TRANSPLANTATION OF HUMAN FETAL TISSUE

Patterns of Tissue Transformation after Transplantation

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Transplantation of fetal tissue in clinical practice in Russia has a solid experimental basis. "Tissue-tissue" relationships that are phylo- and ontogenetically fixed as characteristic of all systems of organs have been described in studies of Zavarzin *et al.* The method of tissue culture in the organism that was developed by Lazarenko in 1934 makes it possible to study the patterns of growth and transformation of tissues and organs in the living organism. This method has been used in studies of epithelial tissues of ecto-, endo-, and mesodermal origin. Five stages of the transplantation process have been identified: tissue depression, activation, tissue growth and differentiation, the period of functional activity, and atrophy. All tissues, except for endocrine tissue, which can live for a long time without atrophy, go through these stages, but in each tissue this process is genetically determined. This paper is focused on the close "tissue-tissue" relationships and presents characteristics of all epithelial tissues. Special attention is paid to the anterior portion of the gastrointestinal system and to the endocrine glands originating from it: adenohypophysis, thyroid gland, and thymus. The contribution of a normally functioning endocrine system to the successful transplantation of ovarian and mammary tissue is also discussed. After transplantation, epithelial tissues are transformed and assimilated in the recipient's organism. This may provide a basis for a novel approach to the problem of the immunological responsiveness of the organism.

Key Words: *transplantation of fetal tissue; tissue transplantation; role of inflammation in tissue transplantation*

One of the twentieth-century achievements in medicine and biology has been the development of methods of organ transplantation and their effective use in medical practice. Unfortunately, this major advance in surgery has only partly solved the problems of correcting the functions of individual systems of the organism, and replacement of a diseased organ (kidney, heart, etc.) with a healthy one cannot be performed, following certain specifications, for all of the numerous disorders of the body's functioning systems. Recently, transplantologists have turned their attention in a new direction. Attempts are now being made to transplant not an entire organ but specifically fetal donor tissue to humans. This makes it possible to correct disorders in the central and peripheral organs of the regulatory systems of the organism. Experience in transplantation of fetal tissue to humans has already been obtained. For instance, after irradiation with radionuclides, a suspension of fetal tissue of the liver, thymus, and red bone marrow was been transplanted to humans, this being aimed at the restoration of damaged hemopoiesis and immunity [34]. Effective regeneration of striated muscle tissue after transplantation of minced donor tissue to the damaged zone in

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the recipient [21] or of minced bone tissue to the damaged zone of the bone [20] has been followed up in biological experiments. These studies, few so far, are very promising and are likely to be of practical importance in medicine. Fundamental and detailed studies of different tissues have helped scientists tackle the transplantation of tissues rather than of entire organs. These seminal studies have largely been performed in Russia - the birthplace of embryology, the science dealing with the development of the organism, organs, and tissues, and of histology, the evolutionary science concerned with tissues [7,10-13]. Zavarzin revealed to the entire world the evolutionary pathways of the nervous system and established, from the evolutionary standpoint, the unity of the blood and connective tissue. On the basis of experimental findings he created a biological theory which offered an explanation of the pathways of tissue evolution. Zavarzin developed the tissue classification which has been adopted in all histological and embryological manuals and is now followed by morphologists and embryologists. All tissues were divided by him into groups as follows: boundary tissue (epithelium), internal tissue (connective tissue, blood, cartilage, osseous tissue, and smooth muscle tissue), and specialized tissue (nervous tissue and striated muscle). Zavarzin's work was further developed by his disciples and followers. Notably, the existence of **"tissue-tissue" relationships** [2,18] was established, relationships that are phylo- and ontogenetically fixed as being characteristic of each system (for instance, the unity of the blood and connective tissue, or of the epithelium and connective tissue). Indeed, these tissues are capable of functioning only when such relationships exist. Valuable data on the classification of epithelium, which were obtained by the methods of tissue culturing *in vitro*, were presented by Academician N. G. Khlopin [23].

In the 30s the properties of tissues within the tissue groups encompassed by the above-mentioned classification were investigated in more detail. A detailed study was started in order to elucidate the biology of certain types of tissues and to uncover their potential. One of the most widespread tissues is epithelium. This tissue fulfills a number of functions: protective, absorptive, secretory, and reproductive. The study of epithelial tissue was aimed at elucidating the embryonic genesis and the structure of this tissue, as well as its ability to be transformed, which is determined by its histogenetic properties. For a better understanding of the potential transformations of the epithelium, this tissue was studied in two parallel directions: during human and animal embryogenesis and in experiment. This protracted basic research was necessary for applied medicine, namely, for the tissue transplantation that has developed in the last few years and has been aimed at correcting a pathological process in the recipient organism.

Since all studies in this field cannot be reviewed in this paper, only the study of F. M. Lazarenko and his disciples - the author of this paper is one of them [24,25,30] - is discussed here. Lazarenko, a Corresponding Member of the Russian Academy of Medical Sciences [14-17], developed "a method of tissue culture in the organism," a special experimental method of grafting tissue. This method, reported in 1934, makes it possible to study the patterns of growth and transformation of tissues and organs in the organism. Lazarenko's inspiration came from his participation in the series of investigations of the blood and connective tissue carried out by Zavarzin and his disciples. In diverse representatives of animals (from lower invertebrates to higher vertebrates) the morphological significance of cellular elements of these two tissues was studied using a similar reactive inflammation in response to the introduction of an indifferent foreign body. This helped classify transplanted cells by their functional biological responses rather than by their shape; i.e., it was only a study of the inflammatory reaction to a foreign body in diverse animals that provided a deeper insight into the nature of this response on the part of the organism. These studies were the springboard for a number of reports on the proliferative processes in the dermal epithelium caused by the introduction of a foreign body and the simultaneous reaction in the connective tissue and epithelium. These publications presented persuasive evidence of the interrelations between the inflammatory reaction in the connective tissue and the proliferation of epithelium. The boundaries of activated and proliferating epithelium and the boundaries of the inflammatory focus exactly coincide. In other words, epithelial proliferation never extends beyond the boundaries of the inflammatory focus and it ceases simultaneously with the arrest of the inflammatory process. Finally, after the scattered findings had been compiled and a number of hurdles had been overcome, in 1934 the new method of "Tissue Culture in the Organism" was created and published. This method is based on homotransplantation of fragments of donor tissue, along with particles of the indifferent substance celloidin, to the recipient organism. Tissues from donors of different age may be transplanted by this method, which makes it possible to elucidate the significance of the age of the transplant.

The operation was performed with stringent observance of the rules of asepsis. Before surgery, pieces of irritant (cube-shaped particles of celloidin 0.5 mm in diameter) were boiled in physiological saline during 1-2 h. For an enhanced inflammatory response and more complete tissue growth, celloidin was boiled in a salt solution of a higher concentration (3-5%). The experiments were carried out on different animals, but predominantly on rabbits. The operative field was prepared at the abdominal wall. Skin incisions 2-2.5 cm long were made bilaterally relative to the linea alba, small pouches were formed in the subcutaneous tissue, and transplants of the organ, mixed with celloidin particles (2 parts celloidin to 1 part minced tissue), were placed in these pouches. The entire mass was introduced with a grooved probe into the subcutaneous pouch and the wound was sutured. At different times during the experiment the transplants were removed for investigation, treated by histological methods, and examined under a microscope. The best growth of transplanted tissues was observed when tissue of a fetus or of a neonate was transplanted and when a young animal was the recipient of fetal tissue.

Thus, the method of tissue transplantation is based on the creation of a local aseptic inflammation caused by a foreign body (celloidin). The recipient organism responds to the trauma by regenerating the damaged tissues. Substances (possibly growth factors) which activate proliferation in the recipient tissues, as well as in the donor-derived tissues, are accumulated in the inflammatory focus, stimulating tissue regeneration. In the created inflammatory focus the effect of the inflammatory substances spreads simultaneously to the transplanted tissues and to the recipient tissues. The grafted donor tissues together with the damaged recipient tissues go through the same stages of regeneration as after aseptic trauma. As inflammation proceeds, the transplanted tissues pass through all the stages of reparative regeneration. The following major stages of transplantation are distinguished: tissue depression, activation, tissue growth and differentiation, functional period, and, finally, atrophy, **which affects all transplanted organs except for incretory organs**, which under favorable conditions can function for a long time. Histological processes in the transplants may be studied in terms of these stages. Conditions optimal for the growth of transplants can be created which result in maximal tissue growth and vascularization of the entire transplant, providing not only for the best trophic conditions but also for the necessary humoral regulation on the part of the recipient organism.

Intimate "tissue-tissue" relationships are necessarily manifested during transplantation. Notably, the relationship between epithelium and connective tissue is not only spatial and trophic, but also unseverable. Contrary to the views of some scientists, in the system formed during the transplantation of epithelial tissue, **one tissue cannot be regarded as the leading one, and the other as subordinate**. Each physiological state is reflected in the integrated system of epithelium and connective tissue, although these states manifest themselves in each of the two tissues in accordance with their functional specificities.

The group comprised by epithelial tissues is genetically nonuniform. Some epithelial tissues originate from the ectodermal, some from the endodermal, and others from the mesodermal primordium. Under similar conditions of transplantation, along with the common regularities relative to the stages of transplantation, these tissues demonstrate **specific properties which stem from their genetic peculiarities**. For example, epithelium of the organs of ectodermal origin (skin, mammary gland, salivary glands) exhibits posttransplant similar characteristics typical of this group of organs. In a case where the donor is a fetus and the recipient a young animal, a short period of depression, lasting for just the first few hours of the experiment, is characteristic of these tissues. This period is longer when there is a marked difference between the age of the donor and the age of the recipient. Only the youngest cambial cells are involved in proliferation, while more differentiated cells die. At the stage of proliferation and differentiation, the epidermis and its derivatives (hair) form only protective layers with cell keratinization around the celloidin particles, isolating the foreign bodies from the recipient organism. The regulation of the new host starts to play a crucial role in the dermal epithelium. These proliferations are preserved for a long time (for some 160 days).

When organs of endodermal origin (the mucosa of the stomach, intestine, and gallbladder, the exocrine portion of the pancreas, and the liver) are transplanted, the depression of their epithelium is more pronounced and lasts longer than in the case of organs with ectodermal epithelium. Proliferation involves not only cambial cells, but also the majority of differentiated elements, which preliminarily free themselves of secretory and other inclusions. These cells became morphologically and functionally similar to the young cell forms in these organs. Epithelial cells migrate to the connective tissue formed *de novo* in the recipient or to the renewed tissue from their own tissue frag-

ment. Epithelia of this group of organs never form protective layers around celloidin, as always occurs in the case of ectodermal epithelium. Endodermal epithelium spreads in the connective tissue, forming large cysts (always with a simple epithelial lining) or branched glandular structures there. The proliferations formed in transplants of such different organs as the liver, the exocrine portion of the pancreas, and the intestinal mucosa are similar. The proliferations of endodermal epithelium have a shorter cycle of transformation, and after 20-25 days they undergo regressive changes and atrophy.

Epithelium of the organs derived from mesoderm (the kidneys and the male and female genital tracts, i.e., developing from the Wolffian and Muller ducts) goes through the same stages of transplantation (depression, etc.), but its proliferation and organogenesis are specific, reflecting its genetic origin.

A study of epithelium of the organs developing from the embryonic foregut is of special interest [27]. Among them are the esophagus, the respiratory tract, and some glands (adenohypophysis, thyroid gland, and thymus). The question as to the histogenetic nature of epithelium of the anterior portion of the alimentary tube has not been resolved. Several theories exist on this subject. Shimkevich [31,32] proposed the theory of metarhizis, according to which, after the oral stoma has opened, the cutaneous ectoderm of the embryo spreads along the alimentary tube and replaces the endoderm, including the glandular portion of the stomach. In the opinion of Shimkevich, this accounts for the presence of stratified epithelium in the esophagus. This theory has not yet been confirmed by factual evidence. In tailed amphibians Fogt [33] found an independent part of the blastula, which he called a "prechordal disk"; during the gastrula stage, this formation migrates from the posterior to the anterior end of the embryo and forms the entire anterior portion of the alimentary tract with a stratified epithelial lining. This argues against the metarhizis theory. Since the fully developed epithelium of this portion of the alimentary tract has many features in common with the epithelium originating from the ectoderm, some scientists have assumed that the "prechordal disk" is part of the ectoderm, and the organs developing from it can be regarded as fully equivalent to ectodermal organs. However, some findings contradict such an assertion. For example, it is well known that during embryonic development, until the onset of the stage of multilayer structure, esophageal epithelium has a monolayer and then bilayer structure, which is then replaced by ciliated multirow (as in the trachea) epithelium, which becomes rearranged into multilayer (stratified) epithelium only in the final stage. The question as to the nature of the epithelium of the foregut, from which the above-mentioned organs develop, is of principal importance. As long as this is unclear, the pathological processes arising in this region can hardly be understood and the morphogenetic potentials of the integumentary and glandular epithelium of the central endocrine (pituitary and thyroid) and immune (thymus) regulatory systems of the organism are difficult to predict. In an attempt to tackle this problem, we followed Lazarenko's trend of studies and used his method of tissue transplantation. The role of the embryonic foregut is very important and complex. In fact, it is in this zone that the integumentary and glandular epithelia of functionally and morphologically different organs develop from common epithelium of the gill pouches.

Epithelium of all named organs was transplanted by the method of Lazarenko. Under identical conditions all epithelia went through the same stages of transplantation: depression, proliferation, differentiation, and reversed development. Fetuses, neonates, and adult animals served as the donors, and young and mature animals as the recipients. We assumed that similar conditions of grafting epithelium of different organs originating from the foregut epithelium would make it possible to discover the general histogenetic processes and their transformation into specific processes, associated with the divergent development of the organs from a common presumptive region, and, evidently, would make it possible to identify a specific group of organs in which the posttransplantation processes are unique.

The integumentary epithelium of the esophagus [1] and of the larynx [21] is very labile during growth and differentiation. Monolayers are later rearranged into multilayers, which spread over the connective tissue, surrounding the celloidin particles and isolating them from the recipient organism. Intercalary glandular primordia develop from these layers. The epithelium is never keratinized, as always occurs in dermal epithelial grafts. Mono- and multirow layers typical of the epithelial lining of the respiratory tract, but in which ciliated cells are absent, are formed by the bronchial epithelium [3] at the edge of the transplant rather than at the celloidin boundaries. As in the case of transplantation of esophageal epithelium, multilayers grow in the zones of severe inflammation. Thus, transplanted epithelia of the esophagus and respiratory tract exhibit a broad structural heterogeneity within

the limits of their determination. This covers the spectrum of their rearrangements and reflects, albeit incompletely, the potential of the dermal and intestinal epithelium. Epithelium of the foregut organs "accumulates" the ability of the dermal epithelium to form multilayer structures and of the intestinal epithelium to form monolayer structures. A broad spectrum of plasticity is a biological peculiarity of the foregut organs, which enables them to perform complicated functions at the interface between the alimentary and respiratory systems.

As mentioned above, Lazarenko's method makes it possible to create a local focus of aseptic inflammation which is encapsulated. The blood vessels, along with the nerves of the recipient, penetrate through the capsule into this focus. Inside this unique "chamber" grows the inflamed recipient- and donor-derived connective tissue, and in this the donor epithelium. Tissue growth in the focus is governed by regulatory factors of the recipient organism. It was thus important to elucidate under what conditions the epithelium of the endocrine glands (which develop from the same epithelium of the foregut as the just mentioned esophageal, laryngeal, and bronchial epithelium) is capable of proliferating and differentiating. This relates to the epithelia of the adenohypophysis, thyroid gland, and thymus.

Transplants of these glands proliferate in the same manner as the epithelia with a nonendocrine function. In the inflammatory focus they undergo the same stages: depression, proliferation, differentiation, and reverse development, i.e., all processes strictly correlate with the stages of resolution of inflammation in the zone of the transplant. In the "chamber" containing the inflammatory focus the transplanted epithelium of different endocrine glands engrafts in the young connective tissue formed by donor and recipient tissue elements. At first, the transplanted epithelium of the above-mentioned glands grows around the celloidin and at the edge of the necrotic zone. Integumentary layers are then formed as multilayer (stratified) and monolayer (simple) structures. Thus, they exhibit wide polymorphism. They primarily follow the pattern of epithelial growth of the nonendocrine organs of this zone, which can be attributed to the fact that they have historically developed as boundary tissue. Later, epithelial sprouts extend into the connective tissue; not only inflammatory factors are prerequisites for differentiation of these sprouts, but also the endocrine regulation of the recipient organism, which is provided by vascularization of the transplant and the intercalation of nerve elements along the recipient's blood vessels penetrating the capsule and entering the inflamed connective tissue with the network of epithelial sprouts. Only under such conditions are new functional structures formed in the zones of the transplant. The donor tissues near the transplant consolidate with the new host organism of the recipient and are entirely under its regulation.

For example, three factors markedly affect the structural transformations of the transplanted adenohypophysis [4,5,26,29]: the hormonal background of the recipient, the site of transplantation, and the state of the donor material. The pituitary of a fetal donor or of a pregnant female exhibits the greatest potential. The processes in the transplant become more protracted in the case of simultaneous transplantation of tissues from several donors. Not only unspecialized major cells, but also secreting oxyphils and basophils after their degranulation are involved in the proliferation of the adenohypophysis. Like the major cells, they transform into cambial cells after getting rid of their secretions. In the transplant zone new sprouts and clusters of epithelial cells are formed in the layers between the celloidin, where on days 6-7 differentiation first of acidophils and then of basophils occurs. In the group of basophils histochemical analysis showed the differentiation of cells containing adrenocorticotropic hormone (ACTH), thyrotropic hormone (TTH), somatotropic hormone (STH), and prolactin. During transplantation, the above-mentioned types of basophils, which are not directly associated with the hypothalamic nuclei, are formed *de novo*. Their differentiation is underpinned by the "tissue-tissue" and "cell-cell" interactions. The emergence of new hormone-producing cells in the zone of the transplant and their functional activity attest to changes in the state of the recipient. During the formation of thyrotropocytes the activity of the thyroid epithelium is altered. Marked proliferation of the recipient mammary gland is evidence of prolactin production, while an increased weight of hypophysectomized individuals indicates a low content of somatotropin in the transplant. These regularities were discovered in immature rabbit (7-8 weeks) recipients. Specific features of transplants were also observed in other experimental variants. In mature intact recipients with a balanced hormonal background the transplanted material virtually does not proliferate. Solitary cells survive and die. Injection of various doses of female sex hormone in the recipient organism was attended by the synchronous response of donor acidophils and basophils, which manifested itself as an increase of their functional activity.

Combined transplantation of fragments from the adenohypophyseal and hypothalamic nuclei prolongs preservation of gonadotropocytes and acidophils in the transplants. Repeated combined grafts of these tissues to hypophysectomized recipients completely restores the activity of the gonads, including spermatogenesis, and in some animals repairs the structure of the thyroid gland. Experiments on hypophysectomized recipients demonstrated that "hormonal starvation" is an important factor, which helps the transplant take and hastens its functioning, this resulting in weight gain of the animal and affecting the structure of the thyroid gland. Experiments on the pituitary demonstrated more active proliferation of the tissues of transplants when the gland was preserved. The site of transplantation also plays an important role. The optimal conditions for long-term functioning of a transplanted adenohypophysis are created by its transplantation in the bone marrow and vascularized mesentery. Under these conditions the transplant had a physiological effect up until day 90.

During transplantation of tissues of the thyroid gland [8,9], its epithelium also goes through the stages typical of the integumentary epithelia of organs of the foregut, i.e., its growth correlates with the course of inflammation in the zone of the transplant containing celloidin particles. After a short stage of depression, proliferation begins. During this period, epithelial layers, intercalary sprouts, and cell clusters are formed. The cells of interfollicular sprouts and the differentiated cells of small follicles embark upon proliferation. The formed layers, as well as all epithelia of the organs originating from the foregut, exhibit broad polymorphism, which points to their genetic similarity. In the clusters of epithelial cells located in the connective tissue, lumens are formed which turn into the follicles characteristic of the thyroid gland. It was found, using radiography, that radioactive iodine is incorporated in the follicles of both the recipient's own gland and the lobules formed *de novo* in the zone of the transplant, which proves that the new lobules of the organ are functioning. When fragments of the organ are transplanted to the site from which the lobe of the recipient's thyroid has been removed, new lobules of the thyroid gland grow earlier, and the growth is better if the recipient is a young animal. Under conditions of hypophysectomy or during transplantation of the thyroid gland to the denervated zone in the recipient, organogenesis and differentiation of transplanted tissue do not occur.

The thymus has also been transplanted by the method of Lazarenko [6]. In a case where the tissue of a neonatal animal was transplanted, the graft did not proliferate in an adult recipient in which involution of its own gland had already occurred. Lymphocytes migrated from the fragments of transplanted tissue, and the epithelium underwent regressive changes without emerging from the state of depression. When the thymus of neonatal animals was transplanted to 2-week recipients, in which their own gland had not undergone involution, and the hormonal factors did not cause suppression, edema was observed in the zone of the transplant; inflammation of donor and recipient tissues increased in this zone, lymphocytes migrated from the transplanted pieces of thymus to recipient tissue, and stromal epithelium proliferated as epithelium of the nonendocrine organs. Cambial elements spread in the connective tissue as massive sprouts and cell clusters, which were not colonized by lymphocytes as occurs in the fetal thymus, i.e., in this case the transplanted thymic tissue did not exhibit its organoblastic potency. More frequently, epithelial sprouts have a multilayer structure and more seldom a monolayer structure. In this case the structural heterogeneity of the epithelium reflects its origin from the anterior portion of the foregut, and epithelial growth is governed by the inflammatory processes.

The third series of experiments was carried out on young animals (5-7 days). Total thymectomy was performed in the recipients. The excised gland was minced and, together with celloidin particles, which cause aseptic inflammation, was implanted in its entirety in the subcutaneous tissue of the same animal. In this case specific conditions were created: first, the recipient exhibited functional insufficiency due to extirpation of the entire organ; second, the recipient received minced tissues of its own organ; and, third, the animals chosen were at a very early age. In this series of experiments the thymic tissues proliferated and went through all stages of growth under the influence of inflammation. The period of tissue depression lasted a short time. Lymphocytes migrated from the transplanted fragments. On day 2 of the experiment the epithelium sprouted massively in the inflamed connective tissue. From day 20 organoblastic processes started in the transplant. The connective tissue surrounding the epithelial clusters began differentiating, and as a result, the new epithelial sprouts ceased their growth. On day 45 of the experiment the epithelium loosened, and the cortex and medulla became identified. The epithelial structure was colonized by lymphocytes, and the thymic lobule was formed, in which Hassall's bodies could be observed by days 40-50.

It was concluded [6] that during phylogenesis the thymus is formed as a functionally active lymphoepithelial system, which is able to break down under unfavorable conditions and to restore itself under favorable conditions.

After such results were obtained in studies of three endocrine glands with a common origin from the foregut, it was decided to verify whether the inflammation-induced posttransplantational growth of tissues is typical of all endocrine glands, and how their differentiation into the functionally active organ depends on the hormonal regulation of the recipient organism. For this purpose an inflammatory focus was created to which in one case ovarian tissue [20] was transplanted and in another case the tissue of the mammary gland [28], the growth and function of which are known to be associated with the hormonal background of the organism. When fragments of the ovary with the primordial and dense follicles are transplanted to intact female recipients, the follicular epithelium of the ovary exhibits a high resistance and viability during trauma and inflammation. The epithelium is preserved in the graft for a long time without progressive changes and then dies. When certain hormonal shifts occur in the recipient organism, the follicular epithelium undergoes progressive changes. This occurs in the transplants if fragments of the recipient's own ovary are transplanted to a pregnant female after extirpation of one or both ovaries. Under these conditions the follicular epithelium spreads by means of short sprouts, in which cell differentiation follows the pattern of the luteinized elements of the corpus luteum with characteristic granulation. As a rule, the corpora lutea are formed from the clusters of such cells surrounding the blood vessels and are preserved until day 90. The functional activity of developed corpora lutea may be estimated not only from the cell morphology, but also from the state of the recipient in which, even if the recipient's own two ovaries are removed, pregnancy is preserved, and parturition and lactation occur owing to such corpora lutea.

When mammary gland tissue [28] is transplanted to intact or sterilized recipients, the glandular epithelium grows weakly and dies within the first few days. If the recipient's adenohypophysis is removed, the transplanted glands become inflamed, and epithelium actively sprouts within the connective tissue, but functional differentiation does not occur in these sprouts. Only when fragments of the mammary gland are transplanted to a pregnant female are follicles with a secretory cell lining formed in the epithelial sprouts. The follicles are filled with secretions and are markedly enlarged, since they have no outlet for the secretions. At this time the recipient's own mammary gland also starts secreting. After nursing is discontinued, both the recipient's own gland and the glandular lobules formed *de novo* become simultaneously involuted. In this case hormonal correction by the recipient pregnant or nursing female regulates the function and involution of donor glandular tissue in the graft.

These findings reveal some general patterns of tissue growth and transformation in the transplant. The growth of transplanted tissues is regulated by the local inflammatory reaction. During growth and differentiation the epithelia exhibit their biological properties. During growth they primarily demonstrate their genetic properties stemming from the nature of the germ layer of the tripleblastic embryonic primordium: ectoderm, endoderm, and mesoderm (the outer cutaneous, inner intestinal, and middle mesodermal layers). During growth, the epithelia may rearrange themselves, without becoming transformed into each other, their labile state being limited only by the nature of their own primordium; an exception is the tissue of the organs developing from the anterior portion of the embryonic foregut. These organs are: larynx, esophagus, respiratory tract, thymus, adenohypophysis, and thyroid gland. During development, epithelium of these organs exhibits structural heterogeneity, suggesting the presence of a specific embryonic primordium, which was discovered in tailed amphibians by Fogt [33] and named by him the "prechordal disk."

The growth of all transplanted tissues derived from any embryonic primordium is primarily regulated by the inflammatory reaction in the zone of the transplant. The growth of epithelium in this zone strictly follows the stages of resorption of local inflammation and goes through several general stages: depression, proliferation, growth and functional differentiation leading to the formation of organ structures, and the reversed development of the structures formed *de novo*. In addition to donor and recipient factors of histocompatibility, the inflammatory extract contains growth factors. Exceptions are tissues of endocrine glands. Posttransplantation, the growth of epithelium of these organs is governed not only by the inflammatory reaction in the zone of the transplant, but also by the hormonal regulation of the recipient organism. In tissues of the endocrine glands the inflammatory reaction promotes the proliferation of indifferent epithelium, which in the course of phylo- and ontogenesis lost the ability to form the

boundary layers characteristic of all epithelia, and acquired the ability to intercalate with short sprouts and cell clusters into the connective tissue. Epithelial differentiation in these structures entirely depends on the hormonal requirements of the recipient, which provides clear evidence that transplanted tissues grow and organically integrate with the organism of the new host-recipient under the influence of its regulatory factors.

In conclusion, all these speculations concerning the biological properties of epithelial tissues with secretory and nonsecretory functions and their potential usefulness for transplantation do not include the problem of immunological compatibility of donor and recipient tissues, although the experiments were performed on animals of more than one strain. In this context, transformations of tissues in homotransplants to a certain extent approximate the processes which can unfold after transplant in humans.

The results of homotransplantation of epithelial tissues demonstrate that before the onset of the "tissue-tissue" conflict and quite apart from it, the recipient organism has its own potential **which provides for rearrangement of transplanted tissues and for their integration with the recipient organism.** The local inflammatory focus in the recipient organism is a powerful factor in the rearrangement of transplanted tissues. The results of special experiments performed by Lazarenko on cultures by adding extracts from foci of inflammation caused in a recipient by celloidin indicate that the local inflammatory focus contains stimulating, probably growth, factors. The highest activity was observed in the case of extracts obtained from the foci on days 2-3. After storage *in vitro* at 2-3°C they lose their activity on days 3-4. The action of inflammatory extracts on transplanted tissues primarily results in the formation of "tissue-tissue" relationships. In these experiments epithelium and connective tissue acted as a single essential complex. Temporarily, before the onset of the "tissue-tissue" conflict, the time of resolution of the inflammation is sufficient for exploring the promising biological potential of tissues. Their spread is limited by histogenetic properties and by the pattern of neurohumoral regulations in the recipient organism; when these regulations are disrupted, the patterns of growth and differentiation of transplanted tissues are disturbed.

Thus, basic research, performed in Russia over many years indicates that the knowledge acquired can be useful in the practice of tissue transplantation for the correction of certain disorders in organs and systems of the human organism. Transplantation of tissues and entire organs has both general and specific regularities of the posttransplantational process, which are not identical. Experimental studies in the transplantation not of organs but of tissues, coupled with advances in modern immunology, are about to make therapeutic tissue transplantation a reality.

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Transplantation of Human Fetal Tissue as a Promising Method in the Treatment of Diabetes Mellitus

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Experience accumulated in Russia during the last century in the treatment of diabetes mellitus by transplantation of human fetal tissues is analyzed from the historical and geographical viewpoint. Over the last 15 years about 3000 patients have been treated using this method. Such treatment has mainly resulted in stabilization of the labile forms of insulin-dependent diabetes: in 80% of recipients the exogenous insulin requirements have been reduced by 20-85%, and in some cases a short-term insulin independence has been established. Discontinuation and partial regression of secondary diabetic complications have been observed: pain and paresthesia in the extremities have diminished or disappeared; in the case of angiopathy of the lower extremities the incidence of indications for amputation due to gangrene has been reduced; the pathological process in the fundus of the eye has been arrested and visual acuity has increased in 45-65% of patients with diabetic retinopathy. At the prenephrotic stage of diabetic nephropathy transplantation has been attended by a reduction or disappearance of proteinuria and normalization of arterial pressure in 40-50% of patients.

Key Words: *transplantation of human fetal tissue; treatment of diabetes mellitus; neuropathy; angiopathy; retinopathy; nephropathy*

The present report is devoted to achievements of researchers from Russia and from republics of the former USSR in the treatment of diabetes mellitus (DM) by the methods of fetal (human and animal) tissue transplantation (FTT).

Transplantation of human and animal fetal pancreatic islet cells (PIC) is a particular case of FTT, and studies carried out in the CIS and other former Soviet republics have contributed to the development of this method [15,26,34,39,40].

As early as in 1901 in the Dissertation "The Morphology of the Pancreas after Ligation of Its Duct in Diabetes and under Some Other Conditions" the Russian pathologist and anatomist L. V. Sobolev theoretically substantiated the value of organotherapy in DM [36]. He reached such a conclusion from his own experimental findings demonstrating that the pancreatic islets of Langer-

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