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TRANSPLANTATION AND INDIVIDUALITY.[1]

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INTRODUCTION.

In this paper I shall report very briefly on a series of experiments which have been carried out in our laboratory by ourselves and our associates and in which the method of transplantation was made use of in the analysis of individuality.

Reactions of tissues serve as indicators with which to judge the interactions of individualities when parts of organisms are transferred into a new soil. Conversely, by means of the reactions of tissues, which we observe under those conditions, we attempt to obtain an insight into the forces which are active between tissues and into their finer biochemical correlations. Upon these forces depends the preservation of the structure of the organism and thus its maintenance. Thus we hope to contribute to the building up of a physiology of tissue in contradistinction to the physiology of organs. In addition we have studied the literature of transplantation, in order to obtain data which permit the comparison of the interaction of individualities in lower and higher animals and thus to determine whether there are indications that a gradual change has taken place in the course of evolution. We shall include in our consideration fertilization which can be considered as an intracellular transplantation.

Transplantation is the separation of a piece of tissue from its normal surroundings and its transfer into a new environment, either at a new place in the same host; this we call "autotransplantation"; or into a related individual: "syngenesiotransplantation"; or into a not related individual: "homoiotransplanta-

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tion." Within the same species differences of groups and strains, varieties may arise.

Transplantation into a different species we call "heterotransplantation." Here, nearly related species, which interbreed, further distantly related species, which do not interbreed, species which belong to different genera, families, classes can be distinguished. To this spectrum of relationships corresponds, with certain limitations, a spectrum of interactions of tissues after transplantation.

We judge individuality in man primarily by characteristic social-psychical reactions. It is, therefore, I presume, originally a term connoting psychical attributes. Each individual is supposed to form an indivisible whole. It is one organism separate and distinct from all others. No two organisms can be identical. This finds the sharpest expression in the conception of a soul which is supposed to be the real bearer of the individuality, which is unlike any other soul and indivisible.

To the psychical individuality corresponds individuality of the body. The body also is supposed to represent one indivisible whole, different from every other body; in short one common factor uniting all the parts, and distinguishing them from all the parts of other individuals.

This conception, however, does not quite harmonize with the mosaic such as has been revealed by Mendelian analysis of inheritable characteristics of organisms. Mendelian analysis has shown an organism to consist of a very great number of unit factors, the various unit factors being approximately the same in many organisms of the same species, and the individuals differing from each other in the mosaic of unit factors of which each one is composed. A common factor or set of factors present in all parts of the organism and truly representing its individuality is not provided for in this scheme.

Individuality Differential.

And yet, such a characteristic present in all parts does exist. It is the same everywhere in the same organism and differs in different organisms. We may call this characteristic individuality differential as far as it distinguishes individuals, and species differential as far as in addition it differentiates species, the one differential being superimposed upon the other. That such a common factor truly representing the individuality does exist can be shown through a comparative study of transplantation of one part of an organism into the same and other individuals, related and not related, of the same species, and into individuals of various different species. Such transplantations reveal the presence of an individuality differential, either directly through the interaction of tissues and of tissues and body fluids, or in certain cases indirectly through the immunity which follows such transplantation of tissues or parts of organisms.

A systematic use of transplantation for the analysis of individuality is of rather recent origin. Carried on, however, in a more or less haphazard way the study of transplantation dates back a considerable number of years. My own interest in transplantation as a means of analyzing the biochemical difference in the constitution of individuals was first aroused about nineteen years ago, and again a few years later, when I compared the result of transplantation of tumors in the same individual and in another individual of the same species. The transplanted pieces behaved quite differently in both of these cases.

Auto and Homoiotransplantation.

It is, however, only recently that the difference in the result of auto and homoiotransplantation has been more generally recognized. On the other hand, that heterotransplantation does usually not succeed has been established considerably earlier.

The Mechanism which Determines the Interaction of Tissues.

For a number of years my associates and myself have carried out experiments tending to analyze the factors which connect individuality and transplantation, and here I wish to describe very briefly a few of our experiments and to draw some more general conclusions, the latter merely in a tentative manner. Our experimental analysis is not yet concluded and at the present time there are under way certain investigations which we hope will help to clear up some of the doubtful points. For our purpose it might be best to select a few examples of our experiments in order to illustrate some of the more important factors that come into play under various conditions of transplantation. We shall first discuss transplantation of pigmented skin, in the guinea pig, then as examples of glandular organs, the thyroid gland and kidney, and lastly the uterus as an organ containing a variety of tissues, epithelium, myxoid or predeciduomatous connective tissue and unstriated muscle.

Transplantation of Pigmented Skin in the Guinea Pig.

If we transplant black skin of the guinea pig into a defect in white skin of the same individual, the black skin usually heals in and even begins after a few weeks to penetrate into the neighboring white skin. If instead we transplant it into a defect in the white skin of another guinea pig, the skin may temporarily heal in, but sooner or later it is cast off, in the majority of cases at an early date following the grafting. In a few cases, however, the transplant took. I suspect these were cases in which host and donor were related to each other, so that in reality we had to deal with syngensio- rather than homoiotransplantation. Now in these exceptional cases the black skin did not only not penetrate into the neighboring white skin, but on the contrary, it gradually became paler and its pigmentation disappeared in the end entirely. The black skin became transformed into white skin. Microscopically we found in such cases in addition a gradual accumulation of lymphocytes under and in the strange epidermis. The number of these cells need, however, not be very marked. Lymphocytes are small cells with a relatively prominent round nucleus which originate in lymph glands, gain entrance into the circulation and are capable of active movement, which, however, is probably not as active as in the ordinary polynuclear leucocytes. These lymphocytes, as we stated, are attracted by the foreign skin, but not by the skin of the same organism. We notice after this kind of homoiotransplantation, a primary incompatibility between the strange skin and its environment. As a result of this incompatibility between body fluid of the host and the transplant changes take place in the metabolism of the latter which cause the deficient healing in of the transplant and which later attract the lymphocytes. In addition there occur abnormal reactions in the transplant which render impossible the normal restitution of pigment in the graft. Some of these changes in the transplant may take place so soon after transplantation that the conclusion suggests itself that in this case an incompatibility between the graft and the body fluids of the host interferes directly with those tissue reactions on which depends the healing in of the graft and the reëstablishment of the normal pigmentation. How far these primary changes in metabolism of the graft injure the transplant directly and to what extent they act possibly through induced changes in vascularization of the graft still remains to be determined. It is, however, more probable that the incompatibility between body fluids and graft leads to a direct interference with the transplant.

Transplantation of Thyroid and Kidney

If we transplant thyroid gland into the subcutaneous tissue only the peripheral gland tissue survives, the center of the graft being ill nourished in the first few days following the detachment of the gland from its soil dies. The peripheral gland acini proliferate soon after transplantation. After autotransplantation blood and lymph vessels grow through this ring of well-preserved and temporarily growing thyroid tissue into the necrotic center, and especially in the peripheral part of the latter they form a ring of vessels which is very noticeable; from here vessels penetrate into the center of the necrotic material. They are accompanied by a relatively limited number of fibroblasts which at the inner aspect of the thyroid ring form a loose, almost myxoid connective tissue around the blood and lmyph vessels, a tissue not unlike that found in certain stages of development in the embryo. Further removed from the thyroid ring, in the real center of the necrotic material, there may be produced a nucleus of dense fibrous tissue. But its existence is only temporary after autotransplantation. Sooner or later the blood and lmyph vessels and fibroblasts penetrate into it, absorb it and substitute for it the same kind of loose vascular connective tissue; this again gives way more and more to the peripheral real thyroid tissue. As a result of the absorption of the central connective tissue and of the marked development of the peripheral thyroid tissue and of the good vascular supply the normal organ structure is more and more reëstablished. This occurs within three to five weeks after transplantation. Lymphocytes are at no time prominent in the transplant.

After homoiotransplantation of the thyroid gland the first stages are similar to those observed after autotransplantation; but soon two important differences become noticeable. The well developed ring of lymph and blood vessels in the peripheral part of this center is much less prominent after homoiotransplantation; the connective tissue ingrowth, on the other hand, is much more marked. The whole center becomes soon converted into a dense fibrous mass, much larger in volume than in the autotransplant. It may still be well supplied with vessels, but they are less prominent than after autotransplantation. In contradistinction to what happens in the autotransplant this fibrous mass is not absorbed and not substituted first by myxoid and later by thyroid tissue. This transplant never attains similarity in structure with the normal gland. Even around the individual acini the fibroblasts may become active and form fibrillar and fibrous tissue. The activity of the connective tissue may go still further, and occasionally fibroblasts may penetrate into the interior of some thyroid acini and help to destroy them.

The direct destruction of the graft by the host is a very characteristic feature after homoiotransplantation. It is however, not so much the activity of the fibroblasts as of the lmyphocytes which brings about this result. While in the autotransplant the lymphocytes are practically absent, in the homoiotransplant they begin to appear as early as five and seven days after transplantation. However, they become more prominent only about nine or ten days after transplantation, and from then on they rapidly increase in number in many cases. They approach the transplant mainly by way of the lymph vessels, and in consequence in the homoiotransplant the lymph vessels may become as prominent as if they had been injected. This I found especially noticeable in the rat, on account of the peculiar distribution of the lymph vessels at the inner aspect of the thyroid ring. The lymphocytes appear at this place in especially large masses and from here they penetrate in a peripheral direction into the thyroid acini proper and destroy them. Other lymphocytes approach the thyroid from the periphery and from here push forward in a central direction. All these lymphocytes surround, invade and destroy the thyroid tissue directly after homoiotransplantation and they are, therefore, the chief agent of destruction. They interfere with the nourishment of the acini by surrounding them and cutting them off from the vessels; they exert furthermore a direct pressure upon them and invade and substitute them. In addition the fibrous tissue which is so prominent after homoiotransplantation also tends to shut off the nourishing material from the vessels. Furthermore it compresses the glandular structures and fibroblasts occasionally invade them, as we have stated above. These lymphocytes and fibroblasts form, therefore, an agency of attack which usually succeeds in destroying the homoiotransplant of the thyroid somewhere between the fifteenth and twenty-eighth day following transplantation.

We may again assume that in the strange host the body fluids are not completely adapted to the transplanted gland structures. In consequence their metabolism is to a certain extent altered. This alteration, however, is not of sufficient intensity to cause a direct destruction of the transplanted glandular structures. This alteration in metabolism attracts the lymphocytes, diminishes the vascularization of the transplant and increases the invasion of the graft by fibroblasts, which, however, under these altered conditions do not remain intact, succulent cells, but instead form fibrillar and dense fibrous tissue.

In principle it is similar after transplantation of the kidney; but the greater denseness of this material brings about certain minor modifications in the result. Thus in the kidney after autotransplantation we do not find the inner ring of lymph and blood vessels so noticeable as in thyroid autotransplant. But in all essential respects the conditions are parallel to those after transplantation of thyroid. The formation of fibrous tissue is much more prominent after homoiotransplantation of the kidney than after autotransplantation. The lymphocytes play here a similar part. In the end the homoiotransplant is again destroyed in the same way as in the case of the homoiotransplanted thyroid. But this destruction of the kidney may be completed at a somewhat later date. After autotransplantation kidney tissue usually remains preserved.

We have begun comparative studies of auto and homoiotransplantation in other species. There are indications that in principle conditions are similar in those species which we have begun to study, but there may exist some quantitative and perhaps also some qualitative differences in different species, just as we found certain differences in the behavior of the thyroid and kidney. Thus to mention only one difference, we found that in the rabbit the polynuclear leucocytes are much more prominent after transplantation than in either rat or guinea pig.

Syngenesiotransplantation.

If instead of transplanting the thyroid gland in the guinea pig into not related individuals of the same species, we transplant it into nearly related individuals of the same family, for instance from brother to brother or sister, or from parents to children, we find an intermediate condition between the results of auto and homoiotransplantation, or rather we find all degrees of an intermediate condition. Thus while after autotransplantation lymphocytes are almost absent and after homoiotransplantation they usually begin to become prominent during the latter part of the second week, they may after syngenesiotransplantation, appear as late as the second half of the fourth week; sometimes they may appear somewhat earlier or at other times later. But they usually end by destroying the transplant even in relatives. We find therefore a noticeable delay in the reaction on the part of the host. Evidently at first the metabolism of the syngenesiotransplant is little altered by the body fluids of the host. Gradually, however, the alteration becomes here also sufficiently strong to attract the lymphocytes. As we have stated above the vascular and connective tissue reaction on the part of the host tissue usually takes place between the seventh and twelfth days after transplantation, at a time, therefore, when the alteration of the metabolism has usually not yet become very marked. The blood and lymph vessel supply may therefore in the case of syngenesiotransplantation be as satisfactory as after autotransplantation, although later the lymphocytes begin their destructive work. There is a prolonged latent period in the case of syngenesiotransplantation and the vascular and connective tissue reaction falls into this latent period.

As we have stated above we find in syngenesiotransplantation all degrees of intermediate condition in different individuals of the same family, for instance in different brothers. In some individuals host and graft may be almost as unsuitable to each other as after homoiotransplantation. In such a case the metabolic alteration of the transplant may have reached a considerable strength at the period, when the vascular and connective tissue reaction is determined. In this case the dense fibrous tissue of homoiotransplantation may be produced in syngenesiotransplantation.

Most beneficial seems to be the exchange of tissues between brothers and sisters. Very good, but perhaps sligthly less advantageous is the transplantation from parents to children. Peculiarly enough, we found that after transplantation of the thyroid in the guinea pig from child to mother the result is about as unfavorable as after transplantation into a totally strange individual of the same species. This peculiar phenomenon we intend to analyze still further. A similar intermediate condition we found after multiple simultaneous transplantation of organs into relatives in the rat. In this case we have, of course, to take into consideration the fact that different organs and parts of organs differ in their power of resistance in the period following transplantation, and that the relation between the parenchyma and stroma also differ in different organs. Again we found in the latter series all degrees of intermediate condition and different organs behaved in the same host in an analogous way, if they came from the same donor.

Transplantation of Uterus.

In the transplantation of the uterus, we are especially interested in the behavior of the myxoid or predeciduomatous, cellular connective tissue and in the unstriated muscle tissue which are characteristic of the uterine structure. Soon after transplantation the death of a part of the myxoid connective tissue, which is not unlike connective tissue present in the embryo, and of the unstriated muscle takes place in the auto as well as in homoio graft. This is the result of the injury caused by the process of transplantation and the defective nourishment directly following the grafting. But from about the sixth to the tenth day following transplantation a much better, more complete recovery of the myxoid and unstriated muscle tissue takes place in the auto- than in the homoiotransplant, and while subsequently in the autotransplant these two tissues maintain themselves, in the homoiotransplant a gradual substitution of the injured myxoid and muscle tissue by fibrous tissue takes place sometime between the fourteenth and twenty-fourth day. On this soil of fibrous tissue the epithelium does not thrive so well as on the myxoid connective tissue of the autotransplant; it decreases therefore in size, and becomes lower; later it is again attacked by lymphocytes and thus gradually destroyed. The lymphocytes though appear here somewhat later than in the homoiotransplanted thyroid and kidney; but as in the case of the other organs their attack is mainly directed against the epithelial tissue, although they do not leave entirely free some of the other tissues. Again we find as the result of those abnormal substances which form after homoiotransplantation,—we may call these substances homoiotoxius—an attraction of lymphocytes and an altered behavior of connective tissue cells. But in addition we find in this case a very early injurious influence of the homoiotoxins on two sensitive tissues, namely myxoid or predeciduomatous and unstriated muscle tissue. They show the injurious effect of the conditions prevailing in the strange host at a time, when lymphocytes have not yet had a chance to play any considerable part. How far these two tissues are injured directly by an inadequate constitution of the body fluids of the host (by the "homoiotoxins"), and how far the latter influence primarily the vascular supply, the latter in turn influencing the life of the myxoid and unstriated muscle tissue, is uncertain at present. It is however more probable that their destruction is primarily due to the inadequacy of the body fluids rather than to an insufficient vascular supply, which latter would then be the direct consequence of the lack of adaptation between body fluids and transplanted tissue. There is another point of interest in the transplantation of the uterus. We find that the primary transformation of myoxid into fibrous connective tissue leads secondarily to changes in the epithelium which rests on the connective tissue. We find thus a chain reaction and in addition to the direct results indirect results of the homoiotoxin action.

Mechanism of the Reactions.

These experiments prove that the introduction of parts of organs or tissues which originated in a strange individual causes disturbances which lead to changes similar to those found as the result of the action of toxic substances. These substances act not unlike those given off by certain microörganisms, as for instance the tubercle bacillus, which cause changes of a not acute character. Lymphocytes are attracted and besides the relations between various tissues are quite markedly altered. We have every reason to assume that these disturbances are due to products of metabolism given off by the introduced tissue, which act as homoiotoxins. We have learned that the action of these substances is graded in accordance with the relationship between donor and host. It is as yet doubtful, how far these disturbing substances are those given off in the normal metabolism of the transplanted cells—substances which are toxic merely because they act on a strange host—and how far they are the product of an abnormal metabolism of the introduced cells, the pathological change being due to the action of the body fluids of the new host upon the strange cells. It is probable that the second alternative holds good at least in many cases. Landsteiner, von Dungern and others have shown that in man certain groups of individuals can be distinguished according to the interaction of blood cells on the one hand, and agglutinins preformed in the blood on the other hand.

While such agglutinins have not been observed in animals, in certain cases it has been found possible through immunization with blood corpuscles belonging to the same species, but to different individuals to produce hemolysins which dissolve corpuscles of the same species and combine especially with the corpuscles of the individual whose blood had been used for injection. These observations, as well as our own experiments to which we referred already, as well as others to be mentioned later render it at least probable that such an interaction takes place between a constituent of the body fluids of the host and the strange cells and that this interaction leads to the formation of toxic substances. While these toxic substances probably interfere in an injurious manner with certain sensitive tissues and lead to their destruction in an indirect manner, in the case especially of certain epithelial structures they merely alter the metabolism in such a way as would be perfectly compatible with the life of the tissues. But this alteration in metabolism sets into motion secondary processes, in consequence of which lymphocytes, vessels and fibroblasts show an altered relation to the transplanted epithelium and these tissue reactions lead secondarily to the death of the transplant.

Syngenesio and Homoio Toxins as Products of Metabolism.

We have assumed that the substances which are characteristic of the individual and which call forth the reactions which we have described, pass into the surrounding medium as the result of the metabolism of the tissue. In all probability they are not merely decomposition products of proteins. In order to exclude this latter interpretation we studied the behavior of the host tissue towards homoiotransplanted bloodclots in which the blood cells live for a certain period without, however, carrying on an active metabolism. We found that such blood cells do not call forth any of the reactions characteristic of homoiografts; neither lymphocytes nor connective tissue nor vessels behave towards them in any specific way whatever. These homoiodifferentials are as far as we know, common to all the active tissues of an organism. They are the same in the different organs of the same animal. As we stated above, we could show this fact in the rat by multiple simultaneous transplantation of different organs of an individual into the same host. Under this condition all the organs elicit proportionately the same individuality reaction, because the relation between the individuality differentials of host and donor is everywhere the same. Particularly the lymphocytic reaction allows us to estimate this relationship of the individuality differentials in an approximately quantitative way, as our syngenesiotransplantations have shown.

Multiple and Successive Transplantations.

We can demonstrate this fact also by multiple simultaneous transplantations of the same kind of organ, for instance, the thyroid from different individuals into the same host. The lobes of thyroid taken from the same animal behave then in an approximately similar manner, while the lobes taken from different animals may behave very differently, each calling forth a lymphocytic reaction in a quantitative way in accordance with the relationship between host and donor. One piece can call forth a marked reaction, while at the same time and in the same host another piece proves rather indifferent. This indicates that the reaction is of an entirely local character, called forth by the substances diffusing from the transplanted cells into the neighboring tissue. It is not primarily a general reaction of the character of an immune-reaction, which would depend mainly on the presence of substances originating in response to the inoculation of the tissue and carried through the circulation equally to all parts of the body. The local character of the reaction we could prove still in another way, namely by carrying out successive transplantations of the same kind of organ into the same host. Under these conditions the latent period of the lymphocytic and connective tissue reaction was approximately the same after the first and second transplantation. An immune substance which could have accelerated the second reaction had, therefore, not been formed. In certain cases, however, such an immune substance may actually develop and hasten the appearance of a reaction around the transplant. This takes place after inoculation with certain tumors. Thus it comes about that the function of the lymphocytes has been misinterpreted in the case of tumor inoculations. It is believed that they are solely concerned in the production of an immunity against tumor growth. Our observations on the action of lymphocytes in the case of transplantation of ordinary tissues, which date back a considerable number of years, clearly prove that the rôle of lymphocytes is a much more general one, namely, a direct and local, quantitatively graded response to the homoio and syngenesiotoxins. The immunity reaction in certain cases of tumor transplantation is merely a special case in a set of phenomena of much wider biological significance.

Constancy of the Individuality Differential.

This individuality differential is a relatively constant factor that varies not at all or at least to a very limited extent in the same individual after the animal has reached the age, when it is able to obtain its nourishment independently of its mother. Such conditions as pregnancy, temporary undernourishment, certain infections do not suspend the function of the individuality differential. In addition we could show in a separate series of experiments that particularly those changes which call worth compensatory hypertrophy in the thyroid gland do not noticeably interfere with the reaction against the homoiodifferential. The lymphocytes may invade in enormous numbers the gland even after it has become hypertrophic and again in the end they succeed in destroying it.

The Effect of Homoiotoxins on Other Growth Processes.

While thus compensatory hypertrophy does not noticeably modify the action of the homoiotoxins, the homoiotoxins may on the other hand, as our recent experiments have shown, to some extent interfere with the development of compensatory hypertrophy of the thyroid gland, not only by bringing about the destruction of the gland, but apparently also by diminishing the frequency of the hypertrophic changes. In a similar manner our previous experiments had shown that homoiotoxins may to some extent interfere with the production of the maternal placenta and the placentomata such as they can be produced experimentally in the normal as well as in the homoiotransplanted uterus. After homoio-transplantation the experimental formation of placenta is diminished. The homoiotoxins interfere, therefore, to some extent not only with purely regulative processes such as occur after transplantation of organs, but also with those changes which lead to compensatory hypertrophy and to placenta formation. They evidently have an injurious influence on a variety of growth processes, and diminish the intensity of those tissue reactions which initiate placenta formation.

Heterotransplantation.

If we compare with these results of auto, syngenesio and homoiotransplantation, heterotransplantation (transplantation into a strange species) we find some interesting differences. After heterotransplantation tissues generally live only a short time, which varies between a few days or even less and two weeks or slightly more. In a few exceptional cases tissue may even live as long as three or four weeks. For a short period there may be found a slight proliferation of the heterotransplant. But usually the injurious action of the host and particularly of its body-fluids is very marked after heterotransplantation. The quantity of living, well preserved tissue is therefore very much reduced. These differences between the hetero and homoiotransplant are usually quite marked as early as the latter part of the first and the beginning of the second week. There may be added to the direct injurious effect of the host and its body fluids a destructive action of lymphocytes and an invasive action of fibroblasts. But both of these are usually relatively slight; and especially the lymphocytic reaction is markedly less prominent after hetero- than after homoiotransplantation. Fibroblasts and bloodvessels of the host show little activity around the heterotransplanted parenchyma. The vascularization is therefore poor and the number of fibroblasts growing directly around the heterotissue is usually restricted. The connective tissue that does grow has the tendency to form fibrous tissue. At some distance from the transplanted parenchmya the fibroblasts and bloodvessels behave otherwise as if they had to deal with an inert foreign body. While thus the lymphocyte and connective tissue contribute only slightly to the destruction of the heterotransplant—the fibrous tissue exerting an injurious pressure on the heterotransplant—large masses of lymphocytes may collect in the tissue surrounding the heterograft. These lymphocytes, however, are relatively innocuous.

If we ask, how it comes about that after heterotransplantation, notwithstanding the greater strangeness of host and donor, the destructive action of the lymphocytes is not only not more marked than after homoiotransplantation, but on the contrary much more restricted, we may suggest that after heterotransplantation the grafted tissue is injured to so marked an extent, that a depression in metabolism occurs and the quantity of toxic substances attracting the lymphocytes and produced in the metabolism of the tissue is much diminished. All this applies to the transplantation into not nearly related species. If we transplant into nearly related species, results are much better as has been established by W. Schultz. It seems that in this case the tissues behave almost like homoiotransplants. However it appears probable to me that a comparative study—which so far has not yet been made,—would show that even in this case the results are distinctly less good than after homoiotransplantation. If we disregard the hetero-transplantations into nearly related species, there is after hetero-transplantations not a close connection between the results of transplantations and the relationship of the species used. The heterotransplanted tissues are all so near the minimal threshold which just permits life for a short time, that various secondary factor often become of more importance in determining the duration of life and extent of proliferation of the graft than the character of the species differentials. There exists, however, as we have shown an indication that even here such a relationship enters as one of the determining factors.

Spectrum of Relationships and Interaction of Tissues.

If we now compare the effect of the various kinds of transplantations on the character of the interactions between the tissues of host and graft, we come to the following conclusions:

1. The autotransplants have the greatest degree of efficiency in preserving the integrity of the graft and in maintaining inviolate the boundaries of the organs and in preventing the ingrowth of the connective tissue of the host. The autotransplant behaves in this respect most like the normal organ. From there a decrease in efficiency takes place if we pass to the syngenesio- and to the homoiotransplants. In the heterotransplant this power of preserving the integrity of the graft and of warding off the attack by strange connective tissue has become very slight. There is, however, still noticeable a slight action of the transplanted parenchyma even in this case; but on the whole the tissue behaves not

unlike an inert foreign body. Correspondingly the amount of fibrous tissue formed increases and the extent of vascularization decreases in the direction from autotransplant to heterotransplant. The ability of the transplanted parenchyma to maintain a dominance over the stroma, to keep the fibroblasts intact, and if possible in a myxoid condition and to cause the absorption of the connective tissue stroma decreases in the direction from auto to heterotransplant. Similar is the curve which represents the stimulating power of the parenchyma on the vesselgrowth. It needs further investigation to determine how far the vascular reaction is a primary phenomenon and how far the connective tissue reaction depends upon it. The lymphocytic reaction on the other hand reaches a maximum in the homoiotransplant and decreases again in the heterotransplant.

Theoretical Considerations. Contact Substances, Autosubstances and Toxins.

Our results are best understandable, if we assume that the cells in their metabolism give off a series of substances which regulate the relation with certain other kinds of cells, and in particular the relation of parenchyma (epithelial, glandular, special kinds of connective tissue cells and unstriated muscle) to the surrounding connective tissue, blood and lymph vessels and lymphocytes.

We must conclude that the cells living under what we might call "autocondition," give off another substance or another set of substances from those living under "syngenesio," "homoio," "hetero" conditions. We have found a graded injuriousness of the latter kind of substances for the cells of the surrounding tissues. They stimulate the surrounding tissues to reactions which are pathological and which in the end lead to the destruction of the cells which produce these substances and call forth these reactions. We have therefore called these substances "syngenesio," "homoio," "hetero" toxins. Conversely we may designate those substances which are given off by the normally functioning cells under "auto" surroundings as "auto" substances. They regulate the action of connective tissue cells, vessels and lymphocytes in the most adequate way, and in a manner peculiar to each organ, in a way which keeps away lymphocytes, which limits the activity of fibroblasts which under those conditions cannot invade the tissue of another kind and merely enter in such relations with these tissues as are demanded by the normal structure and function of the organ. The auto substances thus bring about the restitution of the normal structure in an at first disorganized organ, just as these substances maintain the normal structure and function in the normal organ. The syngenesio, homoio and hetero conditions on the other hand lead to those pathological conditions which we have described. There are other facts which equally point to the conclusion that substances which in general we may designate as "contact substances" are given off and regulate the relations of various kinds of tissue to each other.

We may mention a few examples of conditions under which contact substances come into play.

(*a*) In our study of the cyclic changes in the mammary gland we found a relation between the state of the glandular parenchyma and the surrounding connective tissue stroma. We found that an active gland has an active stroma, while a resting, retrogressing gland has a resting, more or less fibrous stroma.

(*b*) Similarly we find around the various gland ducts which are metabolically inactive usually a resting fibrous stroma, in contradistinction to the cellular stroma around the active gland tissue.

(*c*) Wherever cells of the parenchyma are multiplying we generally find the stroma cells and the vessels to become likewise active and conversely where connective tissue cells and the vessels are active the cells of the parenchyma, for instance, epithelium, receive a stimulus to grow.

(*d*) There are indications that contact substances play also a certain rôle during embryonic life and that here they help to determine the formation of some organs. Thus a lens producing contact substance is given off by the optic disc. It stimulates growth and a special differentiation in the overlying ectoderm.

Thus we know at the present time a large class of contact substances and it is probable that future studies will still add to the number of these substances.[1]

[1] Several years ago Dr. Walsh and the writer found that a substance given off by the ovum determines the development of the follicle in the ovary.

Contact Substances and Hormones; Their Relation to the Individuality Differential.

These contact substances are contrasted with the hormones, for instance those given off by the corpus luteum which regulates the activity of the mucosa of the uterus and probably of certain other organs. They are given off by certain organs, and carried through the circulation to distant organs. They have a specific distant action. In contradistinction to some of the contact substances these distance substances do not possess an individuality or even a species differential.

Contact Substances and Changes in Old Age.

I cannot conclude a consideration of this aspect of the subject without pointing out the similarity of conditions which we find under "homoio conditions" with those found in old age. In both cases we observe a tendency to the formation of a fibrous stroma and to a decrease in good vascularization. This condition also corresponds to that found in states of metabolic inactivity. May we not therefore refer old age changes not only to the lack of certain hormones given off by glands (as for instance thyroid and corpus luteum) with internal secretions, but also to a quantitative or sometimes perhaps even to a qualitative change in the character of contact substances, to a diminution in the production of what we have called the "auto substances"? Such a diminution in auto substances would be the necessary result of a diminished activity of the parenchyma. Thus a vicious circle would be established. The diminished activity of the parenchyma causes changes in stroma and vascularization and the latter further depresses the activity of the parenchyma.

Inheritance of the Individuality Differential.

We have seen that there is in each individual and in each cell, at least in the large majority of all cells of an indivdual, an individuality differential which is present in addition to the ordinary Mendelian unit factors. The inheritance of the latter has given rise to numerous investigations which on the whole have tended to show the general applicability of Mendelian rules in the interpretation of phenomena of inheritance. The concept of the individuality differential is too new to have received much attention from students of heredity. But von Dungern studied the group agglutinins to which we have referred above and mentions that they are inherited according to the rules of the inheritance of simple Mendelian monohybrid factors. G. Schoene likewise inquired how the characteristic of tolerance for skin grafts was transmitted from parents to offspring and this author also came to the conclusion that it was inherited according to the rules of simple Mendelian heredity. Neither of these investigators, however, gives convincing data in this respect nor does Schoene refer to the finer tissue reactions in his interpretations. Our own experiments lead us to a different conclusion. In the union of a female and male germcell of two individuals belonging to the same species, two different individuality differentials are hybridized. How are the individuality differentials of the children? Do they follow that of the father or that of the mother or do the differentials of some children follow that of the father, while those of others follow that of the mother? We find that the individuality differentials of the offspring are not identical—at least in the large majority of cases—with the individuality differential of either of the parents, but that they have an intermediate character; there exists, however, as we have shown, all transitions between one and the other of the two individuality differentials, if we compare the behavior of different children. We have therefore a mode of intermediate or blending inheritance. If we interpret this fact in Mendelian conceptions we must conclude that the individuality differential is represented by multiple factors.

Individuality and Species Differential of Substances. Specifically Adapted Substances.

The cells and tissues of an organism contain, as we have seen, the individuality and species differential; they characterize each individual and distinguish it from all other individuals. They make a real indvidual out of a conglomeration of cells and tissues. In order that these cells and tissues develop into an individual organism and subsequently function as such, substances are given off by the tissues and organs which act upon adjoining or distant parts of the body and thus bring about a correlation of functions which makes possible the orderly development and maintenance of the organism. Some of these substances still preserve the individuality and species differential. We may, therefore, conclude that not only cells, but also substances given off by cells may still have the individuality or species differential. This applies to some of the contact substances which we have postulated. They may have the individuality differential. In most substances, however, the presence of an individuality differential cannot be demonstrated, but merely the existence of a species differential. Of especial interest among these are certain substances which make use of this species differential in their function and which are therefore most effective if they interact with other substances having the same species differential or rather a supplementary species differential adapted to the first differential. Such substances I have called "specifically adapted substances." To this group of specifically adapted substances belong, as I found in my earlier work, substances which are present in the tissues and erythrocytes and which interact with a constituent of the circulating bodyfluid in order to accelerate the clotting of the blood and lymph. These substances I have called tissue coagulins. They seem to be identical with the thrombokinases. The species differential fulfills in this case a definite and important function. Subsequently Hedin discovered in the gastric juice a substance inhibiting the milk coagulating enzyme. Both these substances interact with the species differential. More recently Dr. Frank Lillie found a specificially adapted relation between a constituent of the egg, an agglutinin, and the spermatozoa of the same species. In this case, however, the common species differential functions in substances belonging to two different individuals, while in the former cases the interaction occurs in substances of the same individual. On the other hand a large number of important substances which have the function to correlate and unify the action of various organs, particularly certain growth substances and the common hormones are not only not individual specific but not even species specific. This applies for instance to the growth substances emanating from the corpus luteum in which I found the absence of the individuality differential. The lack of the species differential applies to growth substances extracted from the placenta, to the growth substances which determine the formation of the lens, to substances inducing metamorphosis in amphibia and compensatory hypertrophy in mammals; it applies to the common hormones of the adrenal gland and thyroid.

In this case we have to deal with relatively simple substances, some of which are apparently of a lipoid nature, while others are of a still simpler composition. On the other hand we have every reason to assume that the individuality and species differentials are proteid substances or at least that they occur only in combination with proteid substances.

In the case of the tissue coagulins we have found that the species differential of the tissues interacts with an adapted substance in the body fluids. In a similar way we find in general an adaptation between body fluids and cells which is based on the presence of the individuality and species differentials. It can be demonstrated directly in the case of the natural hemolysins, but probably applies as we have pointed out above, to the relations of all tissues to body fluids. It exists, as we found recently, even in the case of invertebrates where we established the interaction of species differentials in the case of the experimental amœbocytic tissue and the blood serum. We shall refer to it again later. It also applies to the relation between the antigens and immune substances.

Supplementary Differentials in Body Fluids.

In all those cases the individuality or species differential of the tissues interacts with an analogous substance in the body fluids. It is, however, not certain that the substance or group in the body fluids is identical with that in the tissues, although they fit into each other specifically. A difference between the two could be demonstrated in the case of tumor immunity. While species immunity can be produced with body fluids as well as with tissues of a certain species, individuality immunity can only be produced with the tissue differential, but not with the corresponding differential in the body fluids. We may designate the substance present in the body fluid and interacting with the individuality and species differential of the tissues as the supplementary individuality and species differential.

Phylogenetic and Ontogenetic Evolution of the Individuality and Species Differential.

The analysis of the individuality differential which we have given so far applies altogether to the higher animals, mammals and birds. Almost all the experiments to which we referred in this paper were made in these two classes. Does this fine differentiation of individuality, the delicate discernment of individual relationship such as we have found in the cells and tissues of higher animals, also exist in the lower animals? Is it a characteristic of all animal cells or has it gradually evolved together with other differentiations in the course of evolution? Have the differentials, or rather the reactions they call forth, had an evolution like structure and certain functions? So far as I am acquainted with the literature this question has never been put and no planful investigations have been carried out tending to answer it. In a general way, however, it is known that in lower forms and in earlier embryonic stages transplantability is greater, in correspondence with the greater regenerative power of these organisms, or in dependence on the greater power of isolated parts of these beings to sustain themselves separated from the remnant of the animal, as particularly W. Schultz has pointed out. But the evolution of species and individuality differentials has not been considered in a conscious way as far as I am aware.

I have recently studied the literature of transplantation with the view of determining whether the experiments which were carried out by various investigators for the solution of problems of a different character might throw some light on this question. While in some respects I found the evidence here and there somewhat contradictory, still I believe that certain conclusions may be arrived at on this basis with a fair degree of certainty.

To begin with invertebrate embryos, the experiments of Driesch, Morgan, Goldfarb and others show that parts of embryos of the same species can be readily grafted upon each other. The homoiodifferential does apparently not play any rôle. These embryos on the other hand react against union with the part of an embryo belonging to a different species, against an heterodifferential; the reaction, however, seems to be less marked than in mammals. Similar are the results obtained with transplantation of gonads in larvæ of lepidopteræ (Meisenheimer, Kopec). In nearly related species the results of grafting are better than in distant species.

It is similar in adult invertebrates. Here also no difference seems to exist between auto- and homoiotransplantation and while a reaction takes place against heterotransplants, it is again considerably less pronounced than in the higher animals. Of value are here especialy the experiments of Joest, Harms, Leypoldt and Rabes in Lumbricidæ and of Wetzel in *Hydra*. While heterodifferentials and also reactions against heterodifferentials exist here, the reactions are much less intense, if we make allowance for the lower temperature at which these reactions take place and which would naturally retard the reaction considerably. In Lumbricidæ the heterotransplant may remain alive in toto, while even in amphibia part of the heterotransplant becomes necrotic. In adult invertebrates also heterotransplantation succeeds only in certain, not too distant, species. We studied recently the species differential in such simple forms as the blood cells of arthropods. We found that the blood cells of limulus are specifically adapted to their own blood serum. Their activities are optimal in *Limulus* serum. *Limulus* serum surpasses any other serum so far tested.

In order to determine this relationship we made use of experimental amœbocyte tissue and we compared the rapidity and quantity of outgrowth from this tissue in different sera. The pictures we obtain under those conditions are very similar to those presented by outgrowing embryonic connective tissue. We find then even in the blood cells of invertebrates a specific adaptation between the species differential of the blood cells and the supplementary species differential of the body fluids.

If we pass to the lower vertebrates, we note in amphibian larvæ a condition somewhat analogous to that in invertebrates. Especially the grafting of amphibian embryos, a method originated by Born and subsequently used by Braus, Harrison and others, is interesting in this connection; furthermore the transplantation of skin (Lewis, Weigl), of the eye (Uhlenbath) and the experiments of Spemann add valuable data. There is apparently no difference between the results of auto- and homoiotransplantations. On the other hand a heteroreaction again exists, but is less marked than in the case of higher veretebrates. Transplantation into nearer related species succeeds better than into further distant species.

In adult amphibia we find the first indication of the existence of a homoiodifferential. However, in adult fishes and amphibia the reaction against homoiotransplantation seems to be less marked than in adult mammals and birds, although we must confess the evidence concerning the fate of homoiotransplanted tissues in these classes appears somewhat contradictory. We have furthermore to consider the difference in temperature at which reactions occur in lower and higher vertebrates. This factor might render the homoio reaction much slower in amphibia. Despite these difficulties we may provisionally conclude that the reaction against homoio and heterodifferentials is somewhat less pronounced in lower than in higher vertebrates.

The interesting observations of Murphy and Rous who made successful heterografts of tumors in the allantois of chick embryos suggest that the individuality reaction is absent even in the embryo of higher vertebrates which serve as hosts. This agrees with an observation of Braus which seems to indicate that in amphibian larvæ used as hosts the heteroreaction appears at a certain stage, namely, when the circulation has been established in the transplant. Likewise if we transplant embryonic mammalian tisue into adult hosts the homoioreaction seems to be somewhat elss pronounced in the case of certain tissues; the reaction, however, does exist. Embryonic mammalian tissues call forth a very rapid heteroreaction in adult hosts (Saltykow).

To summarize, we find absence of homoioreaction in invertebrates and larvæ of lower vertebrates. The heteroreaction exists here, but is less pronounced. In lower adult vertebrates the homoioreaction as well as the heteroreaction exists, but again both are probably less pronounced than in mammals.

There has, therefore, as far as we can judge from the experiments so far recorded, taken place an ontogenetic as well as a phylogenetic evolution in the formation of the individuality differential. Ontogenetic and phylogenetic evolution has apparently led to an individualization of the organisms. There is added gradually to the reaction against the species differential the reaction against the individuality differential.

If we inquire into the mechanism on which this gradual refinement depends, several factors would have to be considered:

1. The individuality differential might as yet be absent in the lower forms, especially in invertebrates, and appear only in vertebrates.

2. The individuality differential might be present in all animal organisms, but the supplementary substance in the body fluids might develop only in certain ontogenetic and phylogenetic stages and consequently the reaction on the part of the host might be very weak.

3. The individuality differential might be present and the host might react towards it, but somehow the tissues of lower organisms show a very low degree of sensitiveness to these reactions. In other words, is this individualization due to the gradual acquisition of the individuality differential or to the development of a reaction on the part of the host against the individuality differential or to a greater sensitiveness on the part of the higher tissues to this reaction? Authors have so far not differentiated between these three possibilities, and the data on hand do therefore not permit us to decide the question definitely.

There exist, however, some facts which have a bearing on this question. In the first place we find a very interesting exception to the statement that individuality reactions are absent in lower forms: in a certain rhizpod. *Orbitolithes,* Max Schultze observed as early as 1863 a peculiar reaction which was further analyzed by P. Jensen. Two pseudopodia belonging to the same individual unite, the protoplasms flowing together at the point of contact; but if two pseudopodia belonging to two different individuals touch each other a contraction occurs and a reunion fails to take place. An individuality differential seems to be present in these protozoa and to lead to a marked direct interaction of protoplasms. There exist, perhaps, a few similar reactions in certain other unicellular organisms. In other similar protozoa, however, the reaction has not been observed by more recent investigators.

If it were possible to generalize from this observation, we should conclude that the individuality differential is present in all animal tissues; and that the lack of reaction must be due to one of the two other causes. On the other hand there are some indications that the chemical constitutions of the cell proteins of the embryo differ from those of the fully developed forms. To mention only one fact of this kind: while according to Roessle embryonic tissue contains the same antigen for hemolysins as the adult tissue, it lacks according to Braus the substance which after injection into animals of a different species or class calls forth the production of precipitins; neither does embryonic tissue bind precipitin which had previously been produced through hetero injection of adult material. Probably the precipitin reaction is in this case a less reliable indicator of the presence of the differential than the hemolysin reaction, which seems to be positive. It is possible that the absence or presence of the supplementary substance in the body fluids may at least in part, be responsible for the hetero reaction; this is suggested by the observation of Braus according to whom extremities of amphibian embryos grafted on hosts which are as yet in an embryonic stage show the effect of the unsuitable soil, as soon as the body fluids of the host begin to circulate in the grafts.

If we take all these facts into consideration, it seems on the whole more probable that the individuality differentials exist in all animal organisms, but that the individuality reactions are lacking in lower forms.

Individuality and Species Differential and Fertilization.

There exists an interesting correlation between the lack of the individuality differential in lower ontogenetic and phylogenetic forms on the one hand and between the lack of an individuality reaction on the part of egg and sperm chromosomes throughout all classes on animals. Homoiofertilization is the normal occurrence and it can be considered as an intracellular transplantation. Homoiotransplantation succeeds in this case as well as autoreaction. Indeed it is a transplantation which usually occurs under homoio conditions. Furthermore, just as in the case of the more primitive tissues a reaction of incompatibility occurs after heterotransplantation, in a corresponding way a reaction of incompatibility occurs, when chromosomes of germ cells with different species differentials meet, as the experiments of Baltzer, Tennent, Moenkhaus, Guyer, Newman and others have shown. With this conclusion is even in agreement the cross-fertilization between widely different classes which have been made possible through the discovery by Jacques Loeb of a method permitting such hybridizations. In this case the incompatible chromosomes are eliminated.

There is an additional similarity between heterotransplantation and heterofertilization. While in both cases the incompatibility increases on the whole in correspondence with the distance of the species, there is no absolute agreement between the effect of heterofertilization and heterotransplantation on the one hand and the relationship of the species on the other hand and in both cases reciprocal relations may lead to very divergent results.

There exists on the other hand, as far as we can judge from a study of recorded hybridizations, one noticeable difference between the reactions of chromosomes and tissues. In the latter there is an indication that the incompatibility between species differentials increases in the course of ontogenetic and phylogenetic development. A study of hybridization on the other hand does not suggest a greater mutual tolerance of chromosomes of different species in invertebrates as compared to those of vertebrates.

Lack of the Homoio Sensitiveness in Certain Mammalian Tumors.

We have so far assumed that all mammalian tissues possess the individuality differential and call forth reactions against the homoiodifferentials. In general this statement is correct. There exists, however, at least one notable exception to this rule. There are certain tumors which are able to grow with the same readiness in another individual of the same species as in the organism in which they originated. This applies by no means to all tumors, on the contrary the large majority of tumors behave in this respect about like ordinary normal tissues which succumb to the homoioreaction, and are only able to grow in the individual a part of which they formed originally. Why there is a relatively limited number of tumors which behave differently, why they are able to withstand the injurious influences of homoiotoxins which destroy the large majority of tumors, we do not know definitely. It is, however, very probable that these tumors also possess the individuality differential, and that their ability to withstand the homoiotoxins is due to their diminished sensitiveness combined with an increased growth energy. Very often the "homoioreaction" which is ordinarily lacking in these tumors can be called forth through previous immunization of the host.

It is exactly such tumors which lack the individuality reaction which have been used by Tyzzer, myself and Fleisher and again by Tyzzer and Little in order to study the inheritance of tolerance for grafted tumors. Tyzzer crossed for this purpose white and Japanese waltzing mice; Fleisher and myself used diverse strains of white mice. The strain differential is further distant in the spectrum of relationships than individuality differential; and Tyzzer and Tyzzer and Little dealt even with something akin to species differentials. Tyzzer believed that such investigations may throw light on the character and origin of tumors. While this view is probably not tenable, these investigations throw some light on the hereditary transmission of strain and species differentials. I found here again an intermediate mode of inheritance, while Tyzzer and Tyzzer and Little found a more complex mode of inheritance. Again I suggested in interpreting my own as well as Tyzzer's results the presence of multiple factors, an interpretation which was subsequently adopted by Tyzzer and Little.[1]

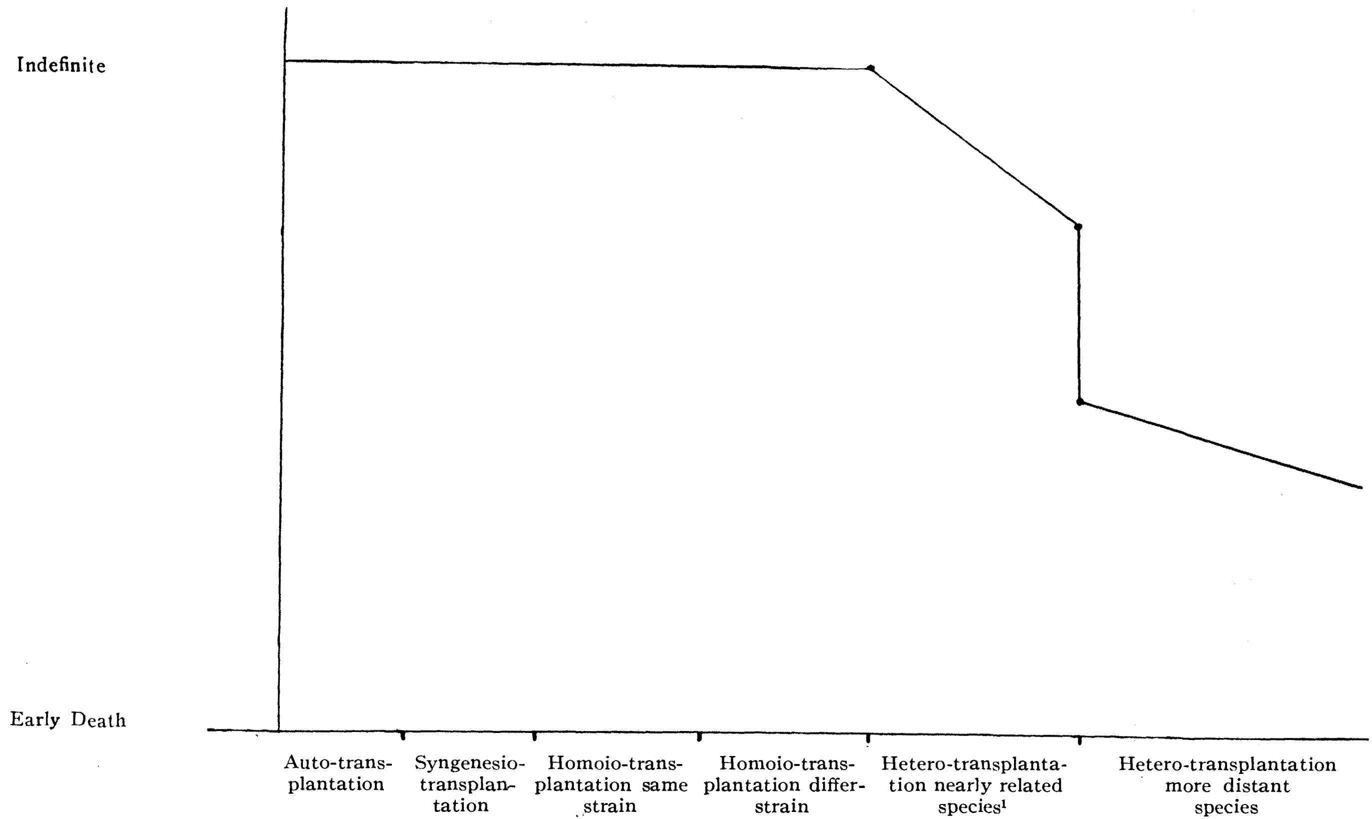
[1] In a paper which just appeared—after completion of this manuscript (C. C. Little, *Journal of Experimental Zoölogy*, 1920, XXXI., 307)—Dr. Little expresses the opinion that the intermediate type of heredity is not the typical mode of inheritance of the individuality differential. I believe that the views which Dr. Little expresses are based on a lack of distinction between species or strain differential on the one hand and individuality differential on the

Individuality Differential and Potential Immortality of Somatic Cells.

The fact that certain tumors can withstand the action of the homoiotoxins has a still wider bearing. We must remember that common transplantable tumors are the direct descendants of ordinary tissue cells, such as we normally find in the individuals of the particular species which we use. The tumors may be derived from a variety of normal tissues and in general the transformation from normal cells into tumor cells takes place under the influence of a long continued action of various factors enhancing growth. Tumor cells are therefore merely somatic cells which have gained an increased growth energy and at the same time somehow gained, in some cases, the power to escape the destructive consequences of homoiotoxins. This ability of certain tumors to grow in other individuals of the same species has enabled us to prove through apparently endless propagation of these tumor cells in other individuals that ordinary somatic cells possess the potential immortality in the same sense in which protozoa and germ cells possess immortality. Thus tumor transplantation made possible the establishment of a fact of great biological interest which because of the homoiosensitiveness of normal tissues, could not be shown in the latter.

We wish, however, especially to emphasize the fact that our experiments did not merely prove the immortality of tumor cells, but of the ordinary tissue cells as well, the large majority or all of which can be transformed into tumor cells. At an early stage of our investigations we drew, therefore, on the basis of these experiments, the conclusion that ordinary tissue cells are potentially immortal; notwithstanding the fact that especially under Weismann's influence the opposite view had been generally ac-

other. I have referred to this distinction in this paper; I have also emphasized how unsuitable transplantable tumors are for the analysis of individuality differentials. In my previous papers I have discussed the influence of such adventitious factors as sex, age and pregnancy on the individuality differentials, and showed that within the limits of our experiments such factors do not noticeably influence the individuality reaction; this applies to guinea pigs above the age of four weeks, as far as the age factor is concerned. We also referred to the apparently abnormal behavior of tissues of the child transplanted to the mother. The factors that are responsible for this peculiarity need, as I stated above, further investigation.



CURVE I. Transplantation in invertebrates and embryos.

[1] This part of the curve is only approximate.

cepted, and as it seems to us, with full justification, inasmuch as no facts were known at that time which suggested the immortality of somatic cells. It was the apparently endless transplantation of tumor cells which proved the contrary view.

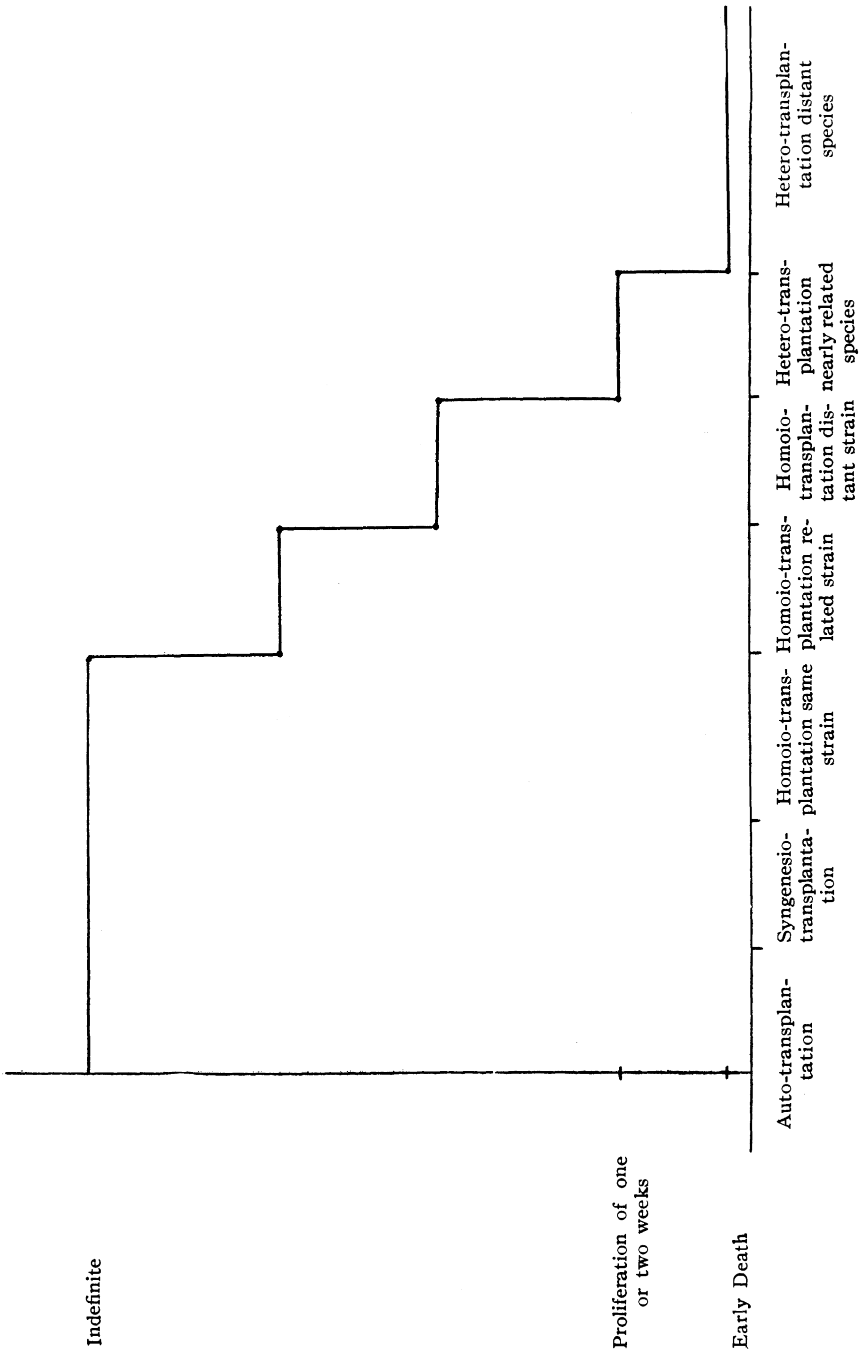
To recapitulate what we stated above: tumors are merely transformed tissue cells. All or the large majority of adult tissues are potential tumor cells. Tumor cells have been shown experimentally to be potentially immortal, therefore tissue cells are potentially immortal.

This wider conclusion I expressed nineteen years ago. Quite recently the immortality of certain connective tissue cells has been demonstrated by Carrel through in vitro culture of these cells. Under those conditions the tissue cells escape the mechanisms of attack to which the homoiotoxins expose the ordinary tissue cells in other individuals of the same species. Under these conditions the reactions of the host tissue against homoiotoxins which would have taken place in vivo, are eliminated. We must, however, keep in mind that this method of proving the immortality of somatic cells applies only to one particular, very favorable kind of cells and it is very doubtful, if by cultivation in vitro the same proof could be equally well supplied in the case of other tissues. On the basis of tumor transplantations on the contrary we were able to show that a considerable variety, perhaps the large majority of all tissue cells possess potential immortality.

Growth Curves and Spectrum of Relationships.

We may approximately represent the effect of syngenesio, homoio, and heterotoxins on various kinds of tissues in the form of curves, where the base lines indicate the spectrum of relationships and the ordinates growth energy of the tissues in the various hosts. We find then that embryonic and adult invertebrate tissues and the embryonic tissues of lower vertebrates from one class (Curve I). This, however, does not necessarily imply that all these tisues behave in an identical manner, but that there exist some essential similarities. Our data are as yet by no means complete in this respect.

Very similar to this curve of the primitive tissues is that representing the growth of the transplantable tumors (Curve II).



CURVE II. Transplantable tumors.

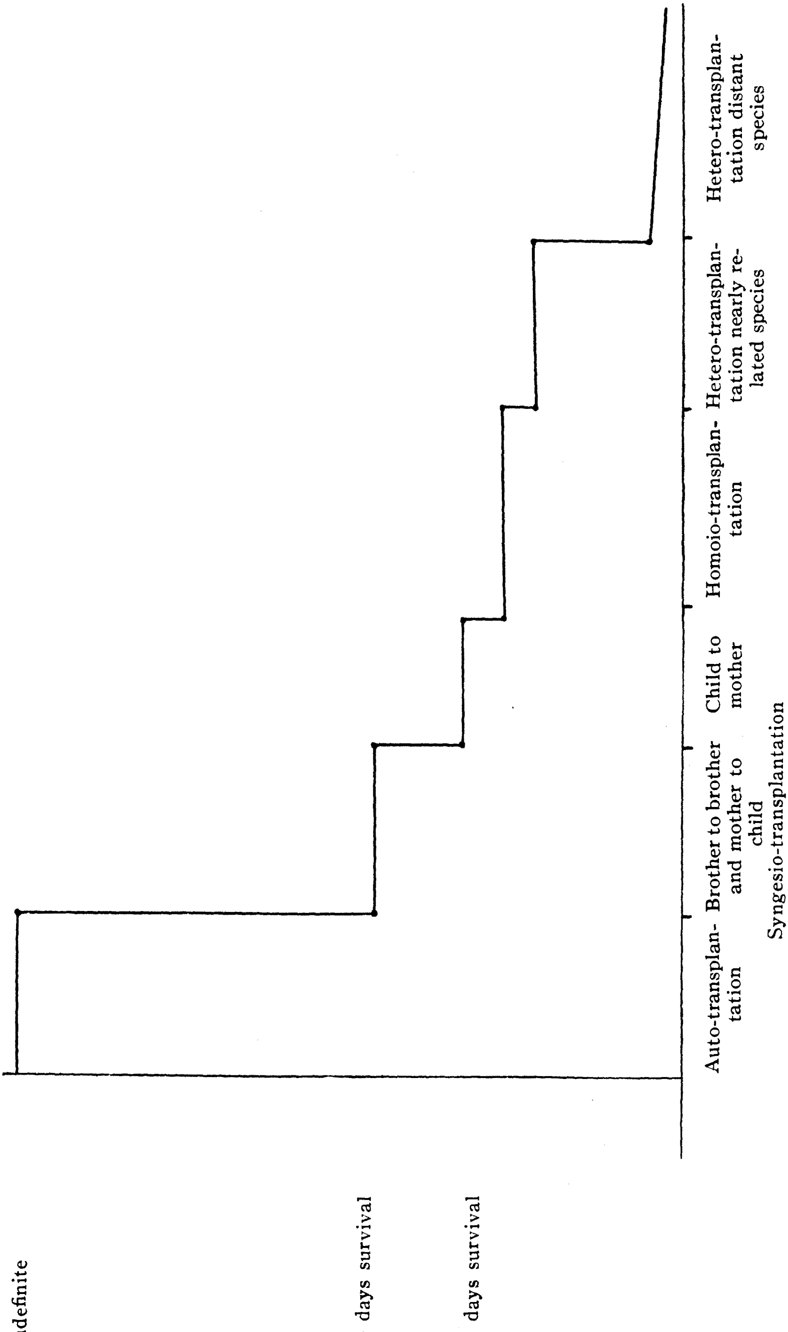
The latter, however, differ from the former in their sensitiveness to strain differences within the same species. In addition there may furthermore perhaps be found some differences in the behavior towards heterotoxins of invertebrate and embryonic tissues on the one hand and of transplantable tumors on the other hand.

From these curves differs very markedly the curve of the adult tissue of the higher vertebrates and similar to this is the curve of the large majority of the tumors, namely of those which generally are not transplantable, although in a limited number of individuals of the same species they may perhaps grow (Curve III.). The adult tissue of amphibia and fishes represents a transitional condition between type I. or II. and III.

Cellular and Psychical Discernment of Individuality.

We have shown that the cells of our body are able to discern in a quantitatively graded manner not only the difference between their own kind, between the constituent parts of the same individual on the one hand, and the cells of other individuals of the same species, on the other hand but that they are able even to recognize in a graded manner degrees of relationship between members of the same family. We found especially the lymphocytic reaction a quantitative indicator of this relationship. We must therefore conclude that there are graded biochemical differences within the same family which these individual cells discern, and to which they react. These reactions represent as far as we are aware, the finest biochemical reaction known at the present time and on the basis of these reactions we may in a tentative manner postulate a graded system of contact substances which regulate the interaction of various tissues.

To return in conclusion to the starting point of our discussion, namely, the usual meaning of individuality, we saw that in the main, it designates a social-psychical way of reaction. We are able to differentiate between individuals as a result of certain functions of our central nervous system. If we now inquire how far the development of this kind of individualization is parallel to the power of cells of higher vertebrates generally to discern individuality, we are handicapped by the lack of data as to the power of animals to discern not merely members of a species,



CURVE III. Transplantation in adult mammals and birds. The curve of the non-transplantable tumors is somewhat similar.

of a litter or mother and mate, but individuals of the same species as such. This problem does not seem so far to have been considered by students of animal behavior. At least inquiries which I made among some prominent investigators in this field, failed to provide any definite data which might be used in this connection. From my own observations I am very much in doubt as to the ability of such animals as the common rodents to discern individuality in the sense in which we defined it. There seems to be little doubt on the other hand that higher animals like dogs and horses have such an individuality discernment, at least to a certain extent.

It is then very probable that the mechanisms which permit the ordinary tissue cells to discern and to react towards individuality have developed much in advance of that mechanism of our nervous system which permits us to recognize individuals in a conscious manner. On the other hand after the latter faculty has once developed, it has reached in man a very much greater degree of refinement in individualization than that exhibited by the discernment of individuality on the part of cells in general.

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