Lymphatic System and Organtransplantation

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The lymphatic system plays an important role in organ transplantation as a component of the circulatory system and as a component of the immunologically active lymphoreticular system. The first aspect is emphasized by problems caused in attempts to restore lymph circulation in transplanted tissues and organs, while the second aspect manifests itself mainly by the initiation of immune processes in which the afferent vessels of the regional lymphatic system may be of importance. Methods for the study of these two specific aspects may vary. It should be emphasized however that the latter have many features in common, especially from the viewpoint of physiology and pathophysiology. The purpose of this paper is to give a short survey of the phenomena involved, some of which are still vague in spite of the increasing attention they are attracting.

I. Problems of lymphatic circulation in transplanted organs

Sequelae of interruption of lymph flow

The development of the technique for organ transplantation was made possible to a large extent by the CARREL vascular suture (11, 12). Simultaneously the important finding was made, that autotransplanted organs, e. g. kidneys, were functioning despite temporary interruption of lymph circulation. This fact which appears to question the vital importance of lymph circulation was later confirmed in transplantation attempts of many organs, particularly lungs, intestines and heart. Additional studies on artificially interrupted lymph circulation in either transplanted organs or in a simplified model organ showed, however, that there are certain sequelae of the interruption of lymph circulation. These may be exemplified by the temporary diarrhea and steatorrhea, occurring as a consequence of impaired lipid absorption after transplantation of the small bowel (32, 51); mesenteric lymph nodes of the autografted intestine are enlarged and edematous because of lymphostasis (47). Following lung transplantation, an alveolar exudate may be regularly observed to impair pulmonary function; the formation of this exudate also is a consequence of lymph flow interruption (30, 51).

Many authors described short-term effects of experimentally induced stasis of intrarenal lymphatics by ligation of the efferent lymph vessels. The changes observed include interstitial edema (44), increased intratubular pressure (96), increased urine flow (64), increased sodium excretion (96) and, possibly, increased blood flow, LILIENFELD also noted an elevation of the blood pressure (52). Intravenous urograms revealed corresponding changes: an increase in renal size, a dilated collecting system and a

marked prolongation of the nephrographic phase. Early opacification of the renal vein with enlargement of the intrarenal veins and the main renal vein was demonstrated by angiography.

The restoration of lymphatic circulation

The regeneration ability of the lymphatic system is well-established (5, 53, 55, 89, 114). More recent studies showed that the restoration of lymph circulation may be based on four main mechanisms:

1. lympho-venous communications (59, 97, 98, 99);
2. opening of connections, probably preexisting, between various lymphatic systems (for example between the superficial and deep system of the hind extremity) (57, 58, 60);
3. utilization of collateral channels (for example bypass through the superficial system when the deep system is obstructed) (23, 24, 58, 60);
4. innate regenerative capacity of the lymphatic system (89, 114).

Sometimes, for example after skin transplantation, only the regenerative capacity of the lymphatics manifests itself (65, 66, 106). However, all the mechanisms mentioned above come into play during restoration of the lymphatic circulation after extirpation of lymph nodes (23, 24, 53, 59). After the establishment of lympho-venous communications, communications between various lymphatic systems are formed through connections and collaterals, and a network of regenerated delicate lymphatics in the shape of a ball develops at the site of the removed node. Finally, circulation is reestablished. A rather different situation arises with reimplantation of a limb in which the lymphatics have been completely severed by amputation (23, 24, 55, 85, 86, 78). A bypass through connections and collaterals is impossible because of the interruption, but communications between the superficial and the deep lymphatic system are important. The reconnection of the severed lymph vessels takes place in the superficial system in the skin. The regeneration of the deep system is either proceeding very slowly or totally absent. Even if regeneration of deep lymph vessels takes place, they drain into superficial lymph vessels in the majority of cases (Fig. 1).

In organ transplantation (kidney, bowel, lungs) as well as in skin transplantation, regeneration of lymphatics plays a decisive role in effective restoration of lymph circulation. From observations of many authors it appears that onset and time course of lymphatic regeneration after transplantation may vary with different organs. Regeneration time may be as short as from 4 to 6 days after skin homografts (47, 66) or as long as 4 weeks following transsection of a limb (78, 85, 86). The time periods for lymphatic regeneration in transplanted lungs, bowels and kidneys in general lie between these two limits. However, regeneration times reported vary with the method employed for their assessment. It is especially important to know whether the beginning or the end of regeneration have been taken as reference points. Mobley et al., by injecting Evans blue into the renal parenchyma, observed definite evidence of lymphatic regeneration on the third day following transplantation (72). A combination of the Pierce method with i. v. injection of Trypane blue and x-ray lymphography revealed that regeneration of the lymphatics occurred later (48, 53, 56) (Fig. 2).

In bowel transplantation GOOTH et al. observed new growth of lymphatics across the line of resected mesentery by 2 weeks (32). The first lymphographic signs of regeneration after autotransplantation of the entire small intestine were noted on the twentieth posttransplantation day (47). ERASLAN who studied lymphatic regeneration following reimplantation of a lung by injection of sky blue dye into the reimplanted organ observed a definite lymph flow from the lung after 7 days (30). We should

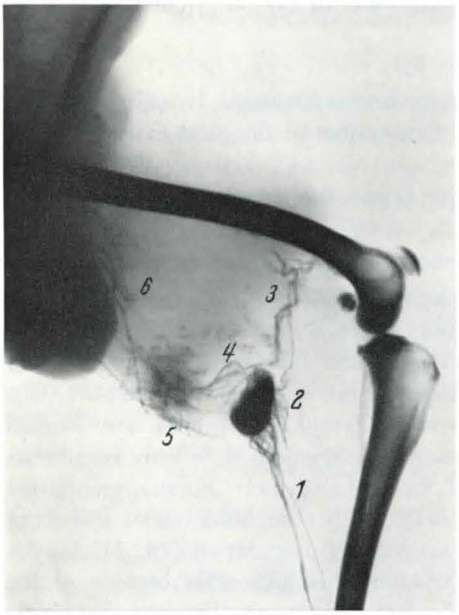


Fig. 1

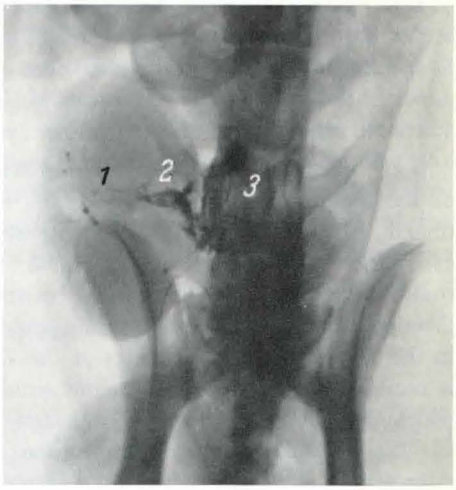


Fig. 2

Fig. 1 Lymphogram of the hind limb of a dog 4 weeks after interruption of circulation in the soft tissues. The site of interruption is marked by number 5. 1. Superficial crural lymphatic system. 2. Popliteal node. 3. Deep system of the thigh. 4. Communication between deep and superficial system. 5. New lymphatic bridging of site of interruption. 6. Superficial lymphatic lymphatics in the kidney hilum. 3. Lateral iliac node.

Fig. 2 Regeneration of the lymphatic system 18 days after autotransplantation of the kidney in a dog. Direct lymphography with Lipiodol. 1. Site of lymph vessel injection. 2. New lymphatics in the kidney hilum. 3 .Lateral iliac node.

realize, however, that the immunosuppressive therapy which is necessary in allotransplantation and which is based on Imuran (azathioprin), corticosteroids, actinomycin C and local ionizing irradiation, significantly affects the process of regeneration. In our studies, e. g., the administration of cortisone postponed the establishment of lymphatic communications between the graft and the bed by 1 to 2 days (from 3–6 instead of from 2–4 days) (106). Studies dedicated to the investigation of the new regional lymphatic system of transplanted organs and its relation to the auto- and homograft have been relatively scarce. We could show for instance, that the external iliac node becomes the regional node after renal transplantation into the iliac fossa, while other

nodes, such as the internal iliac nodes and the mesenteric nodes may also be important, depending on the development of adhesions between the kidney and the adjoining tissue. The same relationships have been described by MOBLEY et al. who in addition invariably observed the formation of a large lymphatic trunk along the entire length of the ureter (72).

In reviewing the mechanisms involved in the restoration of the lymphatic circulation (Table 1) the lymphovenous communications (LVC) should also be mentioned. Their

Tab. 1 Mechanisms of relief of lymphedema in three types of impaired lymph circulation.

Mechanisms of relief of lymphoedema	Model of popliteal lymph node extirpation	Amputation and reimplantation of limb	Organ transplantation
1. Lymphaticovenous communication	Demonstrated by roentgencinematography and radioisotope test	Possible but not yet demonstrated	Doubtful
2. Connections between various L. S.	demonstrated	demonstrated	impossible
3. Collateral lymp circulation	demonstrated	impossible in initial phase	impossible
4. Regeneration of lymphatics	demonstrated	demonstrated regeneration of superficial lymphatic system only	demonstrated

presence assures accelerated dissipation of lymphedema. The outstanding work of THREEFOOT attracted attention to the LVC (97, 98, 99). The existence of LVC can be readily demonstrated during the process of regeneration following experimental extirpation of the popliteal lymph node (20, 22, 26) by a) roentgencinematography showing Lipiodol globules passing directly from the lymphatics into the veins or b) by the observation that radioactivity appears in the femoral vein of the leg with the removed popliteal node immediately after bilateral intralymphatic injection of 131 I-labelled albumin (Fig. 3). The possible importance of existing LVC in transplanted organs has not yet been defined accurately. Based on the observations of THREEFOOT, LILIENFELD et al. assume that LVC start functioning after ligation of the lymphatics in kidneys, playing perhaps a most important role in the relief of renal edema (52). We were unable to demonstrate LVC in kidneys by roentgencinematography. After the injection of Lipiodol into lymph vessels of the renal capsule the contrast medium spread through the lymphatic system but did not pass into the veins (Fig. 4). On the other hand an indirect proof of the existence of LVC may be seen in our observation of lactic dehydrogenase (LDH) resorption from the ischemic kidney. During thoracic duct drainage, LDH elevations due to renal ischemia occur only in the lymph, while the LDH concentration increases in the blood but not in the lymph, when, in addition, the renal lymphatics are ligated. The problem of LVC therefore needs further studies.

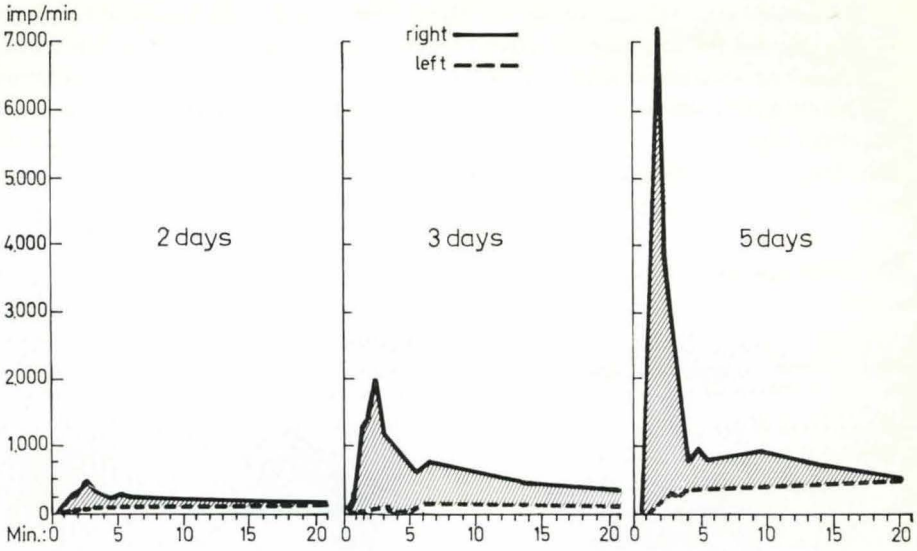


Fig. 3 Lymphovenous communication in dog 2, 3 and 5 days after extirpation of the popliteal node. Radioactivity in the blood of both femoral veins following Albumin (I^{131}) injection into the lymphatics of the right limb.

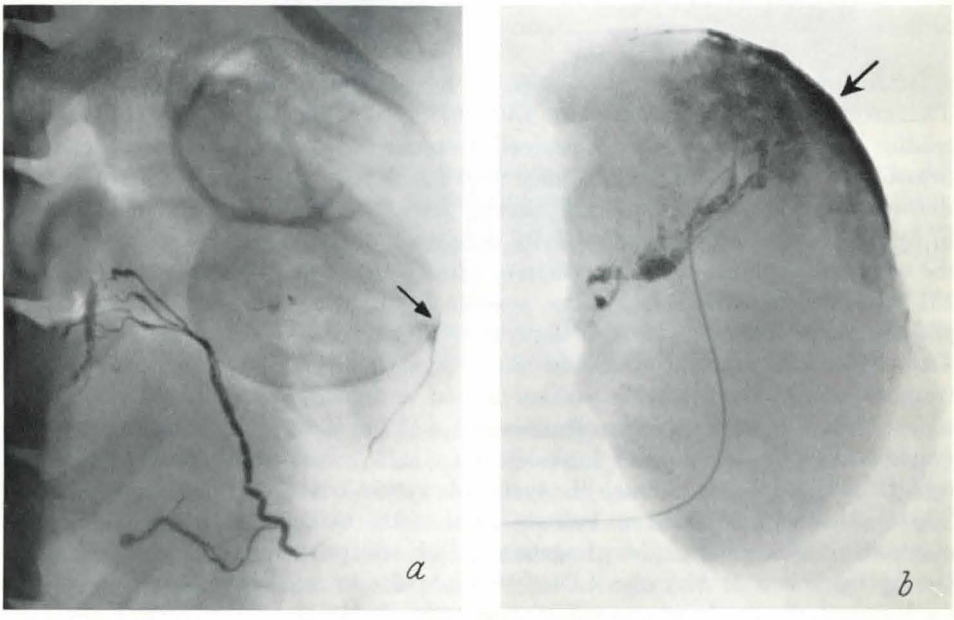


Fig. 4 Injection of Lipiodol into renal capsular lymphatic vessel. Arrow shows the site of injection. a) normal canine kidney. b) the kidney 4 days after ligation of lymphatics.

Lymph edema and posttransplantation complications

As previously stated, consequences of the interruption of lymph circulation appear to be minimal in uncomplicated cases of tissue and organ transplantation; if sequelae do occur they are only temporary. A different situation arises if lymphedema is superimposed upon posttransplantation complications. These complications, for convenience, are best divided into three groups: organ *ischemia*, especially pronounced in allotransplantation of cadaver organs, *infection* aggravated by immunosuppressive therapy, and *rejection* which is a typical immunological complication of homotransplantation.

The causal relationship between interrupted lymph circulation and ischemia is well recognized. RUZNYAK et al. demonstrated that the sequelae of myocardial ischemia are more severe with concomitant lymph outflow failure than with normal myocardial lymph circulation (70, 82). In our experience, the transplated kidney is in greater danger of ischemia before restoration of lymphatic circulation (55, 56).

The danger of infection in lymphedematous tissue is a well acknowledged fact. Every clinician is aware of the susceptibility of lymphedematous extremities to infection, especially with streptococci. The correlation between lymphedema and infection in transplanted organs is considerably less known. KAISERLING observed a rapid development of streptococcal infections in kidneys with ligated lymphatics (44). The finding should be emphasized that retrograde microbial invasion of the kidneys may occur during lymph stagnation (BABICS and RENYI-VAMOS) (2). According to studies of MILLER et al. in dogs an impaired lymph flow in the heart increases the susceptibility to endocardial and myocardial infection after intravenous injection of staphylococci (7). The entire problem, especially in combination with immunosuppression, requires further clarification.

The various clinical manifestations of the *rejection* phenomenon may be partly explained as expressions of different phases of an immune response. The early and malignant type in renal allotransplantation is thought to be mediated by circulating antibodies (49, 111). This resembles xenogeneic transplantation and contrasts with the usual rejection reaction which is of the cellular type. The question remains open whether or not the very severe immediate posttransplantation rejection may be caused by renal lymphedema which occurs in this phase; thus the beneficial effect of local radiation to the transplanted kidney could perhaps be explained by the relief of lymphedema. SCHLEGEL and GUP (90) believe that radiation acts through its effect upon ischemia. The available experimental and clinical data are as yet insufficient to appreciate the possible effects of alterations of lymph flow on rejection reactions. More information could be obtained by comparing the course of the rejection in transplantation experiments with and without immediate reestablishment of the lymphatic circulation. Such studies should now be possible because rapid restoration of lymph flow has been achieved. KIRPATOVSKI et al. connected the efferent lymphatics through cannulas and by direct lymph node anastomosis (46). Reestablishment of the lymphatic circulation following experimental transplantation of the small intestine in dogs was obtained immediately with the use of polyethylene cannulas, while restoration of lymph flow was delayed by two weeks with the method of internodal anastomosis. However, our own observations suggest that lymph circulation may be restored within 2–3 days (Fig. 5).

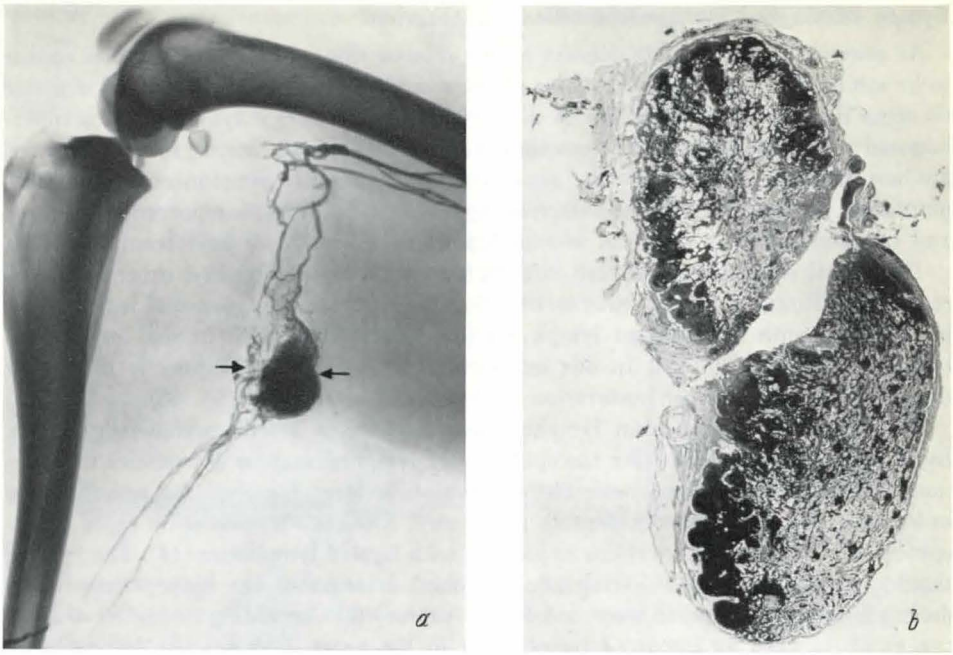


Fig. 5 a) Lymphogram of hind limb of a dog 4 days after dissection and suture of the popliteal node. Note the normal lymphogram. b) Microphotogram of the same node.

Potential importance of renal lymph drainage for the study of transplantation problems

Attention has been drawn by COCKETT et al. (16) and MEYERSON et al. (64) to the role of the renal lymphatics as an important fluid transport system. Experiments of this nature would be useful in the study of transplantation problems. For example, COCKETT et al. noted increasing levels of angiotensin in renal lymph during graded renal arterial obstruction. Oxygen tension in renal lymph was found to exceed tensions measured in venous blood. Small elevations of the venous pressure was followed by an approximately 5-fold increase in renal lymph flow and a 50-fold increase in the protein content of the lymph (MEYERSON et al.). In this context, our finding of a close correspondence between the LDH concentration of the renal lymph and the degree of ischemic renal damage may be mentioned; the possibility of using this correlation as a prognostic test in kidney transplantation is now being studied.

II. The lymphatic system in the immunological process following organ transplantation

Rejection as an immunological process

An assessment of the role of the lymphatic system in immunological processes following organ transplantation is even more complex than that of the problem of lymph circulation. Since our present knowledge of immune rejection of transplants is incomplete, several hypotheses have been proposed each of which has its merits and shortcomings. Our survey will be confined to those views which appear to be more generally accepted with short mention of some other theories.

Long term survival of tissues and organs transplanted from one human being to another or from one animal to another within the same species seems impossible under normal conditions. With certain exceptions, tissue or organ transplants survive only 1–2 weeks. It is well-known that graft rejection is mediated by an immunological process. This was convincingly shown by a number of investigators, beginning with MEDAWAR who published his classical work on the survival of second- set skin grafts in 1944 (67). It is also recognized that during a certain period of time after rejection of the first-set graft, a considerably shorter survival time of second-set grafts from the same donor has to be excepted. The following sequence of events, implicating immunological mechanisms of rejection may be observed during rejection of a first-set graft. During the first few days after transplantation, the morphological appearance of homografts and autografts is identical. Later inflammatory processes, characterized by vascular proliferation as well as by an invasion of lymphoid cells into the graft, become evident. At the peak of the inflammatory reaction the graft becomes necrotic. The time of survival of the graft is inversely proportional to the intensity of the inflammatory process and the rate of its development. In addition, the survival time of the graft is directly proportional to its size, i. e. larger grafts survive longer than small ones. Immune rejection is believed to be mediated a) by a cellular or delayed-type of hypersensitivity (9) and b) by circulating antibodies (95). The mutual relationship between these two principles has not been clarified. According to STETSON (95), for example, humoral antibodies appear to be solely responsible for homograft rejection and this author maintains to abandon the idea of classifying this reaction as an expression of delayed hypersensitivity. On the other hand, the validity of the cellular hypothesis may be demonstrated in a number of observations, as summarized by BRENT and MEDAWAR in 1967 (10). 1. According to DAVID et al. (25) and TURK et al. (103) there is a close analogy between delayed hypersensitivity and the transplantation reaction (9, 77). 2. Lymphoid cells in vitro destroy cells against which they have been sensitized in the absence of humoral antibodies or components of the complement system (31, 80). 3. Transplantation immunity appears to be mediated by small lymphocytes. The sum of these observations shows that rejection is an extraordinary complex phenomenon, a kaleidoscopic spectrum of immunological reactions developing in grafts with probable participation of both cellular and humoral factors.

From a practical point of view, especially in clinical renal transplantation, some further aspects should be considered, such as, e. g. the development of auto-antibodies or of isoimmunization by repeated transfusions. The practical importance of these considerations is derived from the fact that they may explain hyperacute early rejection of transplanted kidneys and also late changes in the transplant during drug induced tolerance.

The participation of the lymphatic system in the physiology of immunological processes

In order to understand the role of the lymphatic system in the immunological processes involved in transplantation rejection, the basic principles of general immunology have to be applied. There are close similarities between the effect of transplantation antigens and other antigens, microbial or non-microbial.

The origin of humoral antibodies. The site where humoral antibodies are produced depends on the route of antigen administration. After subcutaneous injection of microbial antigens humoral antibodies are formed first in regional lymph nodes (28, 29, 36, 37, 61, 62). Of course lymph nodes are not the only site where antibodies develop, since it has been shown that antibodies are produced in the lymphoreticular system throughout the organism (8, 39, 76).

Delayed-type hypersensitivity. Contact sensitization can be transferred to another individual only by transferring formed elements of the blood, lymphocytes (LANDSTEINER and CHASE). TURK (102) described in detail the participation of the lymphatic system in the induction of hypersensitivity. Large pyroninophilic cells, so-called immunoblasts, appear in regional lymph nodes after the administration of chemicals which induce the development of contact sensitivity (73, 103); the peak of these changes occurs on the 4th day. TURK (101) interprets the entire process in the following way: Lymphocytes, sensitized by antigen which is fixed in peripheral tissue, migrate to the regional lymph node where they settle in the cortical area. In this area these committed cells find the right environment for differentiation and proliferation. Their proliferation in so-called "paracortical areas" may be dependent on the presence of the thymus. In neonatally thymectomized animals lymphoid cell migration to, and proliferation in, paracortical areas of the lymph nodes is absent (PARROT, EAST and DE SOUSA). After a period of at least 4 days, the progency of these lymphocytes may leave the lymph node endowed with the capacity to proliferate in other lymphatic tissues, thus propagating the state of sensitization. These lymphocytes are believed to carry a "recognition factor" for the specific antigen, possibly in the form of an immunoglobulin. If these committed cells come into contact with the specific antigen during the course of their circulation and recirculation, they are able to initiate inflammatory processes or to destroy target cells if the antigen is adsorbed to, or part of, the cellular membrane.

Transplantation immunity

The actual contribution of the various mechanisms by which the lymphatic system may be involved in phenomena of transplantation immunity is much more difficult to assess. In 1948 MEDAWAR (68) demonstrated long-term survival of skin grafts transplanted into the white matter of the brain. He concluded that lymphatics must be present in order to initiate effective immunization.

MITCHISON (71) studied the possibilities of adoptive transfer of transplantation immunity against lymphosarcoma. Transfer was possible only by cells of regional but not of contralateral lymph nodes. The observations of SCOTHORNE and MCGREGOR (88) are of special importance in this respect. After transplantation of skin to the ear of rabbits an increase of weight of the regional lymph node and the spleen was noted. A characteristic cellular response developed in the first regional node: pyroninophilic cells were seen to accumulate in the cortex and to a lesser degree in the medulla. This observation was basically confirmed by changes noted following transplantation of other tissues. A number of investigators studied the effects of the removal of regional lymph nodes on transplantation immunity, reaching the conclusion that the integrity of the lymphatic system is a necessary condition for effective immunization against transplants (94). In one of our experiments (104) the regional lymph node of the rabbit

ear was extirpated or damaged by injection of nitrogen mustard while skin homografts were applied simultaneously. Graft survival was prolonged from 11.2 to 22.3 days after removal of the node and up to 25 days after injection of nitrogen mustard. Color lymphography, performed in these experiments revealed that the onset of the rejection process depended on the development of new lymphatic communications from the graft to other lymph nodes which from then on functioned as regional nodes. Further work, culminating in the experiments by BARKER and BILLINGHAM (4), convincingly showed that an intact lymphatic drainage is indispensible for rejection of a skin homograft. BARKER and BILLINGHAM formed circular flaps of skin, maintaining viability by preservation of a slender vascular bundle. The flaps were housed in plastic dishes fixed to the underlying skin. Homografts placed in beds prepared in the flaps did not undergo rejection during the period of flap viability (19–57 days), although control homografts in intact skin were invariably rejected within 8–10 days. There are at present two theories (101) of the mechanisms involved in stimulating small lymphocytes to transform into immunoblasts (34). According to the first hypothesis, antigen draining through lymph vessels from the site of administration to the regional lymph node may directly stimulate nodal lymphocytes. The second suggestion is based on experimental evidence presented by MEDAWAR (69) who believes that lymphocytes may become antigenically stimulated in the periphery and then migrate through the lymphatics to the regional node where the transformation to immunoblasts occurs. Further experiments may show that one or both possibilities are correct. The situation in organ transplantation, where a vascular stump is preserved, is quite different. A classical experiment has been performed by HUME et al. (40). A transplanted dog kidney was wrapped in a plastic bag to prevent lymph drainage. However, rejection of the protected kidney occurred within the same period of time as in controls. It was assumed therefore, that the venous circulation may serve as an effective afferent pathway for immunological sensitization. According to our own experience this interpretation represents an oversimplification. When the regeneration of efferent lymphatics has been completed after organ transplantation an immunological reaction in regional lymph nodes which may lead to eventual rejection cannot be excluded a priori. The paraaortal nodes in dogs were made visible by injection of lipiodol and studied following renal allotransplantation in serial roentgenograms. If the kidney was rejected early the regional lymph nodes did not enlarge. When prolonged renal function was maintained by continuous treatment with Imuran (4 mg/kg daily), the size of the lymph nodes also remained constant. After 5 weeks, Imuran administration was discontinued and we observed enlargement of regional lymph nodes which preceeded functional deterioration of the transplanted kidney (Fig. 6).

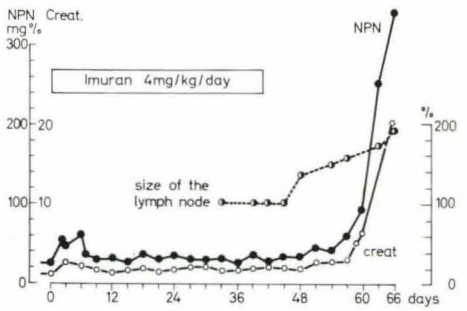


Fig. 6 Diagram of the size of the main regional lymph node of a renal homograft. Note, after cessation of Imuran administration the lymph node is enlarged before rejection manifests itself by a deterioration of renal function. (NPN = non protein nitrogen, creat = creatinine.)

In recent years strong evidence has accumulated pointing to a primary pathogenic role played by lymphocytes. BILLINGHAM gives an excellent review with good references (7). For the study of the effects of lymphocytes upon tissue the normal lymphocyte transfer (NLT) reaction has become important (10). This reaction is elicited in irradiated guinea-pigs by the intradermal injection of normal homogeneic lymphocytes. An inflammatory episode, reaching its peak at 24 hours, is followed by a flare-up between the third and fourth day culminating in a second and more violent inflammatory reaction which reaches its peak at about the 6th day. The lesion then quickly disappears as a result of the immunological recovery of the host. When specifically presensitized cells are substituted for normal lymphocytes the reaction is essentially identical except for its greater intensity. It immediately reaches the level which the NLT reaction achieves only at its second peak. This transfer test has its merits because it helped to clarify some basic problems of immunology, but it may also be a suitable model for experiments with immunosuppressive chemotherapy and antilymphocyte serum.

Possible ways of influencing the rejection process by immunosuppressive agents.

Immunosuppressive agents comprise a great number of drugs of various chemical composition which modify the different elements of the complex process of antibody formation (6). In present clinical practice three substances are widely used: azathioprin (Imuran), corticosteroids and actinomycin C; immunosuppressive chemotherapy is sometimes supplemented by local ionizing irradiation. With the usual parenteral or peroral administration both humoral and cellular components of the immune response may be depressed. In homotransplantation immunosuppressive substances appear to inhibit all elements of the homotransplantation reaction. Onset and peak of the rejection reaction are delayed, and its intensity is reduced. Lymphoid proliferation in lymph nodes draining the site of the graft is diminished (1, 27, 87). Immune depression is not necessarily accompanied by visible destruction of lymphoid cells. The impairment may be caused by elimination of only a fraction of cells necessary for the initiation of the immune response. This would explain the immunosuppressive effect of those agents which cause no major destruction of lymphoid tissue, such as many antimetabolites (6).

Recently the use of antilymphocyte sera (ALS) has attracted great attention. Heterologous sera obtained by immunization with recipient lymphocytes are mainly used (e. g. rabbit antirat lymphocyte serum or horse anti-human lymphocyte serum). The intraperitoneal administration in mice of rabbit antimouse lymphocyte serum is followed by a rapid reduction in the number of the lymphocytes of the peripheral blood to 10 % of control values within 4 hours (81). Long-term numerical suppression of circulating lymphocytes may be achieved by repeated ALS administration. The number of small lymphocytes is reduced, germinal centers are absent, and an unusually increased number of large lymphoid and reticular cells may be noted in lymph nodes of ALS-treated animals. A significant prolongation of homograft survival may be achieved by administration of ALS. Very recent clinical experience in kidney transplantation shows that with the use of ALS the dose of other immunosuppressive agents may be reduced. ALS appears to be equally effective in impairing the rejection of homotransplants and heterotransplants as well as the humoral antibody formation and hypersensitivity reac-

tions. In contrast to immunosuppressive drugs, ALS may influence not only first-set but also second-set reactions. The physiological and biological specificity of ALS for lymphoid tissue can be explained by the higher concentration of target antigens on lymphoid compared with other cells (81). There is no generally accepted theory on the effect of ALS on lymphoid cells. It seems that both inactivation by coating and actual destruction of lymphocytes or their precursors may be important (113). The former hypothesis has been supported by GROGAN and HARDY's study showing prolongation of skin graft survival in rats treated with ALS too dilute to depress lymphocyte levels in the peripheral blood.

Attempts to prolong homograft survival by treatment aimed at the lymphatic system

The methods influencing the immunological process after transplantation via the lymphatic system are summarized in table 2, which is partly taken from the work of HUME and WOLF (41). As already discussed, rejection of a skin transplant is delayed by extirpation of the regional lymph nodes. By this simple method a certain but not permanent prolongation of the survival of primary and secondary allografts was achieved.

Tab. 2 Prolongation of homograft survival by treatment aimed at the lymphatic system.

I. Extirpation of regional lymph node
II. Lymphatic fistula
1. Thoracic duct cannulation
2. Lymph fistula at the level of the regional lymph node
III. Irradiation of the lymphatic system
1. Extracorporeal radiation of thoracic duct lymph
2. Irradiation of lymphatic system with ^{198}Au, ^{206}Bi, ^{111}Ag, ^{90}Y chelated with DTPA and colloidal chromic phosphate with ^{32}P, ^{131}I tagged antigen.
IV. Intralymphatic immunosuppressive drugs – Imuran, heterologous antilymphocyte serum.

Great experimental and clinical attention has been given to the effects of thoracic duct fistulas, by which a significant lymphocyte depletion of the organism may be achieved (74, 84, 93, 105). The reported effect upon graft survival varies greatly. PARKER et al. observed a prolongation of skin allotransplant survival from 12 to 17 days (74), VRUBEL et al. from 16.2 to 28.5 days (105). No uniform results have been achieved in renal transplantation. The reported variance in effectiveness of thoracic duct fistulas may be explained in part by differences in the duration of drainage. TILNEY and MURRAY used thoracic duct drainage in 20 human recipients of renal homografts (100). Among 11 patients with well-functioning fistulas fewer rejection episodes with later onset were observed than in control patients. According to these authors lymphocyte depletion through chronic thoracic duct drainage is suggested as a nontoxic adjunct to current methods of immunosuppression. VRUBEL et al. produced a fistula at the level of regional lymph nodes (107) and observed prolonged graft survival from 13.1 to 21 days while drainage with suction further improved the results (more than 30 days).

The influence on immune rejection of transplants by irradiation of the lymphatic system has been studied extensively. CHANANA et al. investigated the effect of extra-

corporeal irradiation of the thoracic duct lymph upon skin transplant survival in calves. The observation should be stressed that irradiation of the thoracic duct lymph produced a prolongation of the survival of those grafts draining primarily into the thoracic duct, while grafts placed in sites not drained by the thoracic duct remained functional for a shorter period of time.

Results obtained by the injection of radioactive substances into the lymphatic system will be mentioned only briefly. Substances used include ^{198}Au, ^{206}Bi, ^{111}Ag, ^{90}Y, chelated

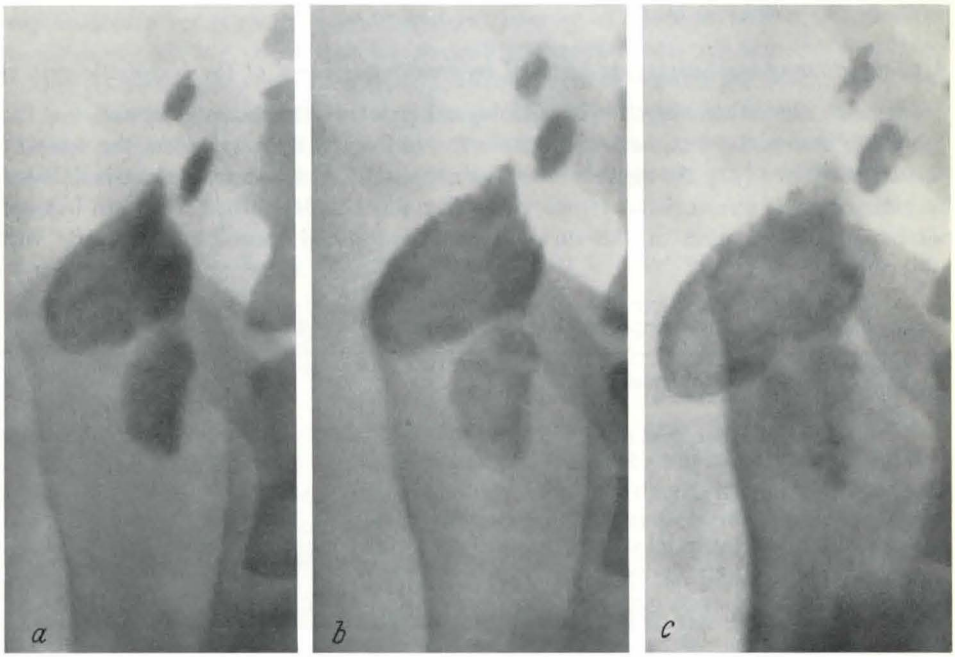


Fig. 7 Enlargement of the regional nodes of a homotransplanted dog kidney demonstrated by roentgenlymphography. a) prior to rejection. b) during rejection. c) at the end of rejection.

with DTPA, colloidal chromic phosphate with ^{32}P and Ethiodol-^{131}I. These radioactive substances are injected into lymph vessels or nodes, or they are indirectly administered into subcutaneous draining regions. Effects have, so far, not been better than with classical immunosuppression. However, there may be some potential in the method since WHEELER et al. demonstrated considerably prolonged homograft survival in a dog which had been injected with radioactive gold into the lymph vessels of the legs and into the mesenteric lymph nodes (110).

Conclusions

A comprehensive review of the importance of the lymphatic system in organ transplantation would have been an impossible task and was not the purpose of the present report. It was our intention to draw attention to the complexity of the problem with its lymphological *and* immunological aspects.

A considerable wealth of information has accumulated which may serve as a basis for future research. It has been emphasized that a transplanted organ is capable to overcome relatively well the temporary interruption of lymph circulation, and that restoration of lymph flow is assured by rapid regeneration of the lymphatics. It is generally accepted that lymphocytes play an important role in the immunological phase of transplant rejection; the significance of the draining lymph nodes, in this respect, is also acknowledged.

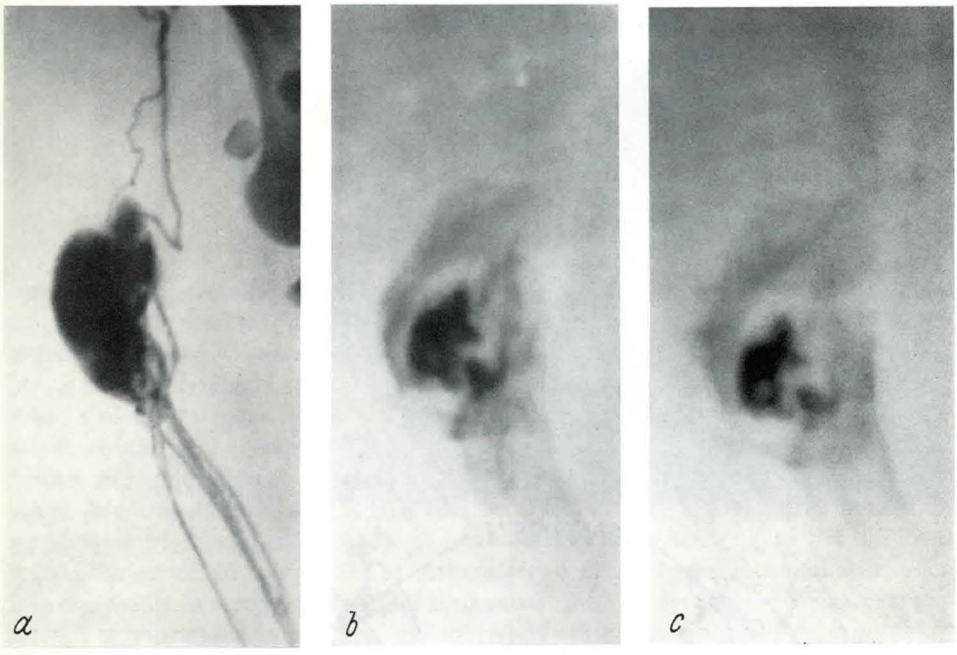
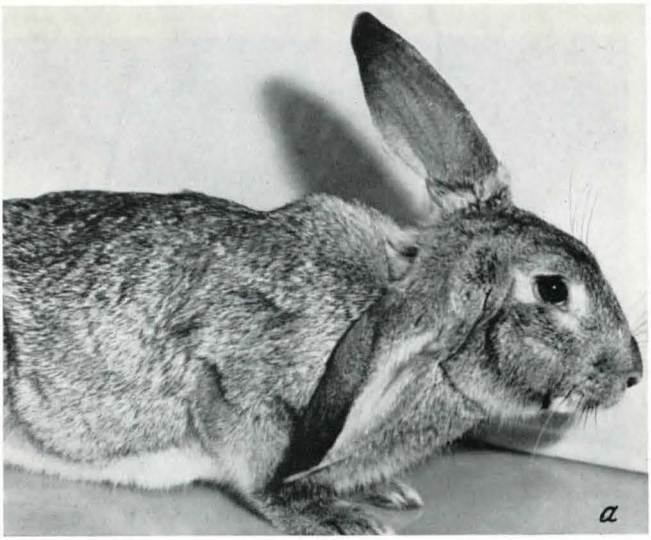


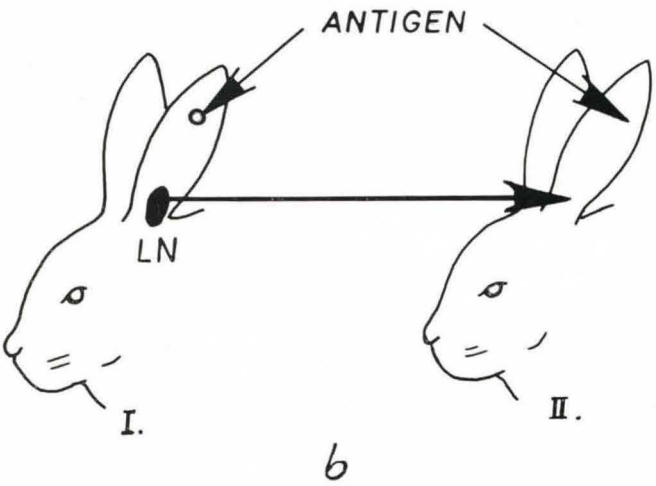
Fig. 8 Syndrome of uneven contrast in the popliteal node of a dog, sensitized by a suspension of heterologous spleen cells. Lymphogram: a) immediately after injection; b) 10 minutes after injection; c) 20 minutes after injection.

There are, however, problems which require further clarification. The role of lymphovenous communications in reducing the early transient lymphedema in transplanted organs has not been satisfactorily elucidated; the effect of lymphostasis on the development of complications following transplantation, however, is well-known. Research on other aspects of lymphology, such as investigations on the cellular composition of the lymph in transplanted organs during various phases of rejection, or studies of lymph circulation in preserved and perfused organs may help to clarify many of the hitherto unresolved problems in organ transplantation. In agreement with Casley-Smith and Shdanov, we maintain that more attention should be paid to the ultrastructure of lymph capillaries and to the topographical distribution of lymphatics within organs (13, 14, 89).

In our opinion, the most important and formidable task of future research lies in attempts to resolve problems which link purely lymphological with immunological aspects of organ transplantation. The following considerations may serve to stress this point. In both graft and recipient a series of drastic changes occur. The transplanted organ is exposed to ischemia, it is temporarily deprived of lymph circulation and of innervation, in addition to the ever present danger of infection and/or rejection. The



a) photogram



b) diagram of experiment

Fig. 9 Immunological model of lymphedema of the ear of the rabbit.

recipient is under the influence of immunosuppressive agents which are toxic and exert complex and largely unknown effects upon defense mechanisms of the organism. Changes in graft and host, moreover, are mutually related: Lymphostasis may influence the establishment of infection as well as rejection mechanisms; infection, in turn, may affect lymph circulation but it also may modify graft rejection.

The examples mentioned in this report give an incomplete picture of the complex processes involved. Only combined lymphological-immunological studies will help to improve our understanding of the mechanisms mediating graft rejection and their possible dependence on each other. The following examples may demonstrate the fruitfulness of a combined approach. Lymph nodes of antigenically stimulated animals reportedly exhibit an enhanced trapping of antigen as compared to that observed in

Tab. 3 Survival of skin allografts with lymph fistula at the level of the regional node.

Procedure	av. survival days
Controls	13.1
Drainage	21.0
Drainage and suction	30.7

non-stimulated controls; this trapping ability appears to be impaired by immunosuppressive therapy (38). We observed an uneven escape of crystalloids from the lymph in lymph nodes of animals treated with immunosuppressive agents. Irregular contrast filling became evident in lymphograms of enlarged lymph nodes following administration of heterologous spleen cell suspensions in dogs (Fig. 8). This may be an expression of the altered trapping function of the node. It may be assumed that analogous changes in regional lymph nodes may affect the lymph circulation of the transplanted organ. We also demonstrated that edema occurred within 48 hours after transfer of lymphnodes of immunized animals and the corresponding antigen, to two different sites of the ear of the rabbit (Fig. 9). All antigens tested behaved in a similar manner. It is reasonable to assume that similar mechanisms may produce lymphedema in transplanted organs which, in addition, are subject to other damaging influences.

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ABSTRACTS

Basic Science

Daniel, P. M., L. G. Plaskett, O. E. Pratt (Dept. of Neuropath., Inst. of Psychiatry, Maudsley Hosp., London S.E. 5, England): **The Lymphatic and Venous Pathways for the Outflow of Thyroxine, Iodoprotein, and Inorganic Iodide from the Thyroid Gland.** J. Physiol. 188 (1967), 25

This experimental study was formulated to determine concentrations of thyroxine in thyroid lymph. A second objective was to assess the relative importance of the lymphatic and venous pathways for the outflow of various compounds leaving the thyroid gland. The lymphatic pathway probably plays a relatively significant role in the outflow of organic iodine. A large part of radioactive iodine in lymph draining from the thyroid gland is in the form of iodoprotein.

Baboons and cats underwent lymph cannulation procedures. Cervical lymphatics and thyroid lymphatics were cannulated. Radioiodine (I^{131}) was given several days earlier. Analytical procedures for two types of lymph and two sources of blood are listed.

Three main fractions of radioactive material were separated by paper chromatography or by precipitation methods. One fraction was considered to be iodoprotein. The authors show that thyroid lymph contains a relatively high concentration of iodoamino acid iodine in addition to iodoprotein. Both iodoamino acid iodine in thyroid lymph and organic iodine in thyroid venous and peripheral blood consist of thyroxine. Thyroxine levels, however are relatively higher in thyroid lymph than in the corresponding thyroid venous or peripheral blood. Thyroid stimulating hormone administration did not affect the thyroxine levels in thyroid lymph and blood. In some experiments cervical lymph was obtained This lymph contained diluted thyroid lymph. Nevertheles, it contained more radioactivity in the form of iodoamino acid and