areas where the epithelium has come away; D is a wart, having nothing to do with the disease. The chief characteristic of these wounds is their abundant exudation of serum. Notice in the region devoid of epithelium, the small granular bodies; they are accumulations of serum in the skin proper. This photograph was taken March 14, 1901, just eight days after first appearance of blisters and ten days after application.

TREATMENT.

The treatment of iodoform dermatitis is, in the first place, to stop the application as soon as the first symptom of itching is complained of and the first little vesicle seen; cleanse the surface thoroughly, using peroxid of hydrogen to loosen up the iodoform that has adhered to it, remove every particle of the drug, for any part of it left acts continuously as a poison and delays recovery. After cleansing, daily applications of carbolated vaselin 5 per cent., or an aqueous solution of carbolic acid, should be made until all vesicles disappear. I have obtained better results from this application than from any other. It is well at each dressing to immerse the part in an astringent solution in hot water for from 10 to 30 minutes. If dry dressing or dusting powders are used, they must be applied freely and repeated frequently, as they become early saturated with the exuded serum.

CELL IMPLANTATION IN THE PRODUCTION OF TUMORS.*

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The problem of the origin of tumors is a part of the physiology of growth. In explaining malignant tumors pathologists made use of two of the most obvious instances of ordinary tissue growth, namely, embryonic development and regenerative phenomena. Accordingly two theories have been advanced to explain tumor growth. The first one explains tumors as originating from embryonic cells, either actually detached from their normal surroundings, or at least functionally detached. With or without changing their place these cells do not

take part in the further development of their neighbors; they remain in an embryonic condition, are not functionally active as the normal surrounding tissue is, until at a later period they begin to make use of their latent, stored up forces. Being locally or functionally disconnected they do not find the tension of the neighboring cells opposed to them and they can now grow indefinitely. This is, in the main, Cohnheim's theory, especially as it has lately been further developed by Wilms. This theory, therefore, combines the two factors named above. It makes use of the embryonic character of the tumor producing cells, and of the fact that these cells are disconnected, implanted, as it were, in a strange environment. The lack of the normal tension or the regenerative factor of growth is added to the embryonic factor.

Some clinical facts seem to support this theory. Many teratomata can hardly be explained any other way. Many mixed tumors suggest such an explanation as to their origin. There seem to be tumors representing transitional formations between the teratomata on the one side and simple tumors, like sarcoma, on the other side. But it is difficult to explain many tumors, especially many carcinomata, on this basis. Therefore, Ribbert, though accepting the first theory as sufficient for many cases, added a supplementary theory, making solely use of the regenerative factor for the explanation of tumors. Through inflammatory processes adult cells become separated from their normal ground. Cells which are no longer subjected to the inhibiting influence of their neighboring cells begin, as ordinary wound healing shows us, to grow, until they find their normal connection with cells of the same kind. Cells which are perfectly detached from their normal ground will probably never find their normal environment producing the necessary tension and will therefore be able to grow indefinitely.

After having thus defined the two factors underlying these two theories, we have to consider how far these conceptions really adequately explain the growth of tumors.

The first problem to investigate is: how do displaced embryonic cells actually behave? A number of facts have been ascertained through experiments carried on in the last twenty, and especially in the last ten years, which to some extent enable us to answer this question. Still, our knowledge is yet limited, especially because some facts have been found in certain species of animals only, and in applying the results of these experimental facts we have to do it with this restriction. Let us first consider what becomes of the earliest embryonic cells, whose normal relation to their neighboring cells has been disturbed. If one-sided pressure is exerted on the segmenting cells of the egg of a frog, e. g., so that the normal succession of cleavage is altered and the relation of the first cleavage cells to each other is different from their ordinary relation, a normal embryo ultimately results. If the first blastomeres are entirely separated from each other each one develops a normal though smaller embryo, the number of cells formed being proportionately smaller, their size remaining unaltered. This holds good absolutely only up to the four-cell stage; isolated cells from the eight and sixteen cell stage still begin the normal development, and some of the blastomeres of the eight-cell stage run through the whole course of their development, but the blastomeres derived from these later stages stop at an earlier stage of their development. Thus the blastomeres derived from later stages differ in their fate from earlier blastomeres, not

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as was to be expected by the former developing more specified parts of the whole, but instead, they form the first stages of whole embryos. No conclusive experiments have been made with regard to the fate of isolated blastomeres of later stages. Sufficiently large pieces of blastulæ also can develop perfect larvæ. At a somewhat later stage certain parts of the embryo must be present in the cut-out piece if the gastrulation shall take place. A certain morphogenetic localization has perhaps already taken place at this stage. Very few data are at hand for later stages. The observation of Roux, however, might be mentioned, who found very frequently in frog embryos with a closed medullary canal, isolated cells of the character of the much earlier morula stage.

Of importance are the recent experiments of Spemann. He found in triton at a stage when the medullary plate is already indicated, that by tightening a ligature across the medullary plate the anterior end of the posterior part will form a head just as the anterior part will do. We see that under these changed conditions ear vesicles can be formed from parts which, if the development would have proceeded normally, would not have formed any part of the head. That, however, does not yet prove that any isolated cell of an embryo at this stage is able to form these structures, but probably the connection of these cells with a large part of the embryo is necessary for this result.

Before drawing any conclusions from these experiments with regard to tumor formation, the results of experiments of a different kind shall be reported. Pieces of the tissue of embryos of different age were transplanted or injected into adult animals. At variable periods afterwards the fate of these pieces was determined. The following result was obtained: Most tissues grow and may even undergo a certain differentiation, corresponding probably (but how far that holds good has not been determined) to the differentiation they would have undergone normally. In some instances, where especial attention was given to this point, it was found that only a part of the transplanted tissue survives, that most of it degenerates and that the succeeding growth takes place from the surviving elements. The rate of growth is different for different tissues; it is most pronounced in the case of cartilage, but other tissues also grow, and epithelial cells may even arrange themselves in glandular form, even if they have been injected at such an early embryonic stage that no differentiation of this kind has yet taken place. Even glandular epithelia with granules characteristic for gland activity may develop. Ultimately, however, all these cells cease to grow and become resorbed. (Nevertheless, it is still to be determined whether certain cyst-like epithelial structures may not remain stationary, indefinitely, without becoming absorbed.) If we inject, instead of embryonal tissue adult tissue the result is, on the whole, the same. Of course, no differentiation comparable to the embryonic development takes place. Transplanted adult cartilage grows markedly less than embryonal cartilage. But a similar difference between the growth of adult and embryonic tissue does not seem to exist with regard to other tissues. In some cases adult cells even seem to grow better than embryonal cells. Further investigation into this question is needed. The data at hand at present do not justify the widely accepted idea that all embryonal transplanted tissues are much superior in their faculty to grow to adult tissues.

Let us now consider what conclusions might be drawn from these facts with regard to the formation of tumors. There are tumors consisting of a number of different

tissues, with a limited growth, more or less resembling an irregularly formed embryo. Such teratomata might be derived from a detached blastomere, undergoing afterwards an autonomous development. Also Spemann's experiment might help us to explain certain tumors of a similar complex character. A wound or tear in the embryonic tissue of a later period might give rise to unexpected "heterotopic" formation, as e. g., to a brain-like tumor, at the caudal part of the spinal column.

But already here we find difficulties. In the first place we find these complicated tumors, although not exclusively, still in the majority of cases in the ovary and in the testicle. The explanation advanced to meet this difficulty is not sufficient and not quite satisfactory. In this connection it may be added that also mixed tumors of a less complex kind are, although not exclusively, mainly found at a few places, and again especially in glandular structures like the kidney, the salivary, lachrymal glands, and, to judge from recent findings, also in the thyroid gland. Roux observed early embryonic cells in different parts of the frog, not only in the "Anlage" of the genito-urinary organs; but, to my knowledge, just in the frog where such aberrant cells seem to be of a relatively frequent occurrence, teratomata or malignant tumors have never been described.

Nevertheless, the origin of this kind of tumors from blastomeres is the most probable one, although it must not be forgotten that it remains a mere hypothesis at present. Our knowledge does not seem to me to warrant us to exclude with an absolute certainty the older view of Waldeyer as to their possible origin from germinal cells, nor the hypothesis of Pfannenstiel as to their origin from ova. Mammalian ova may, in the beginning of the atresia of the follicles, show the first stages of segmentation. This segmentation is under the given conditions irregular, but irregular, also, is the segmentation of the ova of sea urchins in Hertwig's and Morgan's experiments. We must hesitate to exclude merely from data supplied by descriptive embryology possibilities which might be realized under conditions different from the ones under which the normal development takes place. Observations on the ordinary embryologic development would not have admitted the possibility of the development of isolated blastomeres to full embryos or of the formation of a typical lens from the retinal part of the iris in an adult organism. But there is a second difficulty. The growth of detached or separated embryonal cells leads, according to the above reported experiments, to a definite, limited growth. These embryomata, however, may start to grow like a malignant tumor, indefinitely, and may produce metastases. This also holds good of certain of the less complex mixed tumors, which otherwise might, in part at least, be explained as derived from detached embryonic cells or tissues of a later, already more differentiated type.

That leads us to the further consideration, can malignant tumors be explained by the detachment of cells, embryonic or adult? Malignant tumors grow apparently indefinitely; they may penetrate the surrounding tissue. Cells detached from the main tumor may, if they are not destroyed in the beginning (which probably frequently happens), multiply rapidly and form metastases. We saw that detached or transplanted normal embryonic or adult cells behave quite differently in the large number of experiments made. There is only one apparently divergent result published, the experiments of Lack with the scrapings of the ovary of a rabbit. That this apparently different result is due to an erroneous interpretation has been made very probable by Shattuck. How-

ever, it might be objected that there exist all degrees of malignancy. There really do exist tumors with different degrees of energy to grow. It has further been maintained, especially by Lubarsch, that the formation of metastases does not principally depend on the energy of growth of the tumor cells, but on a constitutional factor in the individual affected by the tumor (the capability to resorb transplanted cells being diminished). The transplantation of sarcoma and carcinoma, which has now succeeded in a sufficient number of cases, demonstrates, among other facts, that these objections do not hold good. The formation of metastases is caused by a primary increase in the energy of growth of the tumor cells. The transplanted cells rapidly multiply in a very large number of individuals of the same species. Secondly, transplanted tumor cells continue to multiply apparently without end, and therefore the difference between the transplantation of tumor cells and of ordinary embryonic or adult cells is very striking. With the tumor cell we seem to transplant some so far unknown factor which causes the cells to multiply without end. Different tumors have a varying energy; but this varying energy remains about constant in the same tumor in the course of a long series of succeeding transplantations. If we transplant pieces of a benign tumor, the transplanted cells remain benign. And even when we cut out pieces from such benign tumors at different intervals, the tumor did not, in the experiments made, assume a malignant character. On the other hand, transplantation of hypertrophic granulation tissue into different animals of the same species from which the original tissue was derived, was rapidly absorbed.

If Cohnheim in his lectures still maintained that experimentally transplanted cells may produce tumors, that, however, transplanted pieces of real tumors did not give rise to new growths—to-day we must reverse this statement. Neither the regenerative factor alone is able to change ordinary cells into cells of a malignant tumor, nor the embryonic character of the cells added to the regenerative factor. The results of experiments carried on from different points of view and with different methods corroborate each other. Ordinary embryonic cells, transplanted, have, under conditions, created experimentally only a limited growth. Therefore, we have no reason to assume that the results obtained so far are due to some accident and might be reversed some day. Still, there are factors which have perhaps not yet received the attention they deserve, e. g., the soil into which the tissues are transplanted, although a few investigations have been made into the question of the influence of the soil. It has recently been stated that tissues transplanted into ovaries had a more pronounced growth than those transplanted elsewhere. There does exist, however, another factor of more general significance. In the experiment of Spemann previously mentioned, embryonic tissue of triton could at many places produce a head, where, in the course of normal development the same tissue would have given origin to other organs. A head has, however, never been produced by injection of embryonic tissue. It makes some difference if the regenerating, detached, embryonic cells are on one side still in their normal connection with the rest of the body. It may be that the quantity of the regenerating substance has something to do with the different tissues regenerated by apparently the same cells, as especially Morgan suggests in some other connection. It may be that other correlative factors, perhaps of a specific chemical character, are here at play. There are other facts perhaps to be explained in a similar way. Pieces of

hydra grafted to each other form different organs, if, after the union has taken place, both pieces remain of about the same size or if a large piece is cut off from one of the pieces. Perhaps also the fact that epithelium transplanted into epithelium has a different fate from epithelium transplanted elsewhere may belong to a similar category. The theories based on the supposition of detached, either embryonic or adult cells, as the cause of tumors, are at the present state of our knowledge not sufficient to explain the growth of malignant tumors. If transplanted epithelium enters into the normal union with connective tissue, the expansive growth of the epithelium will soon be arrested under formation of small cysts. If, however, such a regular union does not take place, the epithelium after a preliminary growth soon degenerates and connective tissue penetrates it. Decrease of tension added to sufficient nourishment is therefore not able to induce such epithelium to indefinite expansive growth, although such epithelium transplanted into blood serum, e. g., reproduces a number of the morphological appearances of carcinoma. Nevertheless, many, or perhaps most cells have a faculty for growth which is apparently almost indefinite, with regard to the quantity of tissue which can be produced and perhaps also to the time over which such growth can extend under favorable conditions. Why the transplanted tissues after a preliminary growth cease to continue to grow we do not yet know. Perhaps exhaustion of reserve material in the cells is the cause, perhaps some other factor plays a part. If we shall be able to experimentally prolong and increase the growth of transplanted tissue we will be nearer an understanding of the factors underlying the tumor growth.

The deficiency of the theories discussed here was, it seems, also recognized more or less by their authors. Wilms admits that some other unknown factor may come into play to produce a malignant tumor, though at other places the fact that the growing embryonic cells do not grow in their normal relation with neighboring cells seems to be sufficient to him to explain the boundless growth. Ribbert mentions "accommodation" of certain cells to the conditions of their new environment as necessary for their transformation into tumor cells. Israel, who applies similar principles as Ribbert, modifying them, however, in such a way as to include carcinomata arising from the surface epithelium directly and not from implanted cells, makes use of an hereditary transmission of an acquired increase in the energy to grow. Also Adami, in his theory which otherwise is based on different principles, makes use of an acquired "habit to grow." These or similar factors are perhaps not yet well defined, but they may be accessible to an experimental analysis. In this connection some recent experiments of Lyon might be mentioned, in which he succeeded in proving that an acquired immunity against potassium cyanid may be transmitted to succeeding generations of cells.

At the base of the theories discussed here lies a principle mainly gained by deductive a priori reasoning which was clearly expressed, especially by Weigert. This principle says that there do exist functional Reize (exciting causes), but no formative ones. All cell growth is caused by removing the tension of the neighboring cells. This theory itself is based on a theory of development, according to which no interdependence between normally developing parts of an organism takes place and all regenerative processes are caused by the presence of a reserve idioplasma called into action by removing the tension of the neighboring tissue. This

principle is a negative argument in favor of Cohnheim's and Ribbert's theories, excluding as it were the possibility of any other explanation for cell division. More promising, however, than the discussion of the above stated principle seems to be, at least with regard to the tumor problem, an analysis, and especially an experimental one, of the facts of embryonic development and of the regenerative processes. The latter must be an individual one for the different tissues which may behave differently. And here new methods must be worked out for new problems which suggest themselves. As Herbst and Spemann made it very probable that the touch of certain parts of the optic vesicle caused the skin of the head (and probably any part of the skin of the head) to form the lens, so G. Wolff demonstrated recently that the regenerative growth of the cut-off extremity of a triton does not take place if the medulla and the spinal ganglia are removed. In these cases we certainly can not speak of a removing of mechanic tension as the cause of growth. If the meaning of the removing of tension does not restrict itself to mechanic tension, it would be only used in a metaphorical sense and might mean any change of a chemical or physical nature; it would therefore essentially not be different in its meaning from the conception of a formative "Reiz." These causative factors for growth are at present still mostly unknown to us. Their analysis will also be necessary for a full understanding of the etiology of tumors. For even if micro-organisms shall have been definitely demonstrated as the cause of tumors, great as this achievement would be, the problem would still remain how such physical or chemical conditions created by the micro-organism can be the exciting factor of increased cell division.

DISCUSSION.

DR. H. D. PEASE, Albany, N. Y.—Before many of the phenomena observed in tumor formation and the production of metastases can be explained we shall certainly have to know more about the physiology of normal tissue elements, both embryonic and adult. Such questions lead to a discussion of the problems of cell division, tissue differentiation and inheritance. Even if it is eventually found that micro-organisms have an etiologic relation to malignant tumor formation, many of the phenomena which occur in such formations will require for their explanation a consideration of these problems.

REPORT OF A CASE OF TYPHOID PERFORATION WITH GENERAL PERITONEAL INFECTION

AND FIVE OTHER CONSECUTIVE CASES OF GENERAL SUPPURATIVE PERITONITIS; ALL RECOVERED.

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It is the prevalent opinion of the profession that practically all cases of general suppurative peritonitis should terminate fatally. That this is not true, however, is forcibly illustrated in the cases here reported. The questions arise, therefore: 1. What are the conditions which produce the fatal result? 2. Can these be overcome by medical or surgical treatment, and if so, when and how?

General suppurative peritonitis is not necessarily a fatal disease. The result of a general peritoneal infection depends on the following:

(a) *The type of infection.* If it be a virulent streptococcus type, with little pus formation, the peritoneum is rapidly denuded of the epithelial covering and becomes a "blistered surface" through which absorption rapidly

takes place. Death in these cases is caused by the large quantity of the products of infection rapidly absorbed. If the poison be diluted or the pressure under which the infective products are retained be reduced the patient may pass over the critical period to a convalescence. If it be a staphylococcus or colon bacillus infection, the denudation of the peritoneum is slower, the danger of immediate overpowering of the patient by the absorbed toxins is diminished and the fatal termination is postponed often to four or six days, until such time as the fibrinous exudate which covers the peritoneum is exfoliated, taking with it the peritoneal endothelia. A rapid and fatal absorption may then ensue.

(b) *The period of time that elapses between the infection and the time of operation.* In the past the diagnosis of perforation was based on the combination of symptoms included under the term collapse, which was believed to occur a few hours after the perforation took place. At present the diagnosis of acute infectious perforative peritonitis is based on the symptoms of pain, nausea and vomiting, localized tenderness, circumscribed flatness on piano percussion, elevation of temperature and hyperleucocytosis, in the order mentioned. With these symptoms many of the patients give a history of diseased conditions which predispose to the development of perforative peritonitis. The operation should, therefore, be performed as soon as these symptoms are manifest. If it be postponed until the patient is in collapse the case will terminate fatally. If it be performed, however, in the early stage, the "peritoneal shingles" or endothelia will be found intact, thus preventing absorption. When these natural barriers to absorption are destroyed, as is the case when operation is delayed, a fatal termination can not be obviated.

(c) *The tension under which the products of infection are retained in the peritoneal cavity.* The mere pressure of pus in this situation does not necessarily mean absorption of the infective products. The greater the pressure under which the pus is held in these acute conditions the more rapid the absorption. This is true, not only in the peritoneal cavity, but also in suppurations in the cellular tissue in any portion of the body. Remove the pressure and there is an almost immediate cessation of absorption, as is shown by the sudden subsidence of the symptoms of infection after draining an abscess in any portion of the body, notwithstanding that pus remains in this cavity after it has been opened. The reduction of pressure is one of the basic principles of treatment of cases of general suppurative peritonitis. We believe, and have shown, that irrigation is not necessary in the peritoneal cavity any more than it is in circumscribed suppurations of other tissues.

(d) *The diffusion of the infective material through the peritoneal cavity.* It is well known that when this diffusion takes place in the upper half of the peritoneal cavity the danger is enormously increased, because absorption from this part is much more rapid than from the lower or pelvis portion. On this basis all patients were kept in the semi-sitting position, at an angle of thirty-five degrees, from the time they came under observation, both before and after operation, until the pus was entirely removed. In all the cases an effort was made to allow the pus to settle into the pelvis, where it would be free from pressure and could be easily carried off by the drainage tubes. In this way absorption took place slowly and the patients were saved from the primary, overwhelming dose of toxins, which is so fatal.