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Transplantation of foreign tissues

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THE TRANSPLANTATION OF FOREIGN TISSUES

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INTRODUCTION

If the transplantation of tissues between different individuals could be accomplished with a degree of success approaching that attained with autografts, the clinical uses of such a procedure would be of great scope. For example, a cure for all the endocrine deficiency diseases could be obtained, and possibly damaged organs, such as the kidney in Bright's disease, could be replaced (Stone, 1942).

As will be seen, foreign grafts in man seldom function for more than three or four weeks. The main purpose of this paper is to investigate the causes for their almost universal failure, and to consider methods of overcoming the obstacles.

There is often some confusion concerning the terminology for the various types of transplants. Those in most common use are as follows: Autotransplants--the same individual acts as both host and donor; syngenesiotransplants--host and donor are blood relatives; homografts--host and donor belong to the same species (also called isografts); heterografts--host and donor are of different species. We shall use the term "transplantability" to denote the degree to which a given tissue survives following transplantation.

I. HISTORICAL REVIEW

When plastic surgery began to be practiced in Italy during the Renaissance, little distinction was made between the use of autogenous and foreign tissues in the repair of defects. The best known plastic operation of this period was rhinoplasty, due to the frequency with which noses were severed in duels.

The standard autoplastic method of repair, while yielding excellent results, was inconvenient and painful, so that frequently tissues from other individuals were used. It was evidently not difficult to find some hardy person who, for a price, was willing to go through the formidable procedure of parting with a sufficient quanity of his skin to fashion a new nose. Tagliacotus, Dzondi, and other famous surgeons of the time performed this operation (Freeman, 1912; Updegraff, 1939). (Koch in 1941 states that although Tagliacotus discussed the question of the homoplastic operation, and believed that it would be satisfactory, he never actually performed it.)

Strangely enough, it was thought by many that the graft would survive for as long a time as the donor lived, when it would fall off. This belief was the inspiration for the well-known poem of Butler, written in 1710:

"So learned Tagliacotus, from
The brawny part of a porter's bum
Cut supplemental noses, which
Would last as long as parent breech;
But when the day of Nock was out,
Off dropp't the sympathetic snout."

Little advance was made in the knowledge of this field until Thiersch and Ollier, in the second half of the nineteenth century, noted that autotransplantation succeeded best, and suggested that this might be due to differences in chemical constitution between the tissues of host and donor.

Homoplastic skin grafts taken from the cadaver were first used by Girdner, and subsequently by other surgeons a few years later (Girdner, 1881). This type of skin grafting continued to be employed for many years by Fowler(1889), Davis (1909, 1917), Freeman (1912) and others, but gradually the feeling that they were not entirely satisfactory became manifest.

Alexis Carrel, in the years between 1906 and 1912, experimented with the homogenous and heterogenous transplantation of organs other than skin, and introduced the method of uniting host and graft by vascular anastomosis. Although for a time his efforts seemed promising, in 1914 he was forced to conclude that "during the past few years it has been definitely established that ... homoplastic transplations, although the immediate results may be excellent, are nearly always ultimately unsuccessful; and that heteroplastic transplantations are always unsuccessful".

This gloomy view has since been strengthened in the minds of surgeons. McWilliams in 1924 stated that "reports of success (with homografts) may be relegated to mythology", and modern textbooks (see Webster, 1942) are of the same opinion. Thus, although the future possibly holds out some hope, the indications are that the vision of replacing diseased structures with sound ones has reached the "nothing it set out from".

II. THE FATE, IN GENERAL, OF FOREIGN GRAFTS

A. Results in Mammals

1. Skin. Clinically, the vast majority of the work in this field has been confined to skin grafts. Gatch in 1911 reported a case in which both autografts and homografts were applied to the same individual; only the autografts took. Underwood (1914) noticed that skin homografts began to slough after about three weeks, and Lexer (1921) found signs of degeneration by the eleventh day, the grafts perishing completely in three weeks. Essentially the same results were obtained by McWilliams (1924), Coller (1925), Dobrzaniecki (1929), Bettman (1938) and Greeley (1939), although according to two of these authors (Coller and Dobrzaniecki) the grafts occasionally persist for as long as six or seven weeks.

Large series of skin homografts, all of them unsuccessful, have been reported by Padgett (1932), Brown and McDowell (1942) and Slaughter (1943). In Padgett's series, all grafts had separated by the 42nd day, most of them sloughing between the 14th and 28th day. In the cases of Brown and McDowell, none of the grafts persisted for more than 11 weeks, most of them beginning to disappear during the third week.

The survival period of foreign skin, short though it is, has been taken advantage of occasionally by surgeons. Thus, when a large amount of skin has been lost, homografting may be resorted to as a life-saving measure to cover the denuded areas and stimulate spontaneous epithelialization (Brown, 1937; Bettman, 1938; Brown and McDowell, 1942).

The use of preserved mucous membrane homografts has been advocated by M. Wiener (1943) for the repair of certain defects. The transplanted tissue is not a living graft, however; it merely acts as a temporary structure upon which the host's epithelial cells can build.

2. Cornea, lens, cartilage and fat. In the case of the cornea, homografts appear to be as satisfactory as autografts (Castroviejo, 1934; Thomas, 1937; Tizzard, 1937; Leahey, 1943). Filatov (1937) has reported several cases of corneal transplantation from the eyes of cadavers, which were functioning well after periods of from two to six years. In experimental animals, homotransplantation of the lens is also successful (Fleisher, 1921). However, heterotransplantation of neither cornea nor lens is permanent.

When cartilage and fat tissue are homotranspanted, the graft is largely preserved, and the perichondrium may even proliferate to form new cartilage at points where it was cut. Heterotransplants, however, provoke a connective tissue and lymphocytic reaction on the part of the host, and necrosis is usually complete within four weeks (Loeb, 1926).

Dupertuis (1941) found that homogenous rabbit cartilage grows almost as well as autogenous when taken from young animals. Homoplastic cartilage from adult rabbits did not grow in his experience.

Clinically, Peer (1939) was not satisfied with the results in using preserved homogenous cartilage grafts, but Brown (1940) believes them to have some value, although he prefers autografts. O'Connor (1940) claims excellent results with homoplastic cartilage grafts which have been preserved by refrigeration.

The abnormally long survival period of lens, cornea and cartilage is due, according to Sir Harold

Gillies, to their relative avascularity. Loeb (1930) believes that cartilage may be protected by the mechanical resistance it offers to connective tissue and lymphocytes, and he also suggests that cartilage and fat may exert less attraction to lymphocytes than do other tissues. Living or dead heterogenous cartilage may, however, provoke a marked tissue reaction (Loeb and Harter, 1926).

The protection of the lens by its capsule is probably an important factor in determining its transplantability. Blumenthal (1939) found that when the entire lens, intact in its capsule, was homotransplanted, the host's lymphocyte count increased 6.5%. However, when the whole lens was crushed before transplantion, the lymphocyte count increased by 16.5%. The decapsulated crushed lens caused a 17.9% increase.

Young (1941) points out that cartilage requires very little sustenance; consequently, degenerative changes take place slowly even in unfavorable media.

3. Bone. Homogenous and even heterogenous are used in orthopedic surgery, with results often approaching those obtained with autoplastic bone (Esnaurrizar, 1940; May, 1941; Inclan, 1942). A graft of this type, however,

merely acts as a foundation upon which new bone can grow, and does not itself remain alive.

4. Muscle. In the rat, Elson (1929) showed that while autotransplanted striated muscle was still well preserved after 118 days, it never survived more than 50 days following homotransplantation.

5. Nerve. The transplantability of ganglion cells is probably quite low, although there is little direct evidence on this point (Clark, 1942). Nerve fibers, however, can grow to some extent in a foreign host. Morpurgo in 1923 showed that, when two animals are joined together parabiotically, it is possible for a peripheral nerve to grow from one to the other partner, and to innervate muscle and connect with skin in the strange individual.

Fresh or preserved homotransplanted segments of peripheral nerves may be used to bridge traumatic gaps in the nerves of the host (Young, Holmes and Sanders, 1940; Sanders and Young, 1942; Weiss and Taylor, 1943). The last-mentioned authors have learned that lengths of nerves preserved by freezing and drying may find considerable use in the repair of war injuries. These do not survive for long, but function in the same manner as the bone grafts already considered; the foreign nerve serves only as a structure through which the host's fibers can grow.

6. Endocrine glands. The results of endocrine transplantation are contradictory. In evaluating the reports, especially on the clinical side of the subject, it is well to keep in mind the fact that hypertrophy of ectopic endocrine tissue, psychic effect on the patient and the zeal of the investigator may combine to paint a falsely optimistic picture.

Testis. Lydston in 1915 had encouraging results with the homotransplantation of testes in fowls. Richter (1928) noticed slightly better results in rats when he used the testes of very young animals rather than those of adults. In one of 19 females and five of 17 males, survival of the transplants was proved by histological examination 50 to 100 days later.

Morris in 1914 reported a case of homogenous testicular transplantation into a man whose testes had been removed ten years previously following trauma. He grafted segments of testis into the abdominal muscles, and the patient experienced a remarkable return of virility, which was still present after five months. Lydston (1916, 1919) had three similar results, with evidence of gonadal function persisting throughout the time the patients were under observarion (five months in one case and seven months in the other two cases).

In 1924 Voronoff made extravagant claims for the ability of testicular heterografts to increase virility and prevent senescence. He grafted sections of testes from the chimpanzee or baboon into the scarified tunica vaginalis. The only value of such a procedure is, in all probability, a psychic one. Belfield (1924) states that the homotransplantation of testes into young animals or men often gives a good functional result for a few months, but that the grafts are eventually replaced by connective tissue. In old animals or men the results are rarely even this good. The weight of evidence is in agreement with Belfield's view.

Ovary. Wang, Richter and Guttmacher (1925) were successful in 17 of 24 attempts to transplant ovaries from female rats into castrated male littermates. They cut each ovary into four or five pieces, which were implanted in the rectus muscle of the host. The animals were killed after periods ranging from 43 to 85 days, and the transplants were examined histologically. Pfeiffer (1936) transplanted ovaries to male rats, with functional takes for at least seven months.

Solomons in 1931 transplanted a segment of ovary from one woman into the rectus muscle of another. After a month menstruation, which had been absent before the operation, occurred. The graft was still apparantly functioning after six months. H. Zondek (1935) reports a similar case in which a woman whose ovaries had been removed several years previously was cured by the homotransplantation of ovarian tissue.

Adrenal. Even following autografting, the adrenal does not function as well as the undisturbed gland (Wyman and Suden, 1942). Concerning homotransplantation, H. Zondek (1935) states that, although regeneration may take place for a time, absorption usually occurs soon. R. Loeb (1941) says that "efforts have not met with success, and the procedure is not to be recommended". Nevertheless, there are some reports of successes.

Elliott and Tuckett (1906) attempted to transplant homoplastically adrenal glands, which had been cut in half, into the subcutaneous tissues of guinea pigs. In all cases an intense reaction occurred, causing necrosis of the transplant. In 1927 Jaffe compiled evidence to indicate that this reaction occurs in auto- as well as in homografts, and is due to irritation by epinephrine. He showed further that if all medullary tissue is carefully removed, and the cortex divided into small particles, the cortical fragment survives autografting. Homografting, according to this author, may also be successful. In four of 15 rats, examined one month after homotransplantation of adrenal cortex, living grafts were found.

Wyman and Suden (1932) transplanted rat adrenals into the abdominal muscles of other rats, which had previously been suprarenalectomized. The host animals were killed 81 to 126 days later, and in all cases regeneration and function of the transplanted cortex was still present. When both autogenous and homogenous suprarenals were transplanted into the same rat, the homograft survived approximately as well as the autograft until the time of death 87 to 121 days later.

Heterografts (mouse to rat, rabbit to rat and guinea pig to rat) never survived.

Higgins and Ingle (1938) and Wilder (1938) report a large percentage of survivals in the homografting of adrenal cortical tissue from the newborn to the adult rat. Turner, Haffen and St. Amant(1939) and Dunphy and Keeley (1940) claimed successful homografts of cortex and, in a certain number of attempts, of medulla. The former authors used the space between the kidney and its capsule, and the latter used the ovary as the site of implantation. Turner (1939) also states that adrenal medullary tissue may survive.

A total of nine cases have been reported by Hurst, Tanner and Osman (1922), d'Abreu (1933), Beer and Oppenheimer (1934), Baily and Keele (1935, 1939), Goldzieher and Barishaw (1937), Katz and Mainzer (1941), Thiersch (1943) in which transplantation of adrenal cortex apparantly caused clinical improvement in cases of Addison's disease. In each case, the symptoms were relieved wholly or partially for as long as the patients were observed. These results are summarized in Figure 1. Auslander in 1938 claimed to have successfully transplanted adrenal

AUTHOR	TIME OBSERVED	SOURCE	TECHNIQUE	PROVED BY AUTOPSY
Hurst, Tanner & Osman	10 mos.	Fetus--Stillborn	Into Testis	No
D'Abreu	5 mos.	Kidney Operation	__________	No
Beer & Oppenheimer	14 days	Adult	Small Pieces Into Rectus	Yes
Beer & Oppenheimer	5 mos.	Adult	Small Pieces Into Rectus	No
Bailey & Keele	4 yrs.	Fetus--Stillborn	Into Rectus	No
Goldzieher & Barishaw	9 mos.	Case of Hypercortical Syndrome	Thin Slices Into Rectus	Yes
Katz & Mainzer	15 mos.	Adult Cadaver	Into Abdominal muscles	No
Thiersch	12 mos.	49 cm. Fetus & 30 cm. Fetus	Small Pieces Into Sternal Marrow	No
Thiersch		20 cm. Fetus & Full Term Fetus	Small Pieces Into Sternal Marrow	No

Figure 1. Human Adrenal Cortex Homografts which Caused Complete or Partial Relief of Symptoms of Addison's Disease.

cortex in 14 cases of Addison's disease but, unfortunately, his report is not available.

In addition to the tabulated results, some interesting and, perhaps, useful data were found. Thus Goldzier and Barishaw gave their patient pituitary corticotropic principle to stimulate the graft, a procedure which Turner (1939) also believes aids survival. Thiersch recommends multiple grafts, and he uses the bone marrow as the site of implantation because hypernephromas tend to metastasize to this location, and because of the simplicity of technique and good vascular supply afforded here.

Currie (1924) states that one of his patients with Addison's disease improved steadily for the three months she was under observation following subcutaneous administration of minced sheep adrenals. We may strongly question the fact that this heterograft really survived.

Pituitary. Wolfsohn (1942) has transplanted a total of 18 pituitary grafts from calves into patients suffering with various manifestations of hypopituitarism. In four of these, good results were obtained for periods of from several months to two years or more. Each gland was cut into four discs which were placed in a subcutaneous pocket.

Thyroid. Kocher (1923) has shown that, experimentally, homografts may take. He removed the thyroid gland from animals, waited for the development of hypothyroid symptoms, and then injected particles of homogenous thyroid into the bone marrow. This caused improvement of the symptoms. After a few months the grafts were removed, and myxedema again developed.

A total of 204 human hypothyroid patients were treated in the same way. In addition they were given thyroid extract for some time before and after the transplantation because, according to Kocher, if the need for thyroid is very great the graft is "eaten up". He claims that by this therapy 26% of his patients were cured, 60% were improved, and 14 % were not benefited. Loeb's thyroid homotransplants were less successful with experimental animals (1926) than were those of Kocher. This may have been due to the fact that Loeb's hosts were not adrenalectomized.

Parathyroid. Parathyroid transplantation as a treatment for hypoparathyroid tetany following a thyroidectomy was attempted clinically as long ago as 1911 by W. H. Brown. He tried heterotransplantation of ox and dog glands several times, each time with improvement for eight to 14 days. Monkey parathyroid transplantation improved the patient's condition until a homoplastic graft was implanted four weeks later. The patient was still much improved after this last graft had been in place for two months.

Eiselsberg (1921) also claimed some success with human parathyroid transplantations in which the grafts were obtained from stillborn infants.

Pancreas. Stone (1942) and Tuttle (1942) have expressed the belief that it may in the future be possible to treat diabetes by homoplastic transplantation of pancreatic tissue. However, in the only instance where this was attempted (Murray and Bradly, 1935) there was no change in the patient's disease. In experimental animals, Selle (1935) reports similar disappointing results.

Thymus. Homografts of thymus gland, implanted subcutaneously in rats, live for only a short period (Einhorn and Rowntree, 1938; Einhorn, 1938). Murray (1939) sets the average time of survival at one week, although, he says, it is occassionally considerably longer.

7. Kidney, liver, spleen and bone marrow. Carrel's experiments with homotransplanted whole kidneys, connected with the host by blood vessel anastomosis, will be discussed in Chapter IV. Suffice it to say at this point that the organs functioned for only a few days. This method has been put to use in the experimental study of hypertension, however, where much can be learned by studying homotransplanted kidneys which function well for a short time (Levy, Robinson and Blalock, 1938; Rodbard, Katz, and Sokolow, 1940; Prinzmetal and co-workers, 1940).

Implantation of liver, kidney and splenic tissue, grafted between rats, was found by Friedman and Marrus (1942) to live for two or three days. Murphy's experience with spleen and bone marrow transplanted into the chick embryo will be mentioned in Chapter III in more detail. In brief, his finding was that these tissues grow less readily than most. Bone marrow in tissue culture tends to revert to fibrosis after a time (Doljanski and Pikovski, 1941; Rachmilewitz and Rosin, 1934), and it seems reasonable to suppose that it would not function as myeloid tissue for long in a foreign host.

8. Blood vessels. Carrel (1908, 1910) transplanted both fresh and preserved arterial segments into gaps in

arteries of dogs, and in a high percentage of cases the repaired vessels functioned well over long periods of time. Borst (1913) stated that the transplants probably did not function as such, but rather were replaced by host tissue. According to Loeb (1930), thrombosis is more likely to occur at the junction of host and donor endothelium when homografts are used than in the case of autogenous arterial transplantation.

Blakemore, Lord and Stefko(1943) found that sections of arteries transplanted into dogs homoplastically survived for about 17 days.

9. Plasma clots. It is interesting to note that homotransplanted plasma clots, which presumably contain no cellular elements, have the same effect upon the differential leucocyte count of the host as do other homogenous tissues. However, following heterotransplantation they do not provoke the typical heteroreaction (Blumenthal, 1939, 1940).

B. The Influence upon Transplantability of Relationship between Host and Donor

It is a well established fact that transplantability increases directly with the closeness of genetic relationship between host and donor (Strong and Little, 1920; L. Loeb, 1930, 1937; Gorer, 1938; Blumenthal, 1941). In the case of inbred families of rats, mice and guinea pigs, homoplastic transplantation can be performed with results approaching those of autografts, provided the inbreeding has been carried out through a sufficient number of generations (Loeb and King, 1927; Loeb and Wright, 1927; Reed, 1938; Loeb, King and Blumenthal, 1943).

Reed found that, in such homogenous populations, skin syngenesiotransplants survive almost as well as autografts. Loeb and his co-workers were able to transplant thyroid gland, cartilage and other tissues freely between their highly inbred animals, with results only slightly poorer than with autografts.

Even in the case of non-inbred animals, Loeb (1926, 1927) has demonstrated that grafts of thyroid and cartilage have a somewhat higher degree of transplantability when host and doner are related. Transplantations between different varieties of the same species yield a still more intense reaction than do ordinary homografts, and heterotransplants are usually destroyed quickly by the host.

Clinically, homoplastic grafts, with the exception of those between monozygotic twins, have been demonstrated to yield only slightly better results when a blood relationship exists between host and donor. Skin grafts transplanted from mother to child (Brown, 1937) and from brother to sister (Gibson and Medawar, 1943) have been reported on in considerable detail, the results being almost identical with those of ordinary skin homografts. Padgett (1933), who reports eight cases in which homografting of skin was performed between close relatives, states that these syngenesiografts last a week or two longer than do the ordinary homografts.

When skin is transplanted between identical twins the result is quite different. Bauer (1928), Padgett (1932) and Brown (1937) report a total of six such cases, which were watched carefully for periods varying between two months and three years after the grafting. In each instance the same results were observed as with autografts.

C. The Histopathological Reaction about Foreign Grafts

The microscopic reactions which take place about the various types of grafts as described below, are taken principally from the works of Fleisher (1921) and Loeb (1930). In each case a small particle of thyroid gland implanted subcutaneously is taken as the example, although the results are the same with almost any tissue.

1. Autotransplants. The outer part of the transplant is well nourished and remains alive, while the inner portion becomes necrotic. Fibroblasts grow into this necrotic area and form loose connective tissue. Vessels gradually form until within three weeks the center consists of well vascularized connective tissue, with the surrounding acini well preserved. There may be a slight infiltration of lymphocytes, but these eventually disappear.

2. Syngenesiotransplants. These resemble autografts for some time. Finally, bowever, often as late as the 40th day, lymphocytic invasion begins, which is later accompanied by fibroblastic activity. Thus the graft is eventually destroyed.

3. Homotransplants. These differ from autogenous grafts in that here the fibroblasts grow in greater numbers into

the central necrotic part, and grow around the living acini of the peripheral zone to form a dense fibrous tissue, which causes shrinkage and obliteration of the acinar lumena by pressure. Fibroblasts may also invade the acini and destroy them directly.

On the seventh or eighth day there is an infiltration of the transplant by lymphocytes, which is much more marked than in the case of autografts. Also, there is much less vascularization than occurs in autogenous transplants. The homograft is usually completely destroyed in 20 to 30 days, but may be partially preserved for longer periods.

4. Transplantation into different varieties of the same species. Here the same results are seen as those which follow ordinary homotransplantation, except that the reactions are accentuated.

5. Heterotransplantation. The reaction is much more intense than in the case of homografts. Polymorphonuclear leucocytes, as well as lymphocytes, may collect. There is little or no regeneration, and complete necrosis occurs early.

D. Results in the Lower Animals

In the lower forms of animal life both homotransplantation and, occassionally, heterotransplantation are successful (Lewis, 1904, 1906-08; Harrison, 1924, 1933-34). However, as we progress up the scale, at about the level of the amphibians heterografts no longer grow in the foreign host, and the transplantability of homografts becomes progressively lower (Loeb, 1930).

It is interesting to note that, in animals where heteroplastic grafting can be performed quite satisfactorily, the host in certain cases may exert an effect upon transplanted anlagen which influences their develepement; while in the majority of cases the graft grows in an independent manner charactaristic of the donor tissue.

When limb buds are transplanted between Amblystoma punctatum and Amblystoma tigrinum (two types of salamander), the developement of the limbs takes place in a manner charactaristic of their developement in the donor, and is unaffected by the foreign host.(Harrison, 1924). The same is true of the eye (Harrison, 1933-34). In the case of the heart (Copenhaver, 1933), the size shows functional regulation by the host, but the rate remains the same as that of the donor's species. The gills show a slight amount of influence on the part of the host (Harrison, 1933-34).

III. A CONSIDERATION OF THE CAUSES UNDERLYING THE DISSOLUTION OF FOREIGN GRAFTS

At present there are two general types of theories concerning the mechanism of the interaction between host and foreign graft. The first of these explains the result as being due to a local fibroblastic and leucocytic found in the graft itself or in its immediate neighborhood (Murphy, 1913, 1914, 1926; Fleisher, 1918, 1921, 1922; Loeb, 1930, 1937). According to the second theory, resistance to foreign grafts is systemic and primarily humoral in nature. The latter is the more widely held today (Gibson and Medawar, 1943).

These two views should not be considered as entirely antagonistic, but rather as being complementary to each other. We know that both systemic and local reactions occur, so the problem resolves itself into the question: Which is the more important? These points, as well as other suggestions which have been proposed, will be discussed in the pages which follow.

A. The Athreptic Hypothesis

The first hypothesis proposed to account for the failure of homo- and heterografts was an extension of Ehrlich's side chain theory. Although it applied primarily to tumor transplantation, we shall see later that the same factors govern the transplantation of normal tissues. Ehrlich (1906) believed that tumor cells lack the proper receptors to combine with the food elements of foreign species, and die from lack of nourishment; enough specific food being carried along with the graft to account for its temporary survival.

Although we cannot entirely dismiss this theory, few biolgists now believe in it because of the fact that foreign tumors or normal tissues can survive for long periods of time in embryos or tissue culture, where they have no access to their specific nutritive substances.

B. The Theory of Local Reaction

The importance of lymphocytes in the host's reaction against foreign tissues has been emphasized by the following points: 1. While most tissues grow well in the chick embryo, spleen and bone marrow do not; the cells common to both are lymphocytes (Murphy, 1914). 2. There is a notable absence of round cells about heterotransplants in the avian embryo and adult mammalian brain, and foreign grafts grow well in these locations. Heteroplastic grafts do not survive, however, if the embryo or brain is supplied with lymphoid tissue (Murphy, 1926). (Bullock in 1915 observed that the presence of lymphoid tissue in the form of autogenous spleen grafts had no effect upon mouse sarcoma transplanted into the rat.) 3. Mouse and chicken tumors will grow in rats more easily after the lymphatic system has been largely depleted by heavy doses of X-rays (Murphy, 1926). 4. When autotransplanted lymph node and homotransplanted cartilage are closely approximated in the host, lymphocytes migrate from the lymph node into the cartilage (Crossen, 1928). 5. Lymphocytes practically always appear about the foreign graft and invade it (Fleisher, 1918).

Fleisher was impressed by the connective tissue reaction about the transplant. Loeb (1930), taking into consideration all these facts, as well as the influence of the relationship between host and donor upon the severity of the reaction, accounted for all the observed phenomena as follows:

All, or almost all, of the tissues of an individual have in common certain chemical charactaristics which differentiate this individual from all others in the species. These qualities Loeb calls individuality differentials. Similarly there are generic and species differentials, which separate the members of a genus (or species) from those of all other genera (or species). The term organismal differential has a broader significance, denoting the difference between the tissues of one individual and those of any other individual, whether of the same or different species.

These differentials are dependent upon the chromosomal makeup of the cells of the body, and are inalterable. Between monozygotic twins they are identical; between the members of closely inbred strains they differ but slightly; between less closely related individuals they differ to a greater extent, etc.

Transplantability depends on the totality of genes present in donor and host, and the relation of the two sets of genes to each other. The greater the number of strange genes in the donor, and the greater the degree of strangeness, the more severe is the reaction of the host against the transplant.

Following transplantation into a foreign host, the organismal differential of the transplant, either directly or after interaction with the body fluids of the host, becomes transformed into homotoxins or heterotoxins, depending upon whether host and donor belong to the same or to different species. These toxins attract lymphocytes and stimulate fibroblasts to greater activity. Vascular supply is diminished, lymphocytes invade and destroy the graft, and the fibroblasts form an excess of fibrous tissue which largely replaces the graft.

The organismal differentials, as well as the ability to react to strange differentials, are not fully developed in the lower animals; and in mammals they do not make their appearance in any individual until a late embryonic stage. It is likely that the more primitive differentials, such as the class and generic differentials, develope before the species and individuality differentials.

C. The Theory of Systemic (Immune) Reaction

In the field of cancer research, where homotransplantation of tumors is frequently performed, it has long been known that a transplantable tumor can be rendered non-transplantable if the host animal is first immunized by innoculation with a suspension of the living tumor cells (Tyzzer, 1916). The same effect is obtained if the graft follows a previous successful transplantation of the same tumor to the host (Bittner, 1936). According to Tyzzer (1916) the aquired immunity against a given tumor depends upon the degree of foreignness between it and the host, which in the case of homografts is not sufficient for the production of markedly cytotoxic or cytolytic sera.

The presence of the transplant causes an immune body to be formed by the host which, coming in contact with the antigen (foreign tumor), excites an inflammatory reaction in the tissue about the graft, so that it is isolated and eventually destroyed.

Fichera (1909) and Rous (1910) showed that, as in the case of tumors, an immunity could be built up against normal embryonic tissues in adult hosts. Schoene in 1912 transferred the immunity theory from the transplantation of tumors to that of normal tissues, whether adult or embryonic. Since that time it has been quite definitely proved that the resistance to homo- or heterotransplanted tumors is directed against the foreign cells irregardless of their malignant character (Phelps, 1937; Gorer, 1938; Eisen and Woglom, 1941; Spencer, 1942; Harris, 1943).

For example, Phelps showed that a certain anti-rat sarcoma serum would kill both sarcoma cells and normal spleen cells, and that the corresponding anti-spleen serum also killed both. Similarly Harris found that the serum of rats repeatedly innoculated with mouse sarcoma contains factors cytotoxic to cultures of normal mouse tissues as well as to cultures of the tumor cells.

According to Spencer (1942), immunity against a homoplastic graft is called forth only by living cells. This is in accord with the findings of Siebert (1928), who discovered that the typical reaction against a homotransplant does not occur when the graft has been previously killed by mild degrees of heat. Heteroplastic tissues, however, can elicit the heteroreaction even after they have been killed.

That the immune bodies circulate freely in the body fluids of the host has been demonstrated by Cloudman (1943) and Harris (1943). They showed that when inbred mice are joined together parabiotically, innoculation of a tumor into one partner caused the formation of an immunity to that tumor in both. This seems to be not entirely in agreement with Woglom's statement that this immunity is not passively transferable through the body fluids (1929).

Both in vivo experiments (Tyzzer, 1916) and tissue culture methods (Harris, 1943) indicate that the antibodies formed against homoplastic tissues cause the death of the transplanted cells only indirectly. Heteroplastic grafts call forth definitely cytotoxic antibodies.

Desensitization of an animal immunized against normal homogenous cells has been demonstrated by Bisgard (1938). He found that he could build up an immunity against homotransplants of rabbit thyroid gland by the injection of donor's blood into the recipient, by the injection of extracts of donor tissue into the recipient, and by the injection of recipient's blood into the donor animal some time previous to the operation. When these injections were continued for three weeks or longer, desensitization occurred, following which the transplantability was approximately equal to that seen in animals which had never been immunized.

Acquired immunity against homoplastic skin grafts has been noticed in man on several occassions. Thus Holman (1924) observed that local and systemic reactions followed subsequent homografts after the first one was in place. The reactions subsided upon removal of the foreign grafts. Gibson and Medawar (1943) noticed that, while a first set of homografts survived and even showed regeneration for about ten days, a second set, applied 15 days later, began to degenerate immediately. The results of Pickrell (1943) were essentially the same; in a large series of patients second homografts, applied after the hosts had destroyed the first, became necrotic more rapidly than did the first.

Another phase of the systemic reaction is the effect upon the differential leucocyte count of the host. Homografts provoke a rise in the lymphocyte count of from 10% to 20%, and heterografts cause the polymorphonuclear count to be increased by approximately the same amount (Blumenthal, 1939). A subsequent graft following the initial one causes the leucocytic response to occur from two to four days earlier, but the rise in lymphocytes or polymorphonuclears is less marked. This effect of a previous graft is specific in that it becomes manifest only when the first and second transplants are both homoplastic or both heteroplastic (Blumenthal, 1941).

The antigens responsible for the reaction about a foreign graft may be contained in the substances found by Furth and Kabat (1941) and Henle, Chambers and Groupe (1941). These materials are sedimentable at high speeds, and are found in all normal and neoplastic tissues. They are carriers of the Forssman antigen and Wasserman hapten, and exhibit species, organ, and individual specificity.

D. The Blood Group Theory

In the past it was believed by many surgeons that homoplastic grafts could be successful if host and donor were of the same blood group (Davis, 1917; Masson, 1918; Shawan, 1919; Hoguet, 1920; Baldwin, 1920; Dyke, 1922; Neuhof, 1923). Although this supposition for a time appeared convincing, it has failed to pass the acid test, at least insofar as skin grafts are concerned. It has been quite conclusively shown that skin homografting between persons of compatible blood groups is no more successful than transplantation performed without regard for blood compatibility (McWilliams, 1924; Holman, 1924; Coller, 1925; Blair and Brown, 1929; Dobrzaniecki, 1929; Trusler and Cogswell, 1935; Brown and McDowell, 1942; Gibson and Medawar, 1943; Sachs and Goldberg, 1943).

In 26 of the cases of Brown and McDowell, even the M and N groups of host and donor were similar, but this had no effect upon the outcome.

From these data it might seem justifiable to conclude that the group-specific substances of the blood are not the factors responsible for the failure of foreign grafts to survive. However, we must consider the fact that, by simple immunity reactions, the red blood cells of an individual can be distinguished from those of other individuals in the same species (Todd, 1930; Landsteiner, 1931). Similarly, there are antigenic differences in the sera of individuals of any given species; the serum of one individual can be distinguished from that of any other (Cumley and Irwin, 1943).

Furthermore, it has been shown that the division of human beings into the various blood groups is not limited to the blood, since group-specific substances A, B, M, N and Rh are present in the cells of almost every organ in the body, as well as in the body fluids of most individuals (Landsteiner and Levine, 1926; Boorman and Dodd, 1943).

We may dismiss the possibility of the main blood groups or sub-groups being of any importance in homotransplantation. It has been pointed out by Loeb (1930) and Padgett (1933) that similarity between host and donor in this respect is not even theoretically important as a guide to the determination of transplantability. According to them, the factors causing the disharmony depend upon nearly all of the genes, while the blood groups are determined by only a few.

However, the finer individual specificity of the erythrocytes and blood serum is another matter. When we couple this with the fact that Blumenthal (1941) found plasma clots capable of provoking a typical homoreaction, it would seem likely that blood, as well as other tissues, contains the factors responsible for the failure of foreign transplants.

Why, then, is blood so readily transplantable? There are three possible answers. First, the individual specific substances of the blood are not those which are responsible for the foreign-tissue reaction. This seems unlikely in view of what we have just seen. Second, the transfused cells do not live long enough to cause a homoreaction; or else they do cause the reaction and are thereby destroyed. This cannot be true, as the life of transfused red blood cells is easily long enough to provoke the reaction. Various investigators have given their life span in a foreign host as follows:

Ashby (1919)---30 days or more
Wearn, Warren and Ames (1922)---59 to 113 days
Landsteiner, Levine and Janes (1928)---49 days or more
Wiener (1934)---80 to 120 days

Dacie and Mollison (1943)---100 to 130 days
Any one of these estimates would allow ample time for the homoreaction to develope.

Third, due to their position in the circulation, which is isolated from fibroblasts, compatible homogenous erythrocytes are incapable of being destroyed by the host. This appears to the writer to be the most likely explanation. We have already seen that homogenous cells do not call forth markedly cytotoxic or cytolytic sera from the host, and that fibroblasts are intimately concerned with the homoreaction.

IV. FACTORS INFLUENCING TRANSPLANTABILITY

A. The Embryo as Host and as Donor

1. The embryo as host. Embryologists have known for many years that in the lower vertebrates foreign tissues can grow well during early developemental periods of the host (Harrison, 1933-34). Born in 1896 found that parts of embryos of different species, even as diverse as frog and toad, could be united to form single individuals capable of continuing their normal developement. Lewis performed the same type of experiment, using frog and tadpole embryos (1904) and frog and salamander embryos (1906-08).

Murphy (1912, 1914) showed that, on the chorioallantoic membrane of the chick embryo, all tissues grow well whether they are embryonic or adult, of the same or of different species. He also found (1913) that shortly before the time of hatching degeneration of the transplant begins. These results have since been verified by a number of other investigators (e. g. Strong, 1926; Sandstrom, 1932). Goodpasture, Douglas and Anderson (1938) were able to culture human skin in the same manner for ten days, and suggested this as a method for preserving skin prior to transplantation.

In tissue culture, comparable results are obtained. Cultures of chicken fibroblasts in extracts of homogenous or heterogenous tissues grow well for a time, but ultimately die. Those grown in embryonic juices, on the contrary, are capable of living indefinitely provided the medium is changed often (Carrel and Ebeling, 1923; Carrel, 1938).

Following birth, it appears that the age of the host has little influence (Woglom, 1929). However, Little (1920) obtained slightly better results in transplanting tumors into mice under ten days old than into older animals, and Loeb (1930) states that homotransplantation of normal tissues into guinea pigs elicits a less marked reaction when the hosts are less than ten days old.

2. The embryo as donor. Under the conditions of transplantation, embryonic cells are not controlled by the same factors which ordinarily influence them, and potentialities which would normally remain latent may be realized (Maximow, 1925). Grafting with embryonic tissues should be expected to yield better results than adult transplants because, as Bloom (1937) has pointed out, during the developement of the latter its cells have

lost most of their powers of multiplication and of adaptation to a new environment.

In 1929 Ide injected minced tissues of embryonic mice into adult animals. The homogenous cells grew rapidly, and in some instances attained a weight of 25% to 33% of the host's body weight. During the first 50 days following inoculation, cartilage grew faster than all other tissues. After a year this decreased, and growth of the epithelial elements predominated.

Willis (1935) implanted embryonic homografts into the brains of rats by means of a spinal needle. Tissues taken from half-grown embryos survived almost uniformly, the rate of growth being approximately the same as would have occurred if the tissue had been still a part of its original organism. The rats were killed after periods varying between four and 13 weeks. Upon examination it was found that cartilage, bone, bone marrow, epidermis, mucosal epithelium, teeth, salivary gland and skeletal muscle all grew and differentiated well. Transplants from old and very young embryos grew less readily than those of embryos intermediate in age. In 1939 the same author was successful, in most instances, in transplanting the above tissues subcutaneously.

According to Oppenheimer (1939), all embryonic stages of fish embryos between the blastula and hatching stage can develope normally after implantation into an amphibian host. Green (1941) found that embryonic tissues homotransplanted into the anterior chamber of the eye grow much more rapidly than do adult tissues.

Holyoke (1940) transplanted tissues consisting of splenic rudiment together with dorsal mesogastrium, greater curvature of stomach and pancreas, from rabbit embryos of various ages into the omental bursae of adult rabbits. In most instances the tissues grew and differentiated quite well, depending upon the age of the donor embryo. However, when the transplants were left in the host for longer periods of time, signs of degeneration began to appear (Holyoke, 1943).

This is in agreement with Loeb's theory (1930) that embryonic tissues grow, after transplantation into another individual, only until their organismal differentials are developed sufficiently to call forth the reaction on the part of the host.

Survival of homoplastic human skin grafts from infant or embryonic sources was claimed by Kubanyi in 1924. McNealy cites the case of a man suffering from extensive skin loss, who was treated by the application of foreskins from infants and, later, homografts from his (the patient's) nephew. The grafts from the nephew soon melted away, but the foreskins remained.

Ashley (1937), using foreskins from the newborn, some of which had been preserved for two weeks by refrigeration, reported that in one case 19 of 27 and in another case two of four grafts survived. The 19 grafts of the first patient which did not slough were still present after seven to eight months. Sachs and Goldberg (1943) also claim excellent results with the grafting of foreskins from the newborn. In one of their cases the grafts were still in place after two years. These authors also used skin obtained post mortem from premature infants, which they found to be equally satisfactory.

Blumenthal (1941) discovered that heteroplastic embryonic grafts (mouse to rat) caused a lymphocytic increase in the host's differential leucocyte count. In the case of adult tissues, such a response is charactaristic of homogenous rather than heterogenous transplantation.

B. Tumors

Although the laws of transplantability govern tumors and normal tissues alike (MacFadyen and Murphy, 1939; Blumenthal, 1941), the transplantation of tumors from one individual to another is more easily carried out than is the homografting of normal tissues (Zondek and associates, 1942). Homo- and even heterotransplantation are frequently employed in the modern research on cancer. As an example, Edwards, Dalton and Andervont (1942) were able to transplant a spontaneously arising mouse hepatoma successively through several generations of mice, the growth rate being greater in the last host than in the first.

Even in the case of tumors, however, only a small percentage are transplantable to other animals, depending upon the genetic constitution of the animals involved and the type of tumor. According to Spencer (1942), growth of heteroplastically transplanted tumors occurs only when the transplantation is done between quite closely related species, or when the tumor is highly malignant. Strong (1926) believes that the growth rate of a tumor is not correlated with its transplantability.

C. Location in Host

In 1921 Shirai found that a certain rat sarcoma, which would not grow subcutaneously in pigeons,grew in nine out of 12 cases when transplanted into the brain. He was also successful in the heterotransplantation of rat sarcoma into the brains of mice, rabbits and guinea pigs. In confirmation of this work, Murphy (1923) and Gheorghiu (1926) determined that mouse tumors, which did not survive when implanted subcutaneously or intramuscularly into rats, would grow actively in the brains of these animals, but were destroyed if they came in contact with the ventricles.

In 1935 Willis was able to successfully transplant normal embryonic tissues intracerebrally. These same tissues were not transplantable subcutaneously or intratesticularly. Growth of long bones from cartilaginous rudiments was seen to take place at approximately the normal rate when homotransplanted into the brain (Willis, 1936, 1939). On the other hand, Lazarus-Barlow and Parry (1923) and Harde (1928) found the brain to react in the same manner as other host tissues to tumor homotransplants.

Loeb (1930) believes that foreign tissues grow better in the brain than elsewhere because in this location the species-specificity is not fully developed. Transplantability into the brain may be governed also by the so-called "blood-brain barrier". There is considerable disagreement as to whether or not the cerebral capillaries are permeable to antibodies (Friedeman, 1942).

In 1920 Schochet found the anterior chamber of the eye to be a favorable site for autogenous transplants, and since that time it has been used frequently in experimental work for the transplantation of foreign tissue. Goodman (1934) was able to transplant immature rat ovaries to this location in other rats, the grafts surviving for at least six months.

Bisgard (1938) had similar results with segments of thyroid and of uterine and ovarian tissue in the case of rabbit syngenesiografts which were observed for periods ranging from 42 to 166 days. He had almost as high a percentage of takes in grafts from Belgian hares to albino rabbits. Heteroplastic grafts (dog to rabbit and man to rabbit) did not survive.

Adrenal glands of rabbits (Turner, Haffen and St. Amant, 1939) and of guinea pigs (Schweizer, Charipper and Kleinberg, 1940) have been successfully homotransplanted into the anterior chamber of the eye over periods rang- from 59 to 156 days' observation. Breast and uterine rabbit tumors have been transferred heteroplastically in the same way to the eyes of guinea pigs, swine, goats and sheep by Greene (1940, 1941).

The probable reasons for the hospitality of the anterior chamber of the eye are that it does not allow much connective tissue invasion (Goodman, 1934; Bisgard, 1936) and serves as a good source of nutrition for the transplant.

The testis was found by Gheorghiu (1926) to be as favorable a location as brain for the heterotransplantation (mouse to rat) of cancer. We have already noted that homotransplants of embryonic tissue are less successful in the testis than in the brain (Willis, 1935).

D. Sex

Apparantly sex has practically no influence upon transplantability. A search of the literature reveals only two instances where this factor exerted an appreciable effect. Little (1920) reported that tumors homotransplanted into mice under ten days old grew better than in older hosts, but this difference was confined chiefly to the female sex. Strong, working in Loeb's laboratory (Loeb, 1930), noted that the sex of certain hybrids affected the results obtained with homoplastic grafts.

E. Halsted's Law

In 1909 Halsted found that autotransplantation of parathyroid glands was usually unsuccessful unless there was a deficiency of more than 50% of the parathyroids. He suggested that this might be true of the transplantation of endocrine glands in general. Loeb (1930) does not agree with him, at least insofar as thyroid gland is concerned. Loeb states that as many as four lobes of this gland may be successfully transplanted, which, he says, proves that that thyroid deficiency is not necessary for its successful transplantation. The findings of Dunphy (1940), with respect to the adrenal, are similar.

Nevertheless, Halsted's law, as it has come to be called, is now quite generally accepted, and has been applied to the grafting of foreign as well as of autoplastic endocrine glands by Wyman and Suden (1932, 1941), by Stone, Owings and Gey (1933, 1934) and by Lux, Higgins and Mann (1937). Wyman and Suden showed that homotransplanted adrenal cortex, which grows quite well in adrenalectomized rats, does not survive in non-adrenalectomized animals.

Goodman (1934) transplanted immature rat ovaries into the anterior chambers of the eyes of adult female rats, and found that when the host animals were spayed at the time of transplantation, the grafts in all cases were alive after six months. On the other hand, when the hosts were spayed two months following the transplantation, only 33% of the transplants survived the six months.

Stone, Owings and Gey (1933-34) suggest that Halsted's law might apply to the transplantation of tissues other that endocrine glands. It seems reasonable to suppose that, in some cases at least, we should expect grafts to take only if they are called upon to perform their function in the new host. Skeletal muscle, even when it has not been transplanted from its original location, atrophies if not given any work to do.

In accord with this view are the findings of Rand (1924-25). By transplantation operations in Hydra and Planaria, he showed that any one of the more or less specialized regions of these animals may inhibit regenerative developement of a similar region.

F. Method of Grafting

Carrel (1908) believed that the failure of foreign grafts to live was due entirely to a poor blood supply, and that if such grafts could be given a satisfactory vascularization immediately after transplantation, they might function as well as autografts. Two means of accomplishing this--the flap method and the method of vascular anastomosis--will be discussed.

In the flap (or pedicle graft) method, a piece of skin or other tissue is dissected so that one end remains in its original location, the donor area, the other end then being attached to the host area. When both host and donor areas belong to the same individual (autoplastic grafting) the results are usually quite good. This device is frequently made use of in plastic surgery. In homoplastic grafting, where host and donor areas are on different individuals, the graft may or may not survive while the pedicle remains intact. Upon severance of the pedicle, however, it acts the same as does any homo-graft (Loeb, 1930).

When organs are homotransplanted by the method of vascular suture (artery to artery and vein to vein anastomosis) the results seem, in some cases, to be quite good for a time. In this manner Carrel (1908) performed double nephrectomies on dogs, replanting in each case a kidney fron another dog. These animals lived for several days. The same investigator also transplanted a leg from one dog to another, the leg being still alive after 22 days (Carrel, 1908; Carrel and Guthrie, 1906).

Carrel later (1914) came to the conclusion that when a kidney is transplanted from one animal to another of the same species by vascular anastomosis, the course of events is as follows: The organ functions normally in its new host for a few days, and then albumin appears in the urine. In the second week a perivascular round-cell infiltration appears, and there is increased connective tissue about the vessel and collecting tubules. The secretory tubules and glomeruli are normal at this stage. Later there is a leucocytic infiltration about all parts of the organ, and after a few months it becomes sclerotic and atrophied.

Williamson's experiments with homotransplanted kidneys (1933) were no more successful than those of Carrel.

Stone, Owings and Gey (1933, 1934) suggest that the most rational method of grafting such structures as endocrine glands is by the implantation of a large number of very small particles into loose tissues near large blood vessels, where there is not much danger of trauma. They feel that in this way a good blood supply can be established without the formation of a hematoma. They have found the axilla and groin to be the most favorable locations.

G. Treatment of Host or Donor Tissues Prior to Transplantation

It is only natural that various serological, physical and chemical methods should have been attempted in an effort to increase the transplantability of foreign tissues. To date, none of these has met with more than mediocre success, although the possibilities in some cases appear promising.

According to Brown and McDowell (1942) we should not expect attempts to desensitize the host to the cells of the donor to be successful. The opinion of these authors, which coincides with findings discussed elsewhere in this paper (especially those of Bisgard, 1938), is that injection of donor tissues prior to the transplantation proper would only serve to build up in the host an immunity to the graft, which would actually decrease the transplantability.

Nevertheless, there appears to be a certain amount of logic in the method of Baetzner and Beck (1928), who injected, in increasing amounts, donor serum plus an extract of the organ to be transplanted. They believed that in this way they could turn aside antibodies formed against the graft. Unfortunately, we have but little data concerning results obtained by this method. It may be related to Carrel's finding (1914) that homoplastic transplantation is more successful when the host is suffering from some general infection than when the host is in good health.

Today the most promising field appears to be the adaptation of the donor tissue to the host by cultivation in vitro with the serum of the host. Alexis Carrel first suggested this in 1907, but there is no record of his ever having given it a trial.

Stone, Owings and Gey (1933) used this method in the homotransplantation of dog thyroid and parathyroid glands, and after many failures were finally able (1934) to obtain takes in 45% of their attempts upon previously thyroidectomized or parathyroidectomized dogs. The "takes" in these cases were defined as normal function of the transplanted glands for four weeks, although some of them still functioned after six months.

These writers also report (1934, 1935) several cases of human hypothyroidism and hypoparathyroidism, which have been symptom-free for periods of from a few months to a year following homotransplantation of the gland in which they had been deficient.

The method employed by Stone, Owings and Gey is as follows: The gland to be used is cut into pieces one to two millimeters in diameter and grown in a medium containing beef embryo juice, an artificial serum saline and serum and heparinized plasma of the animal who is to receive the graft. The culture is continued for about a month, the tissues being transferred to fresh medium every three or four days.

Houghton, Klassen and Curtis (1939), using essentially the same technique, transplanted fragments of human parathyroid into the axilla of a woman suffering from hypoparathyroidism following thyroidectomy. During the seven months they observed her after the operation, she was symptom free.

Lux, Higgins and Mann (1937) applied this method to homotransplantation of the adrenal in rabbits and guinea pigs, but none of the grafts took permanently. However, their host animals were not adrenalectomized prior to the transplantation, and they suggest that if this operation had been performed the grafts might have fared better. Even so, they noticed that the histiocytic and lymphocytic response by the host was delayed, and that a greater degree of vascularity occurred than they would have expected in the case of untreated grafts.

Attempts to transplant pancreatic islet tissue by this technique have been discouraging. Selle (1935) cultured in the recipient's serum fragments of fetal and adult pancreas. Upon homotransplantation into completely or sub-totally depancreatized animals they failed to grow, and complete absorption occurred within three weeks.

Murray and Bradley (1935) cultivated a human islet-cell adenoma in the serum of a diabetic patient for three weeks. Subsequent transplantation into the axilla of this paitient had no effect upon his diabetes.

The experiments of Haymaker and Anderson (1936) with rats seem to show that pituitary tissue may be adapted for homotransplantation by being cultured in the serum and plasma of the host prior to grafting.

Stone and his associates are at present engaged in an attempt to secure the adaption between donor tissue and host in a somewhat different manner. It consists in grafting the host with a given tissue and awaiting the developement of the specific defense reaction, and then immunizing the graft against the stimulated host. How they intend to accomplish this is not stated, but their results will be awaited with interest (Stone, 1942).

According to Stone, Owings and Gey, this "adaption" between transplant and host is possibly not a specific phenomonen at all. Instead, their method of cultivation may serve merely to "dilute out" the substances responsible for the reaction. Their findings are in accord with Loeb's discovery (1926) that when cartilage is homotransplanted into the rat, an adaptation between host and graft seems to develope in the course of time.

The influence upon transplantability of physical and chemical treatment of the host, while probably not practical from a clinical standpoint, is nevertheless interesting. The reaction against foreign tissues can be diminished by exposure of the host to strong doses of X-rays (Murphy, 1926; Clemmesen, 1938), or by the injection of benzol (Murphy, 1914). According to Murphy, these agents increase transplantability by reducing the action of the leucocytes.

Of greater practical interest are the results of the action of physical and chemical factors upon the transplant. Siebert (1928) found that exposure of homogenous tissues to mild heat for a sufficient length of time prevented the occurrence of the homoreaction following transplantation. However, heteroplastic tissues under identical circumstances could still elicit the hetero-reaction. Blumenthal determined the intensity of heat necessary for destroying the individuality differential to be 54° Centigrade for 30 minutes.

Blumenthal also found that many chemicals can destroy the ability of the graft to provoke the homoreaction. These include acetone, 95% ethyl alchol, formaldehyde, and solutions of thymol, sodium benzoate, ammonium sulfate, ferrous chloride and ferric chloride.

It is within the realm of possibility that some method, such as those we have just mentioned, will be discovered whereby we shall be able to destroy that part of the transplant which provokes the host's reaction without at the same time injuring the transplant.

V. SUGGESTIONS FOR FURTHER INVESTIGATION

It appears that the use of transplanted embryonic tissues deserves further study, although it is probable that such grafts survive only until a time about comparable to the end of their gestation period. However, it is possible that if tissues of quite young embryos are used, the relatively long period they survive before their individuality differentials develope may suffice to adapt them to the host.

The employment of embryonic homografts, even if this adaptation does not occur, might be of use in certain of the endocrine deficiency diseases. For instance, a subcutaneous implantation of embryonic pancreatic tissue every few months would, if subsequent experience shows that such grafts grow for a time, be preferable to daily insulin injections for the control of diabetes. Although the source of human embryonic tissue is limited, heteroplastic grafts from the embryos of animals having long gestation periods might be able to survive for a considerable period.

A method of preventing fibroblasts from coming in contact with a transplant might permit it to survive for a longer period. This might be accomplished by having the graft surrounded by some material permeable to the fluids and proteins necessary for its metabolism, but impermeable to fibroblasts and other cellular elements.

Both of these methods would, of course, be limited to cases of endocrine deficiency diseases where the functioning of individual cells, rather than the architecture of groups of cells, is the important factor.

The transplantation of whole organs by vascular anastomosis should also be investigated further. New methods have been developed by which a kidney, for example, might survive better on homotransplantation than did those of Carrel's experiments. The kidney could be kept alive for a time by a perfusion method such as that of Carrel and Lindberg (1938) or of Galli-Mainini (1941), and transplanted into the host by artery to artery, vein to vein, and ureter to ureter anastomosis. Instead of Carrel's suturing method, anastomosis over vitallium tubes, as suggested by Lord and Eikel (1942), Blakemore, Lord and Stefko (1943) and Lord, Stefko and Stevens (1943) might be used to decrease the likelihood of thrombosis.

The chances of survival of such an organ might be enhanced if it were protected from the body fluids of the host by some such relatively inert material as cellophane (Wheeldon, 1939; McKeever, 1943) or the rubber of a surgical glove (Page, 1939). This material would cover the kidney completely, being perforated at only three points for the artery, vein and ureter. This is shown diagramatically in Figure 2.

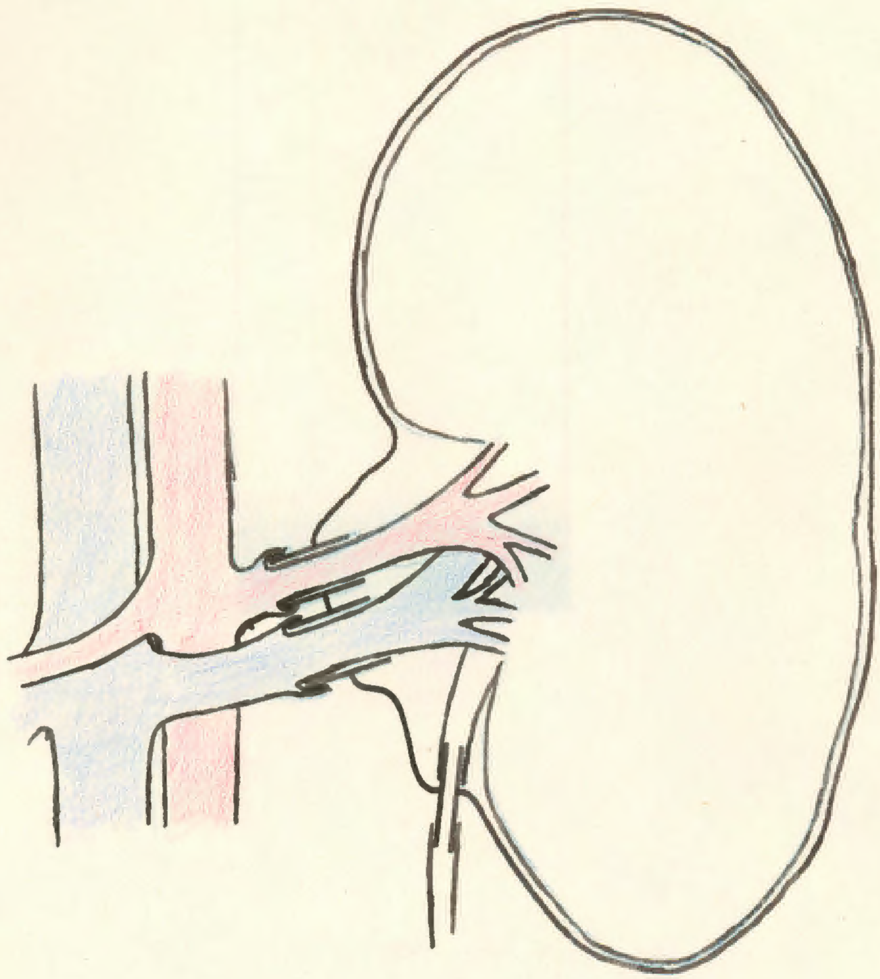

Figure 2. Diagram to Show how a Kidney could be Transplanted without Coming into Direct Contact with the Host Except by the Blood Stream

VI. SUMMARY AND CONCLUSIONS

The transplantation of tissues from one animal to another is more successful the closer the degree of relationship between the two animals. Although in the lower forms of life heterotransplantation may be successful even when host and donor are related only very distantly, successful transplantation between mammals depends upon a close genetic relationship of host to donor. As a general rule, homotransplants between identical twins or between members of a highly inbred strain are the only ones which survive, in mammals, for more than a few weeks.

The mechanism involved in the failure of homografts is probably as follows: Some of the proteins elaborated by the graft are weakly antigenic. In response to the antigen the host forms an antibody which, while not cytotoxic, is capable of stimulating the fibroblasts about the graft so that they isolate it, thus causing its death. The antigenic substances capable of provoking this reaction against a homograft are probably present in all, or nearly all, of the cells and body fluids of any given animal.

Heterografts differ from homografts in that the antigens of the former elicit the production of directly cytoxic antibodies by the host. These grafts may also be phagocytized by polymorphonuclear leucocytes. Lymphocytes collect in large numbers about homotransplants, but their importance in preventing the survival of the graft is probably secondary to that of the fibroblasts.

Embryonic tissues and tumors have a higher degree of transplantability than do other tissues. However, all cells have the potentiality of provoking a homo- or heteroreaction, and in the case of embryonic tissues this probably developes at a definite time corresponding to about the end of the gestation period, regardless of whether the embryonic cells are in their original organism or in a strange host.

Lens, cornea and cartilage, probably due to the fact that their nutritive requirements are low, survive almost as well following homotransplantation as they do after autotransplantation.

Tissues homotransplanted into theanterior chamber of the eye and into the brain survive better than they do in other locations.

At present the use of homografts or heterografts has few if any clinical indications. Several methods of using such transplants may, however, become valuable in the future. These are:

1. The use of temporary homo- or heterografts of embryonic endocrine glands in the treatment of endocrine deficiency diseases.

2. The transplantation of particles of endocrine glands surrounded by a material which is permeable to proteins but impermeable to cellular elements. Homografts of this type might also be used in the treatment of the endocrine deficiency diseases.

3. Subjection of the transplant, in tissue culture, to any of several types of physical, chemical or serological treatment prior to transplantation. Such methods may become applicable to whole organs as well as to particles of endocrine glands.

4. The homotransplantation of whole organs in such a manner that they do not come in direct contact with the host except by the blood stream.

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