in a few cases, improvement may take place even if the diet is started later than this. However, there is also evidence that in older children who have not deteriorated too greatly the diet may cause improvement in mental development, neurological status, and social behaviour.

It is not yet known for how long treatment should continue. There are an increasing number of reports indicating that the special diet has been discontinued without deleterious results, but until this work is fully confirmed no definite statement can be made.

Available published information about the effects of treatment is still incomplete, though eight years have elapsed since the first publication of a practical dietary regime. The Conference wishes to emphasize the importance of using standardized methods of biochemical control and mental testing. It is regarded as essential that, in future, full opportunities should be

provided for the collection of complete data on the progress of all cases reported in Britain.

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REASSESSMENT OF THE ANURIAS AFTER KIDNEY TRANSPLANTATION

BY

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In previous articles the problem of early post-operative anuria was reported (Dempster, 1950, 1953a, 1954a). Several years ago I was concerned with a consistently high rate (16%) of early post-operative anuria after kidney homotransplantation in the laboratory (Dempster, 1953a). A very much lower incidence (5%) of early post-operative anuria followed autotransplantation. Because the same phenomenon was encountered in both autotransplanted and homotransplanted kidneys, it was assumed that immunological causes could be excluded. Early post-operative anuria after autotransplantation was eliminated after the technique had become standardized, but early anuria after homotransplantation continued. Several investigators have observed, though they have not reported, this phenomenon, but some authors (Egdahl and Hume, 1955) deny it occurs otherwise than as a great rarity.

Whatever the incidence or significance of early post-operative anuria after laboratory experiments, there is no denying that after transplantation in man it is high. Hume *et al.* (1955) reported a post-operative anuria in five out of nine cases; Joekes *et al.* (1957) one case; Murray *et al.* (1960) one out of four cases; Küss *et al.* (1961) one out of three cases; Hamburger *et al.* (1962) three out of six cases; Govaerts (1962) two out of two cases; and Shackman *et al.* (1963) two out of six cases. Even if cadaver kidney transplants are excluded, the incidence of early post-operative anuria is high. From the figures indicated above it would appear that about 50% of human transplanted kidneys do not secrete for more than 48 hours.

The purpose of the description of early post-operative anuria was to issue a warning that this complication might be a cause of failure in man, as indeed has been proved in the event. Laboratory experiments were limited in so far as no techniques were available for correlating early post-operative anuria and canine blood groups, leucocyte antigens, and other cognate data. Accordingly it was not possible to suggest methods of

avoiding early post-operative anuria except those forms due to obvious technical problems. Now that several clinics have reported early post-operative anuria in man, it is opportune to reassess, in the light of recent clinical information, the significance of early post-operative anuria following kidney homotransplantation.

The early post-operative anuria previously described by me excluded thrombosis of the renal artery or vein or any other obvious technical factor. In the laboratory it is practical to remove kidneys at an early stage of anuria and to look for obvious causes of anuria. When this was done thrombosis was rarely found. If, however, the removal of a kidney is delayed for some days after the onset of anuria, thrombosis will no doubt be found sometimes (Shackman *et al.*, 1963).

Types of Anuria

In a previous paper devoted entirely to the problem of anuria arising after kidney transplantation in the laboratory four types of anuria were described (Dempster, 1954a). The question now arises whether these early post-operative anurias have a technical or immunological cause. Errors in technique such as vascular thrombosis and inadequate tubular perfusion certainly seem responsible for some early anurias. It is impossible to determine whether physical disturbances in the kidney occur after the operation is completed and the kidney is out of view in its new bed. In the case of some early anurias the technique seems to be satisfactory, and in these an immunological cause might be suspected, particularly since this type of anuria occurs if donor and recipient are not of the same ABO blood groups. Even if the technique is satisfactory and no obvious serological incompatibilities have been detected an identical type of anuria may occur. It may well be that other immunological processes, not yet detectable, are responsible for some cases of early post-operative anuria.

There would appear to be no virtue in changing or ignoring the classification of these anurias in assessing this problem in the human. Four anurias, as encountered in the laboratory, have been distinguished as follows.

Type 1.—Normally, after transplantation there is a temporary delay in urine production. In type 1 anuria there is a continuing failure to secrete after establishing the new circulation. Occasionally 50–100 ml. of urine may be produced in the first 24 hours. The anuria may or may not be associated with a toxic syndrome (Dempster, 1953b). Characteristically, in this form of anuria the transplanted kidney remains soft and does not regain its normal tension, nor does it begin to swell as the homotransplant usually does. The ureter, instead of performing vigorous peristaltic movements, remains inactive. In a few cases of type 1 anuria, arteriograms were made and have seemed to be normal during the first few hours after transplantation (Dempster, 1954).

Type 2.—The transplanted kidney regains its normal tension, begins to swell, the ureter undergoes peristaltic activity, and urine secretion starts quite early; but after 24 to 36 hours of quite adequate function oliguria and finally anuria occur.

Type 3.—The natural course of the homotransplanted kidney ends in anuria. It is an anuria which develops abruptly after a varying period of adequate function. The anuria is usually preceded by a short period of oliguria, during which time the blood urea rises and a toxic state develops (Dempster, 1953a). In some instances the anuria may set in without a premonitory warning of oliguria. The toxic state may be apyrexial in a bilaterally nephrectomized recipient. Anorexia is the most constant symptom of impending rejection. An exact clinical confirmation of the laboratory description has been reported (Michon *et al.*, 1953). The oliguria is invariably associated with a profound fall in the serum trypsin-inhibitor (S.T.I.) level (Tyler *et al.*, 1962). When a typical acute rejection occurs, pain, swelling, and tenderness over the kidney region is severe in the human and the dog. The final urine collection is usually sterile and free from excess protein and amino-acids. A slow onset of oliguria and a decline in renal function several months after transplantation usually poses the problem of a slow rejection. When a slow decline in renal function several months after transplantation has been encountered, a diagnosis of slow rejection has been resisted because our objective tests have not indicated rejection. Diagnosis of rejection involves (1) a full investigation involving aortography to demonstrate blood flow to the kidney; (2) the assessment of the S.T.I. levels; (3) a history of sudden oliguria, fever, and anorexia; and (4) pain and tenderness over the kidney.

Type 4.—This is the anuria associated with a sensitized animal—a second set phenomenon (Dempster, 1953a, 1953c). The anuria is preceded by some hours of quite profuse diuresis. Oliguria develops and anuria is usually complete by 36 hours. It is associated with a toxic state. The S.T.I. level falls to a lesser extent than in type 3 anuria (Tyler *et al.*, 1962). This violent reaction is definitely a host humoral reaction against the kidney. This reaction introduced an immunological dilemma which has not yet been resolved (Dempster, 1955).

Histological Characteristics of Transplanted Kidneys Involved in the Four Types of Anuria Encountered in the Laboratory

Types 1 and 2.—In these there appear to be three patterns: (a) some sections showing minimal tubular damage of a focal character or merely cloudy swelling of tubule cells—a thrombus may be occasionally found in a small venule; (b) some sections showing universal or focal necrosis with a band of congestion at the

cortico-medullary junction; and (c) some sections showing widespread casts in the tubular lumina. It is difficult to understand why absolute anuria should have occurred in the first group. The histology of the other groups adequately explains the anuria but leaves the cause obscure. Since anuric kidneys in the laboratory were usually removed within 48 hours, it is possible that the histology of the first group does not provide a parallel for human anuric kidneys, which are usually removed much later.

Type 3.—Provided the transplanted kidney is removed during the oliguric phase, the renal parenchyma appears remarkably normal. On closer histological examination and nephron dissection a lesion limited to the tubule neck can be demonstrated (Darmady *et al.*, 1955). The histological features may be divided into two phases: (a) those occurring during the functioning phase, and (b) those occurring during the oliguric-anuric phase. During the functioning phase the interstitial oedema is pronounced from an early stage. There is also a varying concentration of pyroninophilic cells which increases with time. The endothelial cells of the arterioles are also pyroninophilic. The tubules appear to be remarkably normal (Darmady *et al.*, 1955). The oliguric-anuric phase involves a rapid invasion of the kidney by polymorphs, lymphocytes, and monocytes. Within 24 hours a liquefying process inexorably destroys the whole kidney and finally no recognizable renal tissue other than an occasional tuft can be identified in an ocean of cells (Dempster, 1957). It is important to differentiate these two phases because the oliguric phase has been reversed in the human by timely local x-irradiation of the transplanted kidney together with cortisone and antimetabolic drugs (Küss *et al.*, 1961). This is a brilliant empirical achievement. The post-anuric phase is not reversible.

Type 4.—The histological picture is distinctive (Dempster, 1953a, 1953c). Widespread tubular damage, interstitial haemorrhage, and oedema occur. There may be a minimal cellular interstitial infiltration in some cases. The tuft capillaries are ruptured and protein can be seen in the subcapsular space. Fibrinoid deposits in the tuft capillaries are conspicuous.

Possible Clinical Causes of Early Anuria

An essential task at the moment is to assess early post-operative anuria after kidney homotransplantation in the human and to try to determine possible causes so as to prevent such tragedies happening in future. It might be profitable to list the possible clinical causes under each type of anuria.

Type 1

This type comprises the following factors:

- (a) ABO-blood-group incompatibility (Murray *et al.*, 1960; Shackman *et al.*, 1963).
- (b) Inadequate renal perfusion: (1) cadaver kidneys (Hume *et al.*, 1955); (2) unknown factors associated with increased renal peripheral resistance after the establishment of the new circulation.
- (c) Unknown factors—pre-existing toxic humoral factors and previous blood transfusions.

Prevention of Type 1 Anuria

Operating techniques should be standardized and preliminary mistakes made in the laboratory rather than

on the human subject. Haemorrhagic necrosis and vascular thrombosis are obvious technical causes of early post-operative anuria, but are excluded, by definition, from type 1 classification. It has been shown that haemorrhagic necrosis (Dempster, 1953b) was apt to ensue if clamps were reapplied to the artery in order to insert an extra stitch on a bleeding-point on the arterial anastomosis. In my opinion clamps should never be reapplied once the circulation has been established. A muscle graft on the arterial anastomosis usually controls bleeding.

Except in obviously favourable circumstances one should avoid cadaver kidneys. It is a frustrating situation, because there must be sympathy for the argument against removing healthy kidneys from healthy donors. One should avoid ABO-blood-group incompatibility. The rise in the anti-A haemagglutinins in a case reported by Shackman *et al.* (1963) is objective evidence of blood-group incompatibility associated with immediate anuria.

Lack of perfusion after the circulation has been established has been suspected but not satisfactorily proved. It is conceivable that in some anuric kidneys the peripheral resistance is abnormally increased and adequate perfusion is prevented. An infusion of "rheomacrodex" during the operative procedure appears to aid renal perfusion. In addition, a bulldog clamp is applied to the external iliac artery distal to the anastomosis. The object is to ensure a maximum flow to the kidney in the first half-hour after establishing the new circulation.

It is not possible to take preventive measures against other unknown causes of type 1 anuria. It is hoped that other causes will be discovered.

Type 2

(a) *Mechanical compression of Renal Circulation.*—It has been shown experimentally that the homotransplanted kidney doubles its weight in the first three days (Dempster, 1955). The increase in weight is due to interstitial oedema. Clinical experience confirms this. Theoretically, therefore, should the kidney capsule not stretch quickly enough in order to accommodate the oedema, compression of the circulation through the kidney may result in anuria. Küss *et al.* (1961) have reported an anuria due to this oedematous expansion 48 hours after transplantation. At a second operation the capsule of the transplanted kidney was split and function resumed again shortly afterwards. Another mechanical factor may be compression of the kidney in the iliac fossa by tight abdominal muscles. In some cases in our clinical experience difficulty has been encountered in closing the muscle wound over the kidney. This is especially so if a profuse diuresis is occurring and the kidney, as a consequence, is tense.

(b) *Blood-group Incompatibility.*—Two clinics have reported anuria at 48 hours with MN incompatibility between donor and recipient (Hamburger *et al.*, 1962; Shackman *et al.*, 1963). This is a possible but not a proved correlation. No anti-M antibodies were actually demonstrated in the case reported by Shackman *et al.* (1963). But the fact that anuria occurred in two cases at about 48 hours where donor and recipient were MN-incompatible requires further study, though theoretically no mishap should be encountered at body temperature.

(c) *Unknown Possible Factors* (casts blocking the tubules and blood sludging).—Hamburger *et al.* (1962)

have reported type 2 anuria in one case (No. 2) where donor and recipient were compatible in all blood groups and shared similar antigens. These authors were of the opinion that pre-existing antibodies were responsible for early anuria in this and in one other case. They have produced no evidence to support their claim, and they appear completely unaware that experimentally early post-operative anuria is well recognized. Their histological illustration of Case 2 resembles the histological features encountered in anurias after autotransplantation (Dempster, 1954a, Fig. 7), and therefore one would require more evidence before exculpating technical mischance and incriminating immunological factors. Without constant autotransplant controls hasty immunological conclusions can be made.

Prevention of Type 2 Anuria

In order to avoid anuria due to constriction by a capsule which is not able to expand quickly enough, it is obviously wise to strip the capsule partially as a routine, as Küss *et al.* (1961) advise, after the new circulation has been established (Dempster, 1962).

Compression of the capsule may not be the only cause of interference with the circulation of a kidney transplanted to the right iliac fossa. Other causes may include: (1) Compression of the kidney against the posterior bony mass of the iliac fossa by tight abdominal muscles, which should be avoided. A large male kidney should not be placed in a small female iliac fossa, for example. (2) Venous congestion due to compression of the renal vein by surrounding tissues after the wound has been closed. The technique of an end-to-side venous anastomosis is the only reasonable one so far as the human is concerned. In the laboratory an end-to-end venous anastomosis is performed (Dempster, 1954b). The entry of the anastomosed renal vein into the external iliac vein of the human is seldom at a satisfactory oblique angle. This being so, there may be a tendency during the first 48 hours for the venous outflow to become slightly obstructed. The complication of the acutely congested autotransplanted kidney has been reported (Dempster, 1950).

It is not possible, on the currently available evidence, confidently to rule out technical causes for all early anurias following kidney transplantation. The question now arises whether the pelvis is the site of choice in the human in view of limited space for an enlarging kidney. It may be that the renal field would be a more favourable site, although serious problems related to the ureteric anastomosis would then arise. Egdaahl and Hume (1955) encountered experimentally only one case of early post-operative anuria in a series of 66 transplants to the renal field. This is a remarkable achievement.

Since most of the non-mechanical causes of early anuria are quite unknown, it is not possible at this juncture to suggest preventive measures. If technical causes can be excluded it would appear that the greyhound, used in our laboratory, and the human may have humoral toxic factors in common which can precipitate early post-operative anuria, because Egdaahl and Hume (1955), using other breeds of dogs, did not encounter a high incidence of post-operative anuria.

Two other distinct clinical entities might profitably be inserted at this point. These are (1) a genuine accelerated rejection, and (2) phases of temporary decline in renal function.

(1) There would appear to be no doubt that in the laboratory transplanted kidneys can be rejected on the third day with the associated typical toxic syndrome. This in our experience is rare and should not be confused with type 2 anuria occurring at 48 hours. This form of rapid rejection will quite likely be encountered in the human.

(2) So far two cases have been encountered in our laboratory in which a definite decline in renal function occurred at 48 hours. On the basis that blood sludging might be responsible for this sudden decline in function, 500 ml. of dextran of low molecular weight (rheomacrodex) was infused intravenously. Within 12 hours diuresis was restored and within 48 hours excretion tests returned to previous levels. The kidneys then continued through a normal natural course for a further period of time. Other authors have recently found that dextran of low molecular weight was of value in preventing kidney damage due to incompatible blood (Atik and Gutierrez-Saenz, 1961).

Hamburger *et al.* (1959) have reported a sudden decline in renal function in one of their cases at the 15th day. Normal function returned about the 22nd day without any relief measures being taken. These phenomena may be related, and one should be prepared for a sudden temporary decline in renal function. We cannot claim that rheomacrodex accelerated recovery in our two laboratory cases, but it should perhaps be given a trial in routine kidney transplantation in man. So long as function continues, one should avoid thinking in terms of a rejection process, and Hamburger *et al.* (1959) are to be congratulated on their masterly inactivity. It is advisable to avoid repeating total body x-irradiation.

Type 3

The previous two types of anuria are unwelcome complications, whether they be technical or immunological. Unless some mechanical cause be found and relieved rapidly, these two anurias are probably irreversible. In some cases the cause of anuria is a complete mystery, and hence the whole problem of kidney homotransplantation is made immeasurably more difficult. Type 3 anuria, on the other hand, is the natural termination of a homotransplanted kidney. The cause of type 3 anuria is said to be the result of an antigen-antibody reaction. It is claimed that the host actively acquires an immunity against the kidney transplant and destroys it with antibodies transported by immunologically competent cells. Most workers are well content with this theory in spite of repeated failure to demonstrate the kidney antigen and the anti-kidney antibody. Some of the evidence against this theory is set out elsewhere (Dempster, 1960; Dempster *et al.*, 1963). Whatever may be the cause of anuria it arises from a subtle intracellular process in the tubules—that is, a reaction of the kidney against its host (Dempster, 1955).

Prevention of Type 3 Anuria

This constitutes one of the great fundamental problems of modern medicine. The following techniques have been used with a small measure of success in man, in whom the natural life of homotransplanted kidneys is not so well defined as in dogs.

(a) *Sublethal Total Body X-irradiation to Recipient Prior to Transplant.*—Dempster *et al.* (1950) demonstrated that skin homografts would survive longer in rabbits which received sublethal total body x-irradiation.

This technique did not succeed in prolonging the survival of homotransplanted kidneys in dogs (Dempster, 1953a; Hume *et al.*, 1960). Merrill *et al.* (1960) and Hamburger *et al.* (1962) have reported prolonged survival in humans with this technique. The significance of the success gained by this technique remains to be assessed because experimentally only slight prolongation was attained.

(b) *Sublethal Total Body X-irradiation Plus Local X-irradiation to Transplanted Kidney After Transfer.*—Küss *et al.* (1961) have reported two cases in which the survival was prolonged for long periods. Post-operative x-irradiation to the kidney was given in both cases together with the administration of cortisone and 6-mercaptopurine. Local x-irradiation also played some part in abrogating a typical rejection process—that is, oliguria and toxic syndrome—in one case. A further case of prolonged survival with this technique has been reported (Küss *et al.*, 1962). Shackman *et al.* (1963) have shown that successful prolongation can be achieved by small doses of total body x-irradiation (150 rads) together with 200 rads to the transplanted kidney. This technique is relatively safe. Its advantage is that the life of the patient is not endangered by bone-marrow failure, and in addition daily administration of drugs is avoided. High doses of total body x-irradiation (over 250 rads) should be avoided because of the possible fatal consequences that follow marrow failure. Neither the dog nor the human patient can withstand the total body dosage meted out to rodents. A dose combining safety with efficiency is 150–200 rads. One patient has now entered his third year and survives entirely on the homotransplanted kidney (Shackman *et al.*, 1963).

A short note in explanation of the possible rationale of local x-irradiation of the homotransplanted kidney may be of value here. A homotransplanted kidney starts to swell from interstitial oedema a few minutes after the new circulation is established. This can be regarded as a reaction of the kidney against certain, so far undefined, toxic factors in the host—that is, a graft against host reaction (Dempster, 1955). It is perhaps the extent to which the oedema develops and is unable to be transported from the kidney by the lymphatics and the concomitant intracellular response of the tubule cells which determine survival or rejection. Ehrlich's concept of every cell being able to defend itself may be relevant here. To search, however, for anti-host antibodies produced by renal tubule cells would be fruitless, since antibody production may not be involved in the defence mechanism of these cells. One can regard rejection as a tubular biochemical defect and interference with transport systems. It is possible that timely local x-irradiation is able to suppress the reaction of the renal tubule cells and at the same time maintain normal capillary permeability.

(c) *Antimetabolic Drugs.*—These have successfully prolonged kidney homotransplant survival in a small percentage of animals (Calne, 1961; Calne and Murray, 1961; Pierce and Varco, 1962). It is conceivable that these drugs can control the reaction of the kidney against its host. There is little correlation between dosage and prolonged survival. One case of prolonged survival in man has been reported. The drugs used were "imuran" and actinomycin C (Murray *et al.*, 1962).

It is encouraging that techniques are now available for achieving limited success in the human. It is of great importance that several techniques be pioneered successfully because no one technique can be expected to be of universal clinical application. Solution of the cadaver kidney problem becomes of paramount importance. Rheomacrodex may play an important part in achieving well-functioning cadaver kidneys.

Discussion

Now that several clinics have published the results of kidney homotransplantation in the human it is obvious that early post-operative anuria is the most important complication. Indeed, the situation at the moment is most depressing in spite of a few successes. It is likely that early post-operative anuria will continue to complicate kidney homotransplantation for some time to come. One has to try to differentiate technical failures on the one hand and possible immunological anurias on the other. The causes may be quite different in man and in laboratory animals.

Although it is possible to make out a case, based on circumstantial evidence, for avoiding kidney transplantation where there is a MN incompatibility between donor and recipient (Hamburger *et al.*, 1962; Shackman *et al.*, 1963), type 2 anuria can occur when the blood groups, subgroups, and leucocyte antigens are all compatible (Hamburger *et al.*, 1962, Case 2). This makes the problem extremely difficult to assess, because an obvious cause of anuria is difficult to find.

Hamburger *et al.* (1962) have postulated that pre-existing antibodies were the cause of early anuria in two of their cases. They have produced no evidence.

The only evidence for an association between early post-operative anuria and pre-existing antibodies is that provided by Shackman *et al.* (1963). The meteoric rise in the anti-A haemagglutinins is adequate proof of the incompatibility resulting from the transfer of a kidney from a group A donor to a group O recipient. There is evidence that ABO antigens are represented on the renal tubule cells (Hogman, 1959). The anuria reported by Shackman *et al.* (1963) was obviously due to an incompatible blood-transfusion reaction. Pre-existing antibodies or toxic factors related to blood groups, platelets, and plasma can be considered as possible causes of early post-operative anuria. To suggest pre-existing transplantation antibodies would introduce a heresy from the point of view of the established theory of actively acquired immunity against grafted tissue.

Several years ago, when it was decided to report complications of kidney transplantation, the early anurias had become as important to us as the problem of homotransplant rejection itself. Now that the homotransplant barrier, whatever that means, shows signs of being penetrated in the human, the importance of early post-operative anuria becomes even more impressive. Where no obvious cause can be incriminated, early anuria is perhaps even more mystifying than the homotransplant problem itself.

From the histological point of view it has been pointed out that the early anuric kidneys may or may not have suffered severe damage. It is not usually possible to differentiate this clinically. Since recovery of function may ensue at a later date, as indicated by the report of Hume *et al.* (1955) it is imperative that one should continue to treat these anuric and uraemic patients by blood or peritoneal dialysis until further investigative measures indicate that an irrecoverable lesion is present.

Summary

There are four clearly defined types of anuria which can follow kidney homotransplantation. Types 1 and 2 occur within 48 hours after operation and are usually irreversible. From clinical reports, so far, the incidence is high—about 50%. An attempt is made to assess the

possible causes, technical or immunological. Obvious causes can be defined, but the majority of these anurias defy explanation. Among the possible causes of type 1 anuria, which is immediate after establishing the new circulation, are ABO-blood-group incompatibility and inadequate renal perfusion. Type 2 anuria occurs at about 48 hours after transplantation and may be caused by mechanical compression due to oedema or sludging in the veins. There is not yet sufficient evidence to exclude technical faults for these so far inexplicable anurias.

Rheomacrodex, a 40,000-molecular-weight dextran, increases renal blood flow and renal perfusion in kidneys where these factors are low. It is of benefit in the laboratory in reducing the incidence of early anuria. It may be of value clinically.

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