

The petrolatum was easily removed from the anterior chamber by paracentesis. Since that time I have abandoned the use of ointments.

DR. WALTER B. LANCASTER, Boston: In regard to the preliminary training of the patient, I think that it is useful in some cases and harmful in others. Like a good many other measures, it ought to be used by individualizing the patients. Some will be made more intractable the more you try to train them. Many patients may seem to be calm and say they have no fear. Often in such cases the pulse is the better guide. Some of the professional anesthetists call attention particularly to this danger with athletes. They need special care in preliminary treatment, and often require sedatives. An important point to observe in the operating room is not to converse. These patients hear and whether they understand correctly or not, put their own construction on what they hear.

THE TRANSPLANTATION OF DUCTLESS GLANDS

WITH REFERENCE TO PERMANENCE
AND FUNCTION *

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The transplantation of normal or tumor tissue is at present attracting wide interest among experimental physiologists and pathologists because of the many fundamental biologic problems which earlier work, both with tumor and normal tissue, uncovered. Among these problems probably the two that are being most actively investigated at present are (1) whether specific nerves (either secretory or regulatory) are necessary for the survival, growth and function of transplanted tissues, and (2) the problem of the reaction of the host to transplanted foreign tissues. For this work the so-called endocrine glands have obvious advantages over glands with external secretions, or the various connective tissues and, indeed, over tumor tissue.

In the course of our work during the past three years, we have studied the transplantation of ovary, suprarenal (cortex and medulla), spleen, parathyroid and thyroid of rabbits. Because the thyroid has several great advantages, namely, its accessibility, its wide range of morphologic changes, which are easily interpreted, and its specific iodine reaction, all useful in checking and controlling results, we have devoted more time and effort to the study of this tissue, and the summary to follow is based for the most part on our experiments with the thyroid gland. Our experience has been confined wholly to autotransplantation and homotransplantation, and for the sake of clearness it seems best to present the data under these two divisions rather than according to the tissues used.

AUTOTRANSPLANTATION

We have made nine experiments with ovarian tissue, transplanting in the subcutaneous tissues of the abdomen after removal of both ovaries. In all cases the stroma, interstitial cells and graafian follicles showed survival and growth over periods varying

from thirty-four to 219 days. Mature graafian follicles were recovered from two rabbits, associated with active hyperemia of the uterus and the typical phenomena of rut.

A point of practical importance which we have observed in the older transplants is the presence of hemorrhagic cysts, due to the fact that the ripened follicles rupture into themselves instead of onto a free surface as occurs in the normal, and these cysts ultimately produce pressure atrophy of the ovarian tissue. Apart from this complication, our work confirms that of many others that these autotransplants are permanent and show all the evidences of functional activity.

As a part of other experiments, we have made six autotransplantations of spleen tissue in the subcutaneous tissue of the abdomen, all of which were absorbed in twelve days.

Parathyroid tissue has accidentally been transplanted many times with the thyroid, and we have often found active normal looking parathyroid tissue in thyroid transplants when examined microscopically.

In the first 100 rabbits used, thyroid was successfully transplanted into ovary, suprarenal, spleen, jugular vein, muscle, subperitoneal tissues and into the subcutaneous tissues of the neck, chest and abdomen. In the second 100 rabbits, transplantations were made uniformly in the subcutaneous tissue of the abdomen, modified by one or more of the following conditions: with the thyroids intact, partially and completely removed; with and without removal of spleen suprarenals, ovaries, and testes; with and without the administration of phosphorus, and with and without the administration of iodine using both normal and hyperplastic thyroids. Of these factors, the removal of a large part of the thyroid gland or the administration of iodine materially modifies the growth and activity of the autotransplants.

Autotransplants uniformly "take" and "grow," the amount of growth being determined by the amount of thyroid removed and also by the administration of iodine or desiccated thyroid. Cristiani and von Eiselsberg also observed that removal of the thyroid caused compensatory hyperplasia of transplants irrespective of their location in the body. We can confirm this observation. In every instance, it was found that the histologic condition of the transplant was identical with that of the thyroid gland. Both undergo hyperplasia simultaneously and to the same degree, and both involute simultaneously and to the same degree.

Following the administration of iodine, transplants take up and retain it to the same degree as the thyroid gland. Many authors have stated that transplants of thyroid were permanent. We have observed transplants for more than a year through the phases of spontaneous and induced hyperplasia and involution, and can confirm the statement that they are permanent irrespective of their location.

Inasmuch as such transplanted thyroid tissue undergoes all the morphologic variations associated with growth and function that are observed in nontransplanted thyroid tissue, and inasmuch as transplanted thyroid shows the same reactions with iodine and the same storage of iodine as nontransplanted thyroid, we believe that this is sufficient evidence that such transplants may grow, involute or function equally as well as nontransplanted thyroid. We cannot accept the belief held by some observers that specific nerves, whether secretory or regulatory, are nec-

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essary for normal growth or functional activity of the thyroid. The evidence obtained from these observations suggests that the thyroid is truly a blood gland in that the stimuli causing either increased or decreased activity may reach it directly by way of the blood stream. These conclusions are based on the study of 289 autothyroid transplantations in 141 rabbits observed during periods varying from three to 381 days. In forty-one rabbits, only autotransplantations were made, and in 100 both autotransplantations and homotransplantations were made; in thirty-two of this 100, negative homotransplantations had preceded the positive autotransplantations.

HOMOTRANSPLANTATION

We have made twenty-six homotransplantations of sexually mature ovarian tissue, all but one of which showed complete absorption of the ovarian structure except for the interstitial and luteal cells. The one exception was probably an instance of the failure of the host to react to the foreign tissue in the usual way. The fact that the lipid cells of the ovary can survive upward of 193 days, while the stroma and egg cells undergo absorption in a few weeks, shows that in the lipid-containing tissue we are dealing with a different order of cells against which the host reacts very slowly, if at all. There is evidence from the standpoint of transplantation, as well as from that of embryology and morphology, that the cells of the suprarenal cortex belong to this series also. Repeated homotransplantations into the same animal of these lipid-containing cells of the ovary would probably determine whether or not the host eventually develops a resistance to this tissue also. Up to the present we have not made sufficient experiments to determine this point. The two important facts observed in this series of homotransplantations of the ovary are that: (1) the host reacts in the usual way and usual time to the egg and stroma cells, and (2) the host reacts very feebly to the lipid containing cells.

We have made eighteen homotransplantations of the spleen, all of which were absorbed in twelve days.

Homotransplantations of thyroid were made in spleen, bonemarrow, suprarenal, ovary, testes, liver, muscle and subcutaneous tissue of neck and abdomen. Purely for the convenience of subsequent examinations, we have used the subcutaneous tissues of the abdomen for all transplants during the past two years.

Up to the present we have made 567 homotransplantations in 205 rabbits of various ages. In 105 of these only homografts were made. As in the case of thyroid autografts, the conditions have been varied as follows: with and without removal of the thyroid, ovaries, spleen and testes; with and without administration of iodine and phosphorus, using phosphorized and iodized thyroids separately and together.

A tabulation of the results shows that complete absorption may take place as early as the tenth day, and usually occurs before the thirtieth day in cases which have not been previously homotransplanted. As is well known, repeated homotransplantation markedly accelerates the destruction of homografts, due to the development of an immunity, the nature of which is little understood. On the other hand, we have under observation two rabbits containing homotransplants of more than a year's duration, which grossly and microscopically resemble autografts. Between these two extremes, there are all gradations in the rate of destruction. This to our minds is the

most significant fact we have observed, and, in reviewing the literature, we have been unable to find reports dealing specifically with these variations in large series of nontumor transplantations.

A thorough understanding of these variations would go far toward explaining the causes of the failure of homotransplantation and, as the students of tumor point out, it is also the most important problem confronting them. It seems well established that these variations depend on the development of an immunity to a foreign protein (tissue), and tumor investigators have shown that the degree of foreignness of the tissue used is the most important factor in its development. A study of our thyroid material suggests that these variations in the rate of absorption may be due to intrinsic differences in the reaction of the host, quite apart from and in addition to the other important factor of the foreignness of the tissue used. In the series of 205 rabbits about 92 per cent. destroyed initial homografts in from ten to thirty days, and subsequent homografts, as is well known, were destroyed more rapidly. The remaining 8 per cent. of the rabbits showed strikingly less rapid reactions even though the same gland was used for the two groups in most instances, and the factor of blood relationship could be considered most remote. The following instance, of which there are several others in the series, may be mentioned in some detail in support of the foregoing statement.

The thyroid slightly hyperplastic, of Rabbit 233 was transplanted into three rabbits (Rabbits 226, 227 and 229), May 8, 1915. Within thirty-seven days the transplant in Rabbit 226 was completely absorbed, and within ninety days the transplant in Rabbit 227 was absorbed, while the transplant in Rabbit 229 is still large and active after 400 days. June 14, 1915, the thyroid of Rabbit 263 was also transplanted into Rabbits 226, 227 and 229 and, in addition, as initial grafts into six other rabbits, and as second homografts into four additional rabbits. This thyroid (from Rabbit 263) had disappeared from all but one of the thirteen rabbits at the time of the first examination, the single exception being Rabbit 229, which still has a homotransplant of 400 days from Rabbit 223. This second positive homograft was removed at the two hundred and forty-third day, and in both gross and microscopic appearances had all the characteristics of an autograft.

These experiments show that one has to deal with variations in the resistance of animals, which is quite independent of the thyroid used. It is clear, therefore, that when one finds an animal in which an initial homograft is positive, subsequent homografts from unrelated animals may remain and act as autografts. On the other hand, we have never seen a positive homograft following an initial negative homograft, no matter what the age, sex or blood relationship of the rabbits used.

Turning now to the second factor in the variations of the rate of absorption, namely, the degree of foreignness of the tissue used, there is evidence that one can modify the rate of absorption by modifying the condition of the host and also the chemistry and physiologic activity of the thyroid used, as is demonstrated in the following experiments:

In three rabbits with thyroids intact (Rabbits 237, 238 and 239), potassium iodide was given in 20 mg. doses for two weeks previous to transplantation. These three were then partially thyroidectomized and transplanted on the left side from the thyroid of Rabbit 254, in which marked hyperplasia had been induced by a previous partial thyroidectomy. The same hyperplastic thyroid was transplanted into the left side

of two other rabbits (Rabbits 255 and 256) which had had similar previous partial thyroidectomies and whose thyroid stumps were hyperplastic. The iodized and quiescent thyroid of Rabbit 237 was at the same time transplanted into the right side of all five (Rabbits 237, 238, 239, 225 and 256). Subsequent examination of the thyroid grafts made from the hyperplastic thyroid into both the iodized and noniodized rabbits shows that in the two rabbits (255 and 256) with previous partial thyroidectomies absorption occurred in thirty days; while in the three iodized rabbits (237, 238 and 239) the grafts disappeared in one (Rabbit 237) after fifty days; in the second (Rabbit 239) it was positive and was recovered at necropsy 144 days later and in the third (Rabbit 238), the graft was positive at 149 days but had disappeared at the two hundred and first day.

Subsequent examination of the right thyroid grafts made with the iodized thyroid of Rabbit 237 shows that in the non-iodized rabbits (255 and 256) absorption occurred in the usual time, while in the two iodized rabbits (238 and 239), this thyroid was removed in one (Rabbit 239) at necropsy 144 days later, and in Rabbit 238 the transplant is still large and active at 382 days and resembles in all respects an auto-graft.

This series of experiments shows clearly that when iodized thyroid is homografted into iodized rabbits, the rate of destruction is markedly decreased. As iodine is a physiologic constituent of thyroid, and as these experiments show that its previous administration to both donor and host delays the rapidity of absorption of homografts, it seems certain that it is possible to modify the usual reaction of the host by strictly physiologic means. While iodine favorably affects the thyroid, there is no evidence that it has a similar action on other homografted tissues. Its influence on the fate of the thyroid homograft suggests, however, that it may be possible to modify the host's reaction to other homografted tissues through one or more of their specific chemical constituents.

SUMMARY

Concerning autografts we have been able to confirm the conclusions of others that thyroid when transplanted shows all the evidence of growth, function and permanence, and to the same degree, as does the non-transplanted thyroid. This work also shows that specific nerves, whether secretory or regulatory, are not necessary either for the control of growth or of function in the case of the thyroid.

Concerning the behavior of thyroid homografts, it seems established that both the host and the tissue used for the grafts modify their duration. These two factors may be quite independent, antagonistic to or helpful to each other. In the case of the thyroid this reaction may be modified by iodine.

Lastly, the future of tissue transplantation as a therapeutic means rests on a solution of the problem of the homograft, and it is also certain that whatever headway is made in overcoming the obstacles to homografting will to an equal degree be applicable to the solution of the tumor problem.

ABSTRACT OF DISCUSSION

DR. ROBERT T. MORRIS, New York: In trying to make rabbits immune to each other's serum, I found that apparently these rabbits absorbed the grafts more readily than rabbits not so treated. This testimony is negative so far as my intention was concerned, but positive in a way, showing that the serologists, at any rate, have a problem before them. Undoubtedly in making transplants we shall sometimes sensitize. In some cases in which we produce allergic phenomena with our transplants, we shall be enabled to

work out further treatment on the basis of the degree and effect of the allergic response.

Sometimes a graft may not serve as a graft, but may have other functions. A patient had lost both his testicles as the result of mumps. I grafted a testicle from another man. The testicle which I grafted gradually underwent absorption, but what happened was this: that graft stimulated the energy of the testicle that had been formed, and that young man now has a testicle one-third the normal size on that side, with full semiesthesia. We have an unlimited field. Supposing, for instance, that we might in the case of tuberculosis of the suprarenal glands transplant a normal suprarenal gland. I have done it, have folded it into the omentum. It takes kindly, and we may then relieve the work on the suprarenal gland, in such a way that even though the graft undergoes absorption, we may obtain some control over the tuberculosis by strengthening the part, and then increasing this patient's general resistance.

AMINO ACID NITROGEN IN THE SYSTEMIC BLOOD OF CHILDREN IN HEALTH AND DISEASE*

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MINNEAPOLIS

The recent trend of investigation in the field of metabolism has served to demonstrate the importance of the amino acids in the metabolism of the proteins. As was shown by Folin and Denis¹ and Van Slyke and Meyer,² amino acids are present normally in the blood. Final proof of this fact was furnished by Abderhalden,³ who succeeded in isolating and identifying several of this group of compounds from large amounts of blood, and by Abel, Rowntree and Turner,⁴ who obtained considerable quantities of amino acids from blood by their ingenious method of vividiffusion. From these and other observations the conclusion has been drawn that the digested proteins of the food are absorbed as amino acids and as such are transported to the tissues.

The amounts of amino acid nitrogen in the blood of different normal individuals or even of the same individual at different times have been shown by Van Slyke and Meyer² to vary widely, the amounts given by these authors ranging from 4.5 to 8.5 mg. nitrogen per hundred c.c. of blood. Numerous reports have been made of variations in the total nonprotein nitrogen of the blood in disease, and in urea nitrogen, which is the largest factor of the nonprotein nitrogen, but only isolated attempts have been made to discover whether or not the amino acids in the blood were subject to characteristic variations in pathologic conditions, and these with but indifferent success.

Segale⁵ reports an increase of amino acids in the serum in anaphylaxis. Kaplan⁶ and later Kaplan and McClelland,⁷ have reported that in syphilis the amino acid nitrogen in the blood is habitually low; but Ellis

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1. Folin and Denis: Jour. Biol. Chem., 1912, xi, 87.

2. Van Slyke and Meyer: Jour. Biol. Chem., 1912, xii, 399.

3. Abderhalden: Ztschr. f. physiol. Chem., 1913, lxxviii, 480.

4. Abel, Rowntree and Turner: Jour. Pharmacol. and Exper. Therap., 1913:1914, v, 275.

5. Segale: Zentralbl. f. Biochem. u. Bioph., 1913, xv, 269.

6. Kaplan: New York Med. Jour., 1913, xcvi, 1172; *ibid.*, 1913, xcvi, 157.

7. Kaplan and McClelland: New York Med. Jour., 1913, xcvi, 157.