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THE BIOLOGICAL BASIS OF INDIVIDUALITY[1]

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WE apply the term "individual" to a living organism to emphasize the distinctive, unique features which such an organism possesses. In individual human beings we note their appearance, motor reactions and psychical expressions and certain inherited or acquired structural or functional peculiarities, such as nevi, allergies. There are in addition two very fine modes of distinguishing one human individual from every other one. These are the individual scents attaching to different areas of the body, representing in their totality a characteristic by means of which a dog can distinguish one individual from every other one; and there are the patterns of the skin ridges in the palms of the hands and in the fingers, which are now so commonly used for identification. Recently it has been stated that also the changes in electrical potential in certain areas of the brain are characteristic of an individual and are relatively constant in him (Hallowell Davis).

All these individual characteristics which we have mentioned so far are localized in certain areas of the organism, in special organs or tissues; they are either structural or functional peculiarities of these tissues and organs. If we consider the individual as a mosaic of many tissues and organs, each one functioning and metabolizing in its own peculiar way, we may consider this mosaic of separate parts as the biological basis of

[1] Read before the joint meeting of the Federation of American Societies for Experimental Biology in Memphis on April 22, 1937, and representing the abridged fourth annual Arno B. Luckhardt lecture of Phi Beta Pi of the University of Chicago Medical School, delivered at the Billings Hospital of the University of Chicago on March 30, 1937. The recent investigations reported were carried out with the aid of a grant from the International Cancer Research Foundation. References to the literature up to the year 1930 may be found in an article by the author on "Transplantation and Individuality" in *Physiological Reviews*, 10: 577, 1930.

individuality, including the psychical characteristics, and in order to understand individuality in this sense we would have to study the peculiarities of the units composing this mosaic in each individual; also the nervous system and the hormone system, which serve as means of communication between the various parts of the body, represent special organs or products of organs and are therefore parts of the mosaic. They are the properties of organisms, the so-called factors, which are analyzed as to their genetic basis by means of hybridizations according to the Mendelian methods.

There is, however, in addition to this mosaic basis of individuality, another basis. There are properties which are not restricted to parts of the organism, but which are common to all, or almost all parts of an organism, which, although not visible, bind them together, make them into a unit and differentiate an individual from every other individual, a species, genus, order, class of organisms, from every other species, genus, order and class. There is inherent in every higher individual organism something which differentiates him from every other individual, which can be discovered by observing the reactions of certain cells and tissues belonging to one individual towards the tissues and cells of another individual of the same species. They act as if there was something in common to all parts of one organism which differs from the analogous characteristics of all the parts in a different organism of the same species. And not only do these cells recognize the different individuals as such, they do more than that, they recognize, to speak in a metaphorical way, the degree of difference between two individuals as based on their genetic constitution.

In a provisional manner we may designate this common characteristic distinguishing one individual from another as his individuality differential; it is common to the various organs of an individual in contrast to the organ differentials which differentiate from one another the different organs, such as liver, kidney, thyroid, cartilage, in the same individual. In the same way there are characteristics common to all members of a species, genus, order and class, and these may be designated in their totality as organismal differentials, among which the individuality differential is the highest and finest one.

There are two principal methods by means of which these organismal differentials can be analyzed, namely, (1) by various types of transplantation and (2) by serological methods. The transplantation and serological methods are not equally well adapted to the analysis of organismal differentials; each has its own sphere in which it can be applied to the greatest advantage. While the serological tests are especially useful in the analysis of the differentials of wider groups of animals, such as species, genera, orders and classes, transplantation experiments are best suited for the analysis of individuality differentials.

We are concerned principally with the study of the individuality differential, and here the basic experiment is the following: We transplant various organs or tissues from one animal, *e.g.,* a guinea pig, into two other guinea pigs not directly related to each other or to the first guinea pig from which the tissues were taken; we call this homoiotransplantation. It is seen that the reactions of the hosts of the multiple grafts towards the latter differ in intensity in accordance with the degree of the genetic relationship between host and donor, but the host behaves in approximately the same way towards the various tissues from the same donor. In one animal the reactions are severe to all the tissues, in the other one they may be very light. These reactions consist in the activity of the lymphocytes, the connective tissue cells and blood vessels of the host towards the grafts; in addition, certain more sensitive tissues are also influenced by the degree of their compatibility with certain constituents of the blood of the host, and the degree of sensitiveness again depends upon the genetic relationship between host and transplant. The reactions of these different types of cells are not equally delicate. It is the lymphocytes which sense or recognize the finest degrees of similarity or difference in the constitution of the individuality differentials between host and transplant. The distinctive reaction of the connective tissue cells takes place if there is a slightly greater difference between these differentials. I said that all the tissues from the same donor elicit the same intensity of reaction on the part of the same host. This is true in a relative but not in an absolute sense. Different tissues have an unequal power to call forth these reactions; thus, for instance, thyroid gland usually induces a stronger reaction than cartilage and perichondrium. This is evidently due to the fact that a certain substance responsible for the reaction, the individuality differential, is given off in sufficient quantities more readily by thyroid than by cartilage, which latter has a more inert metabolism. However, if we grant these differences between different tissues and organs, after all the genetic relationship between host and transplant determines the intensity of the reaction in the tissues possessing individuality differentials.

There is a second experiment which brings out the meaning of the individuality differential. We can transplant various kinds of tissues and organ pieces into the same animal from which they were taken and to which, therefore, they belonged. This is called autotransplantation. We then find that lymphocytes are practically lacking around the graft; connective cells are attracted in only a moderate number and instead of producing dense fibrous tissue, which is characteristic of their reaction against a strange individuality differential, they form a loose embryonal stroma around the transplanted cells. The blood vessel supply is rich, and in the course of a relatively short time the transplant assumes about the condition of the normal tissue or organ in the host. All tissues from the same organism behave in this respect, in principle, in the same way, except that some tissues can withstand the injury connected with the process of transplantation much better than others. We may then conclude that it is not the organ differentials which determine these injurious reactions of the host cells towards the grafts, but the individuality differentials. The chemical constitution of liver and kidney is very different, but this difference has no effect on the host cells—they react in about the same way towards liver and kidney, provided these tissues possess the same individuality differential; however, a slight difference in the chemical constitution of the individuality differential sets these reactions in motion; and it makes little difference whether this strange individuality differential is attached to the kidney, liver, skin, cartilage, uterus or thyroid organ differential. The various organ differentials all behave in about the same way.

This, then, is the first important fact: The host cells recognize in a very subtle way differences in individuality differentials. But they can do more than this; as I stated before, they are able to recognize the degree of difference and to react accordingly. Thus, when a piece of tissue from brother to brother is transplanted—we call this syngenesio-transplantation—the cells of the one who functions as host are not as much stimulated or excited by the presence of a tissue which is so closely related to his own as by the tissues from a non-related individual, the individuality differentials being more similar in this case. However, brothers and sisters may be genetically similar to each other to very different degrees and therefore in some instances the reaction against such a tissue may be about the same as against that of a stranger; but usually the reactions on the part of the lymphocytes are delayed and the reaction of the connective tissue may be diminished.

On the other hand, if a piece of tissue is transplanted which is genetically further removed, which has been a part of an individual belonging to a different species (heterotransplantation), the reactions are more severe. In this instance the body fluids of the host are so different from those to which the tissues of the transplant are adapted that they exert a strongly injurious effect and kill the graft in a relatively short time; the length of time in which this can be accomplished depends, among other factors, upon the degree of resistance of the particular tissue. The reaction of the connective tissue of the host is very strong in these cases of heterotransplantation; besides, it is the polymorphonuclear leucocytes which are attracted first, rather than the lymphocytes, indicating the presence of a substance which acts as a stronger poison, a heterotoxin. The reaction of the lymphocytes is the test for the presence of a milder toxin, namely, homoio- or syngenesiotoxin. However, at a later period when the acutely acting toxins have been largely absorbed, lymphocytes may also be attracted and collect in large masses around tissues derived from a strange species. We see, then, that the host cells not only recognize a strange organismal differential, but they also distinguish between different degrees of relationship or strangeness. But there is a limit to this power of discrimination. If a certain threshold of strangeness has been reached, the reaction is maximal and can not be much increased if the tissues from individuals belonging to still further removed classes are used. In this case serological tests are better able to grade differences. The cellular reactions with which we have to deal in transplantation are comparable to a very sensitive balance which indicates small fractions of a milligram and which can not be used for the detection of differences which are measured by pounds.

Certain experiments show that the similarity or difference between two individuality differentials corresponds to the similarity or difference in the composition of the gene sets in the host and donor, and that the host cells respond, so to speak, to genes which are strange to them. In reality, however, it is not the genes as such to which the host cells react, but the organismal differentials which develop in accordance with the gene sets.

That it is the similarity or difference in the gene sets in two individuals which determines their similarity and difference in reaction is also indicated by the fact that if, through close inbreeding, we render their gene composition more similar, the individuality differentials correspondingly become more and more similar in the course of inbreeding. But it has been found very difficult to produce identity of the organismal differentials in others than brothers, although this can probably be accomplished in the end. However, it seems that different species of closely inbred animals differ in respect to the readiness with which this stage is reached and the transplantation method can therefore be applied in order to test to what degree the gene composition in a closely inbred family or strain has become similar or, expressed differently, the degree of homozygosity which has been reached in such a strain.

There are indications that during embryonal development also the individuality differential develops from a precursor substance; it is certain that at least the mechanism which makes its effects manifest undergoes such a development. Even in very young guinea pigs, before the age of sexual maturity, these mechanisms of defense against a strange individuality differential are not yet fully developed, as is indicated by transplantation experiments of adult tissues. The connective tissue reaction is diminished in intensity and the lymphocytes have therefore a better chance to become active in these young animals.

As to the number of genes which enter into the precursors of the individuality differentials no definite statement can be made. However, considering the difficulty in eradicating reactions against other than autotransplants, even in individuals belonging to strains closely inbred through a considerable number of generations, and considering the improbability of ever obtaining after homoiotransplantations in non-inbred strains an autogenous reaction, also in view of the fact that the reactions are so very finely graded and that a homoio- or syngenesio-reaction, after transplantation of a piece of tissue belonging to another individual, may appear as late as several months following transplantation, it is very likely that the number of genes entering into the composition of the individuality differential is great and that perhaps all the genes participate, although different ones possibly to a different degree. Both organismal differentials and organ and tissue differentials depend entirely, or to a large extent, on the constitution of chromosomes and genes; but the genes and combination of genes which preponderate as determiners of these two types of differentials are evidently not the same and there are indications that it is certain gene sets rather than individual genes which represent the precursors of organismal differentials.

Not every substance present in or produced by tissues possesses an individuality differential. Many less complex substances, degeneration or decomposition products of tissues, such as keratin, fibers of the eye lens, many hormones, vitamins, do not possess individuality differentials; certain of these may, however, possess some of the coarser organismal differentials.

We see, then, that tissues give off substances which differ in their effects in accordance with the relationship of the tissues to the host organism. In their own natural habitat these substances are of an autogenous character and do not incite any abnormal reaction. In accordance with the genetic strangeness existing between transplant and host, these substances assume the character of toxic substances, which call forth abnormal reactions in the host. In near relatives these substances—the organismal differentials—act as syngenesiotoxins; in a strange individual of the same species they act as homoiotoxins and in a different species as heterotoxins. The chemical nature of the latter is distinct from that of the syngenesio- and homoiotoxins.

Furthermore, these substances, the organismal differentials, diffuse not only into the area directly surrounding the transplanted piece, but they also enter the circulation and are carried by the blood or lymph to further distant organs. This may be concluded from the fact that transplantation of a normal piece of grafted tissue induces changes in the proportion of the circulating blood cells, which are parallel to the degree of relationship or strangeness between host and transplant, and which depend therefore on the nature of the organismal differentials of host and graft. These changes have recently been studied and are being studied at the present time by Mr. H. T. Blumenthal in our laboratory. I may mention some of the results obtained by him so far: After homoiotransplantation of a lobe of thyroid gland, of pieces of liver or kidney from guinea pigs to other non-related guinea pigs or from rats to rats or pigeons to pigeons, the count of the lymphocytes rises about five to seven days after transplantation, by approximately 15 per cent. or somewhat more, and after having reached the maximum it begins to fall again. After transplantation of cartilage, however, the rise is lacking entirely or almost entirely, because the amount of homoiodifferential given off is apparently insufficient to reach the threshold necessary for a rise. After syngenesiotransplantation the increase in lymphocytes begins, on the average, at a somewhat later date and remains lower. After heterotransplantation it is the polymorphonuclear leucocytes which show an increase in the general circulation; they then fall to the normal level, and this phase is followed by a second phase in which the lymphocytes rise; after a few days this latter rise is likewise followed by a fall. As far as we can judge, these changes in the number and character of the blood cells are specific. After autotransplantation of tissues these characteristic changes in the composition of the blood cells do not occur, but only some slight, non-specific variations may take place, in some instances, in the first few days following the operation. Neither does introduction of inert foreign bodies, such as threads and agar, cause changes comparable to those following syngenesio-, homoio- or heterotransplantation. These effects produced by transplants on the lymphocytes and polymorphonuclear leucocytes, circulating in the blood, are closely parallel to the effects which the transplants exert locally on the lymphocytes and polymorphonuclear leucocytes.

We see thus that substances corresponding to the individuality and species differentials not only diffuse from the transplanted tissues into the neighboring areas, but also reach the blood and exert their effects in distant parts. These substances thus resemble hormones in their action.

If, then, we may consider it an established fact that when tissues are transplanted from one to another individual of the same species, even to nearly related individuals such as brother and sister, substances are given off by the tissue which call forth noticeable reactions on the part of the host cells, might it not be possible or even probable that such substances, acting on nearby tissues as contact substances or on further distant tissues as hormones, are also given off in the animal's own organism, but that here, instead of acting as disturbers of the tissue equilibrium, on the contrary, they function as instruments by means of which the tissue equilibrium is maintained and regulated in such a manner that it is best adapted to the normal cooperation of the various tissues in the interest of the entire organism and thus to the normal functioning of the organism as a whole? Such substances, representing the individuality differentials, if discharged into their own organism, may then be designated as autogenous substances. We have seen that after autotransplantation the connective tissue cells and blood vessels of the host react towards the transplant in a way that is most conducive to the normal metabolism, structure and function of the graft and that lymphocytes are practically absent. May we not attribute these beneficial reactions to the controlling influences of autogenous substances given off by the transplanted tissues, contrasting with the syngenesio-, homoio- and heterotoxins which are given off by strange tissues? Correspondingly, if two tissues, possessing two different individuality differentials, have been made to adjoin each other, signs of disharmony develop, which are partly or largely due to the action of disharmonious individuality differentials. This applies for instance to homoiogenous skin transplants. Conversely, may we not assume that, since the epithelial cells in the normal skin remain at rest, this is due, at least to a certain extent, to the action of the autogenous substances which keep the neighboring epithelial cells as well as the underlying connective tissue and lymphocytes quiescent?

There exists, then, a mutual adaptation to one another of tissues bearing the same organismal differential, and there exists also a mutual adaptation between the blood plasma and the various tissues belonging to the same individual. It is these harmonious interactions which make the unity of the organism possible and which are perhaps the most characteristic feature of the living organism as an individual. But not only are the substances characteristic of each individual different from those characterizing any other individual, and in this sense specific; there exists, besides, a second type of specificity, which may be designated as specific adaptation. By specific adaptation we mean that it is the individuality, species, order or class differential, in general the organismal differentials, attached to the various tissues or to substances derived from these tissues, which determine how suitable and effective the interactions between these tissues and substances are. If the respective organismal differentials are the same in the tissues or substances the interaction is most effective. This applies, for instance, to the interaction between tissue extracts, blood plasma and blood serum. The character of the organismal differentials attaching to these various substances determines how effective the coagulating power of the extract will be, and how effective also the inhibiting action of the blood serum will be.

We may then distinguish two types of adaptation within the organism. The first one is well recognized; it is represented by the normal physiological interaction of various organs and of parts of organs. It is based on transmission of stimuli or inhibitions through the nervous system, through hormones and through certain other mechanisms. This is largely independent of organismal differentials. The second one is the adaptation based on the identity of the organismal differentials. But in addition a number of chemical interactions in the organism, of which only one example has been mentioned, depend specifically on the character of the organismal differentials which are carried by the interacting substances.

The organism is then a harmonious whole, in which not only the organ functions are adapted to one another, but in which also all the various tissues, which apparently are not functionally related, are specifically adapted to one another, owing to the nature of their organismal differentials. This latter adaptation above all is what characterizes the individual. Such a harmonious relationship must be based on resemblances or identities in certain chemical structures of the most important and complex substances which enter into the building of the organism, especially substances of a protein nature. Thus it has been established that the hemoglobins and hemocyanins derived from various species or still larger groups of animals are the most nearly identical in structure in the nearest related animals, and are the more different in structure the further distant the species are. We may assume that the same chemical gradation in the structure of the organism must go still further, not only each species, but each individual possessing its chemical characteristics, which differ from those possessed by every other individual of the same species.

We believe, then, the conclusion is justified that in certain respects these chemical differentials of organisms are the most characteristic features of individuals as such, and that in their totality and interaction they constitute the most essential biological basis of individuality.