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EXPERIENCE IN THE CONSERVATION OF HUMAN FETAL SKIN FOR SURGICAL THERAPEUTIC TRANSPLANTATION

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/This is a communication from the First Faculty Surgical Clinic, Omsk Medical Institute imeni M. I. Kalinin. (The director of the clinic is Prof M. S. Rabinovich.)/

In the treatment of wounds difficult to heal and other injuries involving skin damage, autoplastic transplantation of skin is a standard procedure. When the first autoplastic transplantation is unsuccessful, it is often difficult to find an additional supply of skin for a second operation of the same type. As far as homoplastic transplantation is concerned, it can occasionally be carried out with connective tissue (fibrous connective tissue, tendons, cartilage, and to some extent bone). Homoplastic transplantation of skin, on the other hand, usually leads to failure if the skin of adults is used. However, a certain measure of success has been achieved by transplanting embryonal skin to adults (Murphy, Pokotilo).

Lately USSR surgeons have concentrated on transplantations of skin with the purpose of stimulating the recuperative capacity of the patient's organism. Homoplastic transplantations have begun to be used for the therapy of various pathological processes, including slowly healing skin wounds and ulcers. Although the homotransplants usually perish in the process, they introduce into the organism during their temporary presence substances which stimulate regeneration and resorption, and thus expedite the healing of wounds.

At various times attempts have been made to utilize for therapeutic purposes products of tissue decomposition of dissolution of the type formed by the transplants. Particular attention was paid to embryonal tissue, which is exceptionally rich in stimulants of regeneration and cell growth. To such products belong histolysates, embryonal extracts and juices, and the embryonal emulsions and ointments proposed recently (1944) by Prof L. D. Gol'dberg of Tomsk. The actual introduction of tissue therapy must be credited to V. P. Filatov. In his therapeutic transplantations Filatov used extensively homoplastic tissue (including skin) which had been conserved by refrigeration.

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According to Filatov, biogenic stimulants are formed in this process of preservation. They support the life of tissues in unfavorable surroundings and stimulate regeneration processes in the patient's organism.

Filatov's tissue-therapy method has been supplemented by the work of Berdichevskiy, Skosogorenko, Krauze, Ratner, and others. It has found practical application in many USSR medical institutions and is considered to be an extremely effective medical method. Homotransplanted skin of live adults and corpses is usually not assimilated. Embryonal human and animal tissue (including skin) has a higher capacity for growth and regeneration and also exerts a stronger stimulating effect. However, it is being applied chiefly in the form of dead matter. We asked ourselves how whole, undamaged skin of unripe human fetuses (i.e., tissue which in its properties resembles that of embryos) would behave on homoplastic transplantation. From the theoretical standpoint, one must assume that such skin must have a better effect than adult skin which, although imperfectly assimilated, still heals on temporarily and exerts a stimulating action. We undertook our investigation to confirm this assumption.

We set ourselves the task of investigating the suitability of "embryonal" skin (actually fetal skin obtained from fetuses 3-9 months old) for effecti transplantations, of testing the possibility of preserving this skin, and of determining its properties as a material for plastic surgery in skin injuries as well as those in connection with its action as a biological stimulant in treating slowly healing wounds and ulcers.

We first carried out a small experiment on conserving the skin of animals. By conserving the skin of adult rabbits for 12 days in rabbit blood serum at a low temperature, we found that the skin is excellently preserved and remains alive. Such skin may heal on temporarily in subsequent autotransplantations and homotransplantations.

We decided to use conserved rather than fresh human embryonal skin in our transplantations for the following reasons. First, a Wasserman test must be carried out on the skin which is to be transplanted, and this alone necessitates storage for several days. Second, we kept in mind Filatov's thesis that conservation enhances the stimulating effect of the tissue. In addition, we wanted to find out whether the tissue's ability to heal on can be influenced by conservation.

We first tried to determine whether human embryonal skin stands conservation. We started with an investigation of the normal structure of the skin of human fetuses 3-9 months old. Embryonal skin for its investigation in the normal (as distinguished from the conserved) state was taken after preliminary treatment of it with an 0.5% solution of ammonia or with alcohol followed by rinsing with a physiological NaCl solution. The same treatment was applied in preparing the skin for conservation. After fixation with 10% formalin, the skin was covered with celloidin. Staining of the sections was carried out with hematoxilin-eosin by van Gieson's method.

The skin of human fetuses differs considerably in structure from that of adults. In the first 2 months of life, the human embryo's skin is a thin epithelial covering consisting of two layers of cells. This covering adjoins the underlying connective tissue in a straight plane devoid of nipples. During the first few months of the embryo's life, the skin is a gel-like mass containing a large number of round cells. Later these cells are transformed into spindle-shaped cells. As the fetus develops further, gradual thickening of its epithelial cover takes place at the expense of growth of cells of the lower epithelial layer and gradual pressing out of the newly formed cells to the surface. The cells transferred to the surface gradually flatten out, but do not at first undergo cornification, which begins only with the second part of the embryonal life. The whole skin of human fetuses up to the age of 4 months is very thin, reddish, and translucent, so that the well-developed network of blood vessels can be seen

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through it. At this period of life, there are neither sweat nor fat glands nor hair in the skin of human fetuses. Hair begins to develop at the age of about 4 months by energetic multiplication of cells in certain regions of the epidermis and reaches the surface of the skin on the fifth month of life in the womb. At the same time, sweat and fat glands and skin nipples begin to form, and cornification begins in the upper epidermis layers. The skin loses its gel-like quality, becomes more dense, and gradually begins to resemble the skin of adults in appearance and structure.

Taking into consideration the peculiarities of this young, undeveloped human skin, which forms in the period of intrauterine life in a moist and warm medium, and is tender, of loose consistency, and without a well-developed horny layer on the surface, we decided not to conserve it in the dry state, but rather in blood plasma at plus 5-7°. However, for a number of technical reasons, principally the absence of a refrigerator at the hospital, we frequently carried out the conservation at a higher temperature (as high as plus 10-15°), particularly in the summer.

We received from the Obstetrical Clinic of the Omsk Medical Institute fresh corpses of fetuses which had recently died. We applied the following technique in isolating and conserving the skin. The skin was taken during the first 24 hours, or, if possible, even during the first few hours after death. In individual cases, the skin was taken at the end of the second day, provided the dead fetus had been kept at a low temperature during the whole time. The results of the macroscopic examination of the fetus were recorded. The blood type of each fetus was determined.

The skin was isolated under sterile conditions. It was treated by a careful rubbing with alcohol or a 0.5% solution of ammonia; it was then rinsed with a physiological salt solution. The whole thickness of the skin was taken without the subcutaneous cellular tissue in strips 3-4 cm long and 1½ cm wide. The pieces of skin were placed in sterilized glass flasks containing blood plasma. The flasks were closed with dense absorbent cotton-gauze stoppers and put into an ordinary refrigerator. Conservation of the skin was carried out in plasma of the same type or of a different type (compatible or incompatible) with reference to the blood type of the fetus. Only in individual cases did we attempt conservation in a physiological solution or in the dry state. The pieces of skin kept in the refrigerator were inspected daily. During these inspections, all visible macroscopic changes were noted and samples for histological examination were taken at various times. For comparison, fresh, unconserved skin of the same fetuses was used. Altogether, 138 pieces of skin after various periods of conservation (up to 30 days) and from fetuses of various ages were submitted to microscopic examination. More than 1,850 sections were examined. The pieces of skin under investigation were treated with 10% formalin, covered with celloidin, and stained in sections with hematoxilin-eosin by van Gieson's method.

On the basis of our investigation we concluded that skin obtained from human fetuses at an age as young as 3-4 months can be conserved without inflicting mechanical damage, notwithstanding the fact that this skin is thin and tender. Embryonal skin stands well treatment with alcohol and 0.5% ammonia. After this treatment, it becomes aseptic to an extent which is quite sufficient for purposes of conservation. Embryonal skin may be taken not only during the first hours, but 1-2 days after the death of the fetus if the dead fetus has been preserved in the cold. Plus 5-7° is a temperature which must be regarded as sufficiently low for conservation purposes under our experimental conditions. It is also possible to preserve embryonal skin for a short time at a higher temperature reaching a maximum limit of plus 9-10°. A temperature still higher than this limit, although it has been applied, was found to have a deleterious effect on the skin being conserved. A temperature as high as this favors the appearance of degenerative changes and expedites the development of a minimal infection, which in all probability is introduced with the transplants into the conserving medium.

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Embryonal skin is equally well preserved in plasma from blood of the same type as that of the fetus and blood which, although of another type, is compatible with that of the fetus. When pieces of embryonal skin are kept in plasma from blood of a type which is incompatible, the embryonal skin apparently perishes earlier. After being conserved for 7-8 days in this manner, the skin exhibits loss of plasticity, flabbiness, and a pale color. Later, the skin perishes, in some cases under formation of what clearly appear to be foci of aseptic necrosis. To draw definite conclusions on this point, further observations will be necessary.

The transfer of pieces of living embryonal skin into blood plasma for conservation can be regarded as a transplantation of the skin into a liquid medium. It is true that there is a sharp lowering of vital functions in the piece of skin thus transplanted. In such transplantations the surviving skin itself rather than the plasma takes up from the surrounding medium the small quantity of material required for survival.

In any event, the piece of living tissue being conserved is exposed to the complex influence of the surrounding medium, the blood plasma. The fundamental biochemical properties of the blood plasma consequently are not unimportant from the standpoint of their effect on the tissue being conserved. For this reason, blood plasma which is compatible with the tissue must be selected.

For convenience, it is best to use plasma of the I(0) type. It is desirable to keep the embryonal skin in the same plasma during the whole period of conservation. If this period is very long and the plasma becomes turbid it is permissible to change it carefully. Conservation of skin in the dry state can be carried out for short periods (not exceeding 1-2 days) only. After this, transfer into blood plasma must follow. Longer storage in the dry state leads to rapid loss of elasticity by the embryonal skin. Flabbiness and (apparently) earlier deterioration also ensue.

Conservation in a physiological NaCl solution is not expedient, because sharp swelling of the tissues and loosening of the skin epidermis set in rapidly. Sterile pieces of embryonal human skin can be preserved for 2-2½ weeks without losing the shape, color, or elasticity of their tissues, if kept in compatible blood plasma at a low temperature and without access of light. If conservation is carried out for longer periods, there is gradual loss of elasticity, loosening, and increasing peeling off of surface layers of skin epidermis, so that visible white flakes appear in the conserving plasma. Histological examination of conserved embryonal human skin showed that microscopically discernible changes usually appear in it at the end of the second or the beginning of the third week of conservation and affect primarily the skin epidermis. (In connection with the histological examinations, all our preparations and records were checked by Prof I. S. Novitskiy, head of the Chair of Pathological Anatomy, Omsk Medical Institute.)

Degeneration usually starts from the surface epidermis layers, so that they are transformed into a structureless homogeneous or fibrous mass. The dead cells of these layers either remain connected with the remainder of the epidermis, or become detached (peel off) in scales or plates. The deep layers of the epidermis are preserved longer and better than that. The cells of the basal layer of epidermis remain unaffected for a particularly long time. In individual cases we found them well preserved during the whole third week of conservation. With longer periods of conservation, or sooner than that when conditions of storage are unfavorable (for instance, when the temperature is not low enough), the total epidermis perishes and becomes detached as a whole.

The connective tissue part of the embryonal skin with all rudiments of hair, sweat glands, fat glands, and blood vessels contained in it is preserved considerably longer and better than the epidermis. Even after deterioration and separation of the total epidermis, the connective tissue in skin conserved for as long as 17-22 days may remain almost unchanged.

The subcutaneous cellular tissue, together with its fat particles, is well preserved in the process of conservation. Nevertheless, degenerative changes, as well as swelling and foci of necrosis, appear sooner and easier in it than in the skin itself.

All degenerative changes mentioned above that appear in conserved embryonal human skin, particularly in the first stages of conservation, bear, to a greater or lesser extent, a focal character. Together with areas which undergo change, unchanged, well-preserved areas also occur. All phenomena of degeneration noted above develop during the conservation of the skin of human fetuses irrespective of the age of the fetus. The time when these phenomena appear and their intensity depend to a great extent on the conditions of conservation and only to a small extent on the individual peculiarities of the fetal skin.

In a number of cases where considerable deficiencies in the conditions of conservation exist (such as an unsteady temperature of conservation which is not low enough, late placing of pieces of skin into the plasma, transference of pieces of skin from one vessel into another, etc.), embryonal human skin is still preserved well, showing its considerable stability and vitality. Summarizing the results of our macroscopic and microscopic observations, we conclude that under our experimental conditions embryonal human skin does not change perceptibly and remains suitable for transplantations during 2-2½ weeks of conservation. Even when degenerative changes start in the conserved embryonal skin, with the result that its surface layers deteriorate, connective tissue with the hair follicles and glands included in it remains intact. The basal cells of the epidermis also remain unaffected in spots. The preserved part of embryonal skin which remains is perfectly suitable for clinical use.

It is possible that in subsequent investigations more favorable conditions for the conservation of embryonal human skin will be found. By using another medium for conservation and finding a better storage temperature, it may be possible to extend the maximum period during which the conserved skin can be utilized. From a purely practical standpoint, we consider our results adequate as far as applications in clinical medicine which involve transplantations and require healing-on of the transplants are concerned. The skin is preserved sufficiently long and dies only gradually when stored for an excessive period of time. This conclusion is borne out by results obtained from actual clinical transplantations which we made on patients, using skin which we had conserved as described.

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