MCV/Q

MEDICAL COLLEGE OF VIRGINIA QUARTERLY

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CONTENTS

COVER

Design by Raymond Geary highlights discussions of kidney transplantation.

OPPOSITE

Patient who has received a kidney homotransplant is undergoing radiation therapy of the kidney to suppress his immune response. X-ray is being delivered by a 2-million volt "Maxitron 2000". The Medical College of Virginia acquired the unit in 1961, through the efforts of the Federation of Women's Clubs of Virginia, the American Cancer Society, the M. C. V. Endowment Fund, and other contributors. The Maxitron is also used for therapy of malignant disease.

The Treatment of Chronic Uremia

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I will begin by telling a little about the development of chronic dialysis. In 1959 we were working on a system to prevent uremia in acute renal failure. We were trying to develop a system to which we could "hook" the patient for as long as a week, so that we would exactly mimic his normal kidney function during the period of acute renal failure, and make his prognosis that of a patient who had kidneys. The system worked reasonably well. We had to make a lot of modifications, such as using a Skeggs-Leonard dialyzer with low resistance. We used a large deep freeze as a dialysate reservoir because we could not afford to change the bath every few hours. The patient was on continuously. We had to cool the external circuit to control clotting problems and infection. We actually had patients on this system for as long as two weeks. It was important to us that we had this system in operation at the time we first devised the cannulas. (The cannulas were devised by Dr. David Dillard, our surgical consultant, and Mr. Wayne Quinton. It is amazing how well their original design has held. As far as I know, it has not been improved greatly, because the cannulas are still the weakest part of the system.)

General Features of the Cannulas and Shunt

The essential system has a long subcutaneous tunnel with a curve of 180° into each vessel. The tunnel is to prevent infection, and the curve is to stabilize the cannula in the vessel. The system does not clot because one tube is in the artery and one tube is in the vein, and the blood runs through. Of course, it all depends on teflon for non-clotting. Allwall had tried the idea in 1944 and failed, because he was using glass cannulas and rubber tubing; we had a teflon system exclusively. This is the basic operating principle of the system: when you want to treat a patient, you simply pull off the shunt, connect the tubing to the artificial kidney, and you can dialyze at will. The best evidence I can give that this system works is the first chronic patient ever to receive cannulas. He is Clyde Shields, who now has been five-and-one-half years on dialysis. He has not passed any urine in over five years, and is today in better health than at any time. We had to learn on our first patients how to manage chronic uremia by dialysis. We did not know how much dialysis it would take, we did not know how to take care of the cannulas, and we did not know what complications to expect. Clyde has his present cannulas in his leg. We used up all the arm sites in the first few months because the straight teflon system would last only a few months and not much longer. The new rubber segment has made a great difference in the cannula system. The nurse used to put the heparin into the bloodstream. We no longer do this, but use an infusion pump. Note, though, that the nurse does the entire procedure. In Seattle, dialysis is completely nurse-technician operated on the chronic program, and doctors are not in attendance.

We had our clear plastic Kiil dialyzer built especially to study dialyzer-flow pattern. One of the things that is so important is a better understanding of what is going across these mem-

branes. If we could really understand what the chemicals are that we had to move, and urea is one of them, then we could build better membranes. As far as the technique of dialyzer design, ours is a good one but it is not perfect. There is streaming, and the minute you get streaming in a dialyzer, you loose efficiency. We had this particular version built to study the flow patterns. This Kiil dialyzer is the design of Dr. Frederick Kiil in Oslo. He took the original Skeggs design and modified it so that it was easier to assemble, and more efficient to use. This is the only dialyzer at the present time that has been proven useful in the treatment of chronics, because it is low in resistance, small in blood volume, and easy to assemble. When the blood finally reaches the venous end of the external circuit, the nurse plugs the venous candula in and the patient is on dialysis.

For some idea of the progress being made in the technology, where we could formerly only treat three patients, we can now take four, thanks to the central pumping system which takes concentrate from a tank, and uses very accurate proportioning pumps. They mix the concentrate with tap water, which is monitored by a conductivity meter, and then the fluid is pumped around the room to the various stations. The whole system is automatic. This then means that we fill this concentrate tank about once a month instead of filling a tank once a day for each patient.

Results of Management by Dialysis

We recently conducted a survey on the current state of dialysis around the world. There are 12 centers that have been in operation for longer than one-and-one-half years. There are seven, and probably more, newer groups just getting started. There have been 95 patients taken into treatment. There have been 28 deaths. What is most important is that 75% of the deaths have occurred during the first year of each program. This underscores the need for adequate preparation, adequate funding, adequate training of personnel, and adequate creation of facilities especially for chronic dialysis. This also means that a realistic approach to the problem is needed, rather than the helter-skelter one that is so tempting when you are confronted with a dying patient. The other 25% of the deaths were due to what we considered to be natural causes. In other words, the one patient who died in Seattle, died one year after starting the program, of a myocardial infarction. And we certainly do not believe that dialysis is going to prevent myocardial infarction. In fact, these patients having only moderately good control of their blood pressures (some have normal and some have moderate elevation of blood pressures), obviously are going to be more prone to the vascular complications of hypertension than the normal population. But these deaths are the natural ones, and the other deaths can virtually be eliminated with proper training and proper preparation.

The rehabilitation rate should also increase as treatment is started earlier, so you will not be dealing with moribund patients. A lot of the failure to rehabilitate has been due, for instance, to starting with a moribund patient who gets severe neuropathy. This has been the case in our one failure to rehabilitate, and an early start would avoid this. As far as prognosis is concerned, the longest one is our patient who has been five-and-one-half years on dialysis. He is in better health now than he has been at any time.

Limitations of Dialysis in Children

If you take the ideal group, dialysis seems to be contraindicated currently in the adolescent and the child, because we have failed to maintain normal growth and to effect sexual maturity in the one patient we treated in this way in Seattle. This does not mean that, with improved membranes and improved techniques, we will not be able to maintain normal growth. And this will be a very sensitive assay of the adequacy of dialysis. Even when confining ourselves to the age group of 15 to 45, we have about 25 new patients per one million population per year. In the United States, there are about 5,000 new patients per year. If the life expectancy is 10 years, this means there will be a patient population of 50,000. This is indeed a staggering number of patients. When we think of our present technology, no wonder adequate treatment seems impossible. On the other hand, I think we are just scratching the surface of what is possible technically, and I would like to underscore that by briefly covering some of the advances made since the program began.

Problems and Complications

The first problem we faced was loss of the cannulas. Mr. Quinton correctly diagnosed the reason as due to stiffness in the teflon. The system would not give with the normal rotation of the limb, and we lost the cannulas in a matter of months due to mechanical failure. Infection has occurred, of course, but it is largely due to abuse of the cannulas by the patient, and inability to coöperate in his daily care. Mr. Quinton worked one year to extrude silicone rubber tubing that would not clot, after Dow-Corning said that it could not be done. Now all patients on chronic dialysis have this shock absorber in the system which greatly prolongs the life of the cannulas. The first patient to get this kind of cannula was in the program in Seattle, and, three years later, he has the original set. The usual life of these cannulas extends from a few months to one-and-one-half years, depending, mainly, on how carefully the patient takes care of his cannulated extremity. Certainly, undue activity is the most important factor in determining cannula failure. We think the flexibility primarily accounts for the increased longevity of the cannulas, compared with the old teflon.

In Seattle, as in most centers, dialysis worked like this: it was an operating room procedure that took a lot of work, a lot of people, and was terribly expensive. Chronic dialysis twice a week, using this approach, cost from $20,000 to $30,000 per patient per year. But in two years, starting with the basic continuous system I mentioned, we have evolved the Seattle continuous-flow, low-temperature system. We have turned it into a nursing procedure. This makes possible, then, the Seattle community center-type operation (under the direction of John Murray, first, and now Jerry Pendras),

where one nurse dialyses four patients at once. The cost projections and the pattern of operation of chronic dialysis all depend on the basic lessons learned in this center, which was very generously and very wisely funded by the John A. Hartford Foundation in 1962. This center was built in the basement of the nurses' home in Swedish Hospital. It shows what could be done in the community, and that it could be done outside the hospital or in a low cost area. The cost of this type of operation currently is $100 per dialysis, or $10,000 per year for two treatments per week, including professional fees. This is really the actual, total cost. Rule off something such as construction and purchase of fixed equipment, and the cost is somewhat less.

We have made considerable progress in understanding the diseases of dialysis. Clearly, all of these diseases, with the exception of peripheral neuropathy, are due to inadequate dialysis. The experience of the older days, where you could not dialyze as much as necessary, or the patients lost weight, vomited, became malnourished, and died, was simply because of inadequate dialysis. Gout, or gouty-like arthritis which is an acute arthritis that is responsive to colchicine and can be reproduced by putting urate in the bath, responds to adequate dialysis. Metastatic calcifications dissolve if you keep the phosphorous low enough with dialysis, and peripheral neuropathy can be stabilized by dialysis. But probably the most important factor in peripheral neuropathy in these patients is the critical illness that may precede the institution of therapy. Invariably, if the patient becomes critically ill at the time you start therapy, in a week or a month he may develop a severe peripheral neuropathy. The degree of severity of this neuropathy varies tremendously from patient to patient, but the clinical picture is constant. There is now an excellent description of this situation in the literature from the Massachusetts General Hospital. The prevention of neuropathy at this stage of our understanding depends largely on starting dialysis or doing the transplant before you are dealing with a moribund patient. We have not yet defined diseases due to much dialysis, but because our membrane is nonspecific, I am sure that some will be defined. Secondary hyperparathyroidism is not a problem, but anemia is a continuing problem. The average requirement, if you rinse your dialyzer properly, is about two units of blood per month. This is an area of obviously great interest. If an erythropoetin could be made available, we might eliminate this. Stanley Sheldon in London believes that more intense dialysis and a higher protein diet will minimize the anemia.

The greatest problem for the patient is controlled hypertension. The real cross these patients must bear is learning to eat a low-salt diet. There is no question that if he can learn a low-salt diet, his blood pressure will be controlled. It takes from three to six months for a patient to really learn to eat a low-salt diet. They cannot cheat. If they eat salt, they gain weight, and it shows up on the scale when they come into the center. Once they learn it, their pressures are controlled either at, or near, the normal level.

The Future of Hemodialysis

With this background, then, I am going to talk briefly about my concept of the future of management of chronic uremia. One point I want to make here is about good conservative care. This is an area which is greatly misunderstood, both by nephrologists and by doctors in general. The most important factor we have found in the management of the chronic is the control of hypertension by means of sodium restriction. All the emphasis in the literature on the management of the chronic has been on the salt-losing crisis and the magic effects that salt has on a patient in uremia. This is not the place to put the emphasis. There is no question that, if a patient is salt-depleted, and his neck veins are flat and his blood pressure is down, that his GFR will drop almost to zero. Salt, then, can have a miraculous, life-saving effect on this patient. But for every one of these, there are 500 patients who are being abused by too much sodium. It is our contention that it is the high blood pressure induced by sodium overload, rather than the disease itself, that is most often responsible for progression of the renal lesion to the fatal end. And we have diagrammed this idea by showing the maximum and a minimum sodium excretion for a patient having progressive loss of his kidney function over a 30-year period. At some point, he gets both a floor and a ceiling on this ability to handle sodium. The inability to conserve sodium has gotten all the emphasis because a few patients, particularly those with pyelonephritis and polycystic disease, waste sodium. But as of now in our renal clinic, we have about 30 chronics with serum creatinines above 2, and there is only one that is a significant salt waster. The more important problem is that they have an upper limit on their ability to excrete sodium and when they start taking in more than they can handle, their blood pressure rises, they get malignant hypertension, and die. We give every patient a blue book to record his blood pressure, weight, and urine volume, although the urine volume is not really important. Then we teach them the relationship between the amount of salt they eat, the change in their weights, and the change in their blood pressures. We saw a patient in 1960 who had "bad hypertension". The sole maneuver there was to put him on sodium restriction. True, his creatinine bounded around a little. When first started, the creatinine will always go up, which is another thing that has received undue emphasis. As long as it does not go up into the symptomatic range, you should not care. Because, if you are not going to control that blood pressure, experience shows that the man will be dead in a matter of months. Four years later, this patient's creatinine is still stable around 8 and his blood pressure is well controlled on a low salt diet. Occasionally it is well to add small doses of blocking agents, but our experience shows that patients with uremia tolerate these drugs very poorly. If they go into dialysis, they are going to have to go on a low salt diet anyway. We prefer to use the diet as our major therapeutic tool. All of our patients, we feel, would have been dead within

months had their blood pressures not been controlled. So the message is, control blood pressure by any means that you can, and you are likely to get a lot more mileage out of your patient's kidneys and avoid the day when definitive therapy is going to be needed. I am not minimizing the importance of giving salt if the patient is sodium depleted, but this is a very special, rare problem. What I am talking about is the garden-variety, day-to-day management of the patient with renal insufficiency.

The Place of Peritoneal Dialysis

Dr. Fred Bohn has been working in peritoneal dialysis for a number of years, and his monograph is well known. Eighteen months ago, peritoneal dialysis in the management of the chronic was discredited, and rightly so, because peritonitis was the rule. Dr. Bohn devised an automatic cycling machine; which is a completely closed dialysate system. He figured out an experiment to sterilize these big bottles of fluid so that no one has to cycle the machine, thereby eliminating the need of the nurse or family. Now, after having lost one patient with peritonitis, he has a second patient going, and believes it is because of this closed system which maintains sterility. After three months of treating this patient for recurrent peritonitis, he resolved that the indwelling peritoneal access prosthesis was the villain, and to make a successful chronic peritoneal dialysis, he had to insert a peritoneal cannula every week, through a tiny incision that heals from one week to the next. Since he removed the prosthesis, he has not had a bit of trouble with peritonitis. It is on the basis of comparing the patient who loses significant amounts of protein through the peritoneal membrane with our patient on hemodialysis, that we think that a synthetic membrane with a larger pore size is needed.

Hemodialysis in Relation to Transplantation

We are very concerned about the future of dialysis in relation to the real hope in this field, transplantation. There is no question that if you have a human kidney inside you, working, this is far superior to an artificial one. You are not tied to a machine, you don't have to worry about getting to the center, you don't have to take care of cannulas, and you don't have to eat a low salt diet. But as we see them, here are the facts on the current status of transplantation: Of the identical twins whose operations were performed five years ago, 70% are now dead of recurrent kidney disease. The recurrence rate is 50% in the Boston group. We had a patient with glomerular nephritis who was sent to the Mayo Clinic and transplanted from her mother. Six days after the transplant, the mother's kidney was destroyed by the same disease that originally had destroyed the patient's kidneys. This is a very important case, of course. A question raised is, had this patient been carried for two or three years on chronic dialysis, would this immune activity have abated and would, then, the transplanted kidney have survived? If we get another such patient, we will try a double transplant, probably first from a cadaver, doing it right away, and then waiting two or three years and trying it a second time. Dr. Don Thomas, who is in charge of our transplant program, recently reviewed the latest summary from Dr. Joe Murray's group in Boston. He concluded that the chances of surviving for two years on a transplanted kidney are somewhere between 5 and 20%. The chances of surviving for four years probably are less than 1%.

I can say with some conviction that the chance of surviving four years on chronic dialysis in the current well-run program approaches 100%. The big *if* in the dialysis program is that you must have a coöperative patient. The one thing stressed by all now doing chronic dialysis is, if the patient cannot coöperate, take care of his cannulas, or stay on the low salt diet, then the chronic dialysis is not a very good form of treatment. The amazing thing we have found is that a group of patients who are coöperating seem to pull along the ones who are not, especially during the early days when they are learning about the program. Most patients will coöperate, because when they begin to feel well and see what salt overload does to them, they learn from bitter experience that it is better to coöperate than to be sick.

I want to make another point that I believe is important because of the neuropathy problem. Despite economics and the intense need right now, the sooner we make a logical transition from good pre-dialysis care into dialysis, and into transplant after dialysis without having a crisis, the sooner our patients are going to be happier. Our new clinic that will be opened at Swedish Hospital has the capacity for 30 new patients. Our patients who now are being treated in town by the various kidney doctors have already visited the center. They know what they are going to get into when the day comes. They have heard about transplants, they are prepared emotionally, and they are getting prepared financially to take on the definitive treatment, long before it will be necessary. This is an ideal that we are far from achieving. When we do achieve it, our patients and doctors will be much happier.

Home Dialysis

So the hope for the future rests on lowering the cost of the present form of treatment (the central pumping system is one example of how we are doing this with the important coöperation of our engineering colleagues), some form of home dialysis, and, of course, the big hope is that we can make real progress in the immunology of transplantation. Now we have a very exciting development, one that I think offers real hope, particularly in the financial area. That is home dialysis. Our first patient on the home program was a young high school girl who is dialysed by our family in her basement. The dialyser is a miniaturized version of our central pumping system that is fully automated. A standard Kiil dialyser is used. We switched from zepharin or formaldehyde to acetic acid, a more effective germicide that is often forgotten. When using acetic acid to sterilize the artificial kidney, some is left in, which the patient readily metabolizes. Then, when ready to dialyze, you simply hook the kidney to the bath

source, acetic acid becomes sodium acetate, and you convert a germicide into a metabolizable substance. Then, as I mentioned, the dialysis fluid is supplied by a miniaturized version of our central pumping system or by a home tank.

We started the patients in an isolated area of the hospital, where the family can be taught a little about what goes on inside an artificial kidney. The family first observes the technique and gradually begins to take over. It takes a surprisingly short time to teach a family to operate a system at home. We totally underrated the motivation of the patient to learn. The family realizes it is their relative's life at stake, and that if they do not learn to run the equipment, they might well lose their relative. They learn much faster than our technicians and nurses who train for our center program.

We are literally just scratching the surface on what is going to be possible in the home program. The cost, which we hope is generous, looks like it is going to be under $5,000 per year. The breakdown is very encouraging, because such things as equipment, maintenance, and depreciation are the kind of things communities can fund. This leaves $3,000 or so per year for the patient to pay. The startup costs are around $8,500 for the first year. This is a very rough figure; we do not have enough experience with home dialysis to know, but at least it is less than half of what our current center type of operation costs. (As of November 1965, there are seven patients on home dialysis in Seattle, and there have been no failures.)

The advantages of home dialysis, in addition to the cost factor, is more intensive dialysis. It can be done in the evening, for example. Instead of spending the evening in the center, they spend the evening at home. When an unattended nighttime dialysis is possible, we have 56 hours a week during the night to dialyze. This would then free all of the patient's waking hours for normal activities. A very important point psychologically, is that the patient himself becomes responsible for the care instead of the institution. There is a real feeling of independence.

Frequent short dialyses are more effective. On twice-weekly dialysis, for a total of 20 hours per week, the patient's creatinine got up to 12. On three times per week, for a total of 18 hours or less time per week, his creatinine got up to 10. So this kind of study projects that the frequent short dialyses are going to keep these patients much healthier than the infrequent, prolonged dialyses can.

One problem is that not everybody is going to be able to go home. We estimate, in our present population of about 20 patients in Seattle, that only half are going to go home. There are going to be other solutions, but the home program is the ultimate one. The center type is perfectly satisfactory if you can afford it, and something in between may be the answer for other patients. Maybe you can get them together in an apartment home—"You dialyze me tonight and I'll dialyze you tomorrow night"—This sounds crazy but it will be necessary if people are going to survive within the economic limits we can provide.

Recent Experience with Hemodialysis in Acute Renal Failure, Chronic Renal Disease with Reversible Features, and in Conjunction with Renal Homotransplants

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During the past 10 years, hemodialysis has progressed from a dangerous procedure requiring one or more physicians in constant attendance, to a safe nurse-technician activity. Similarly, the indications for initiating dialytic therapy have changed as the procedure has been simplified and made almost completely innocuous. It is now felt that one should not wait for the patient to develop advanced uremia before placing him on the artificial kidney, but instead one should use this newer method of treatment before the complications of uremia set in. But dialysis should not be looked upon as a substitute for good medical management; on the contrary, predialytic management is more important now than ever. The most important use for dialysis remains in acute renal failure. More recently, however, it has been used for the maintainance of life in chronic uremia (Pendras and Drickson, 1965; Gombos et al., 1964), the treatment of many cases of poisoning (Maher and Schreiner, 1965) and to support renal homotransplantation (Bower and Magee, 1964).

At the Medical College of Virginia (MCV) the great majority of dialyses have been done in conjunction with the transplant program now under way (Hume et al., 1964). In addition, there has been a significant increase in the number of dialyses done for acute renal failure and poisoning. There has been no dialysis done for the maintainance of life in chronic uremia. The purpose of this paper is to give a brief resumé of the development of the artificial kidney unit at MCV, and to report on the results of its use.

It has been less than 15 years since MCV acquired its first artificial kidney machine. This cumbersome and complicated monster was referred to affectionately as the "rotating drum." It required several physicians to operate it but it did give all those involved with its operation considerable confidence and encouragement that dialysis did work. The next machine that was purchased was the twin coil kidney. This instrument greatly simplified the procedure of dialysis and aroused the interest of many workers in the field both at MCV and throughout the world. The greatest burst of enthusiasm for dialysis at MCV occurred in the fall of 1962 when it was decided to undertake studies in renal homotransplantation in man. The dialysis facilities at that time consisted of the twin coil machine and peritoneal lavage. This latter method of dialysis had recently enjoyed a rejuvenation with the appearance on the market of commercially available prepackaged sterile peritoneal dialysis fluid.

It soon became apparent that both of these methods of dialysis could not meet the demands of the transplant program. For this reason, in January of 1963, the hospital purchased its first Kiil kidney (Kiil, 1960). This machine was designed originally to replace the human kidney during acute renal failure. Later it was found to be well suited for the maintainance of life in chronic uremia and it is today used in the majority of successful chronic dialysis programs. After few modifications it was found that it was likewise made suitable for supporting a transplant program. The next major advance in the dialysis program at MCV again grew out of necessity. The kidneys were being operated in several different areas of the hospital, inefficiently. It became apparent that larger and more permanent quarters were needed to meet the ever-increasing demands of the transplant program as well as the increasing volume of acute dialysis. In the fall of 1964, the present dialysis unit was completed on 4 North of the main hospital building and 10 Kiil dialyzers were located in this area. This space consisted of approximately 1100 square feet divided so that there would be a supporting laboratory and a patient dialysis area. As many as 6 dialyses can be done simultaneously in this area, with facilities available for dialysis at all times.

Method of Dialysis

Each candidate for dialysis has a silastic teflon shunt (fig. 1) inserted

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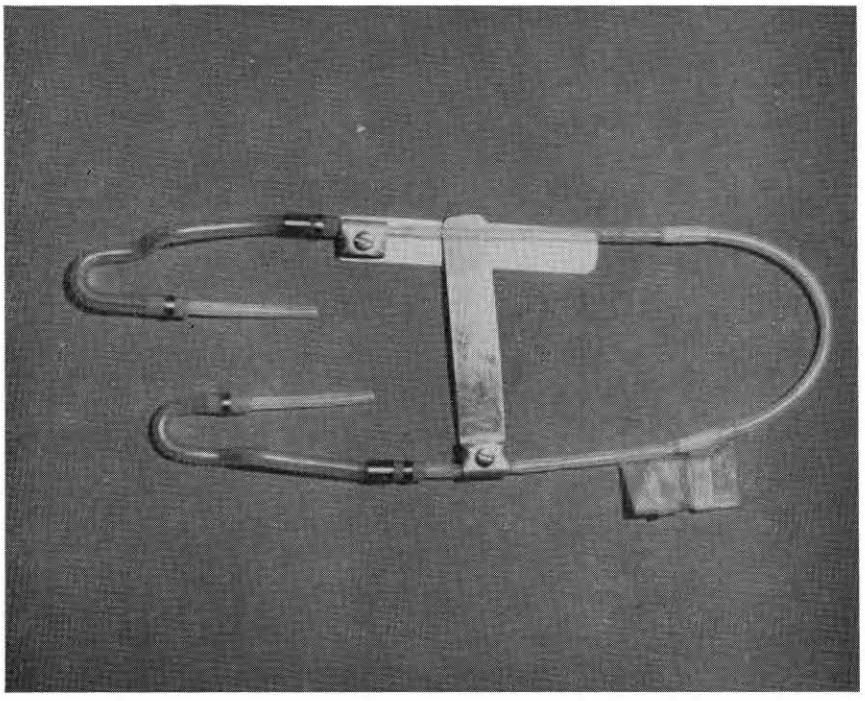

Fig. 1.—Arterio-venous shunt worn by patients that are on repeated dialysis.

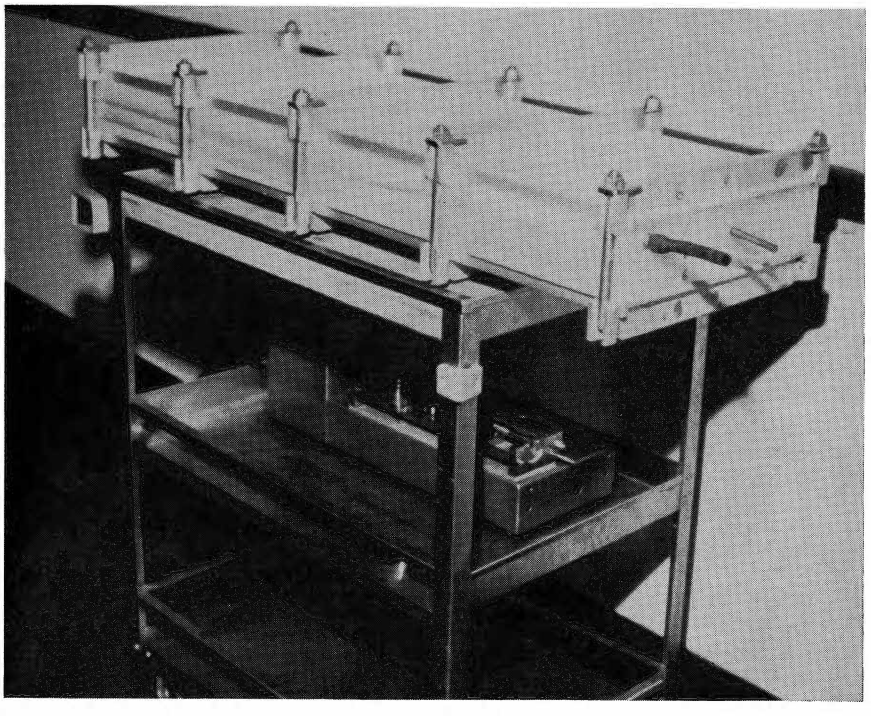

Fig. 2.—The Kiil Artificial Kidney showing the two blood inlets at the middle of the right end and the singly larger bath outlet. The Harvard pump on the second shelf is used to infuse heparin to prevent blood clotting inside the artificial kidney.

under local anesthesia in a small peripheral artery and vein. When the patient is not on the artificial kidney, blood is allowed to flow from the artery into the vein to maintain a constant flow of blood, thereby preventing clot formation. This mechanically exteriorized A-V fistula has not been known to produce cardiac decompensation and it does avoid the need for repeated cutdowns. Before this technique was devised the number of dialyses that could be done in any one patient was limited.

The dialyzer itself (fig. 2) is quite simple in design and function. Its sole purpose is to create a large surface area with a minimum volume of blood out of the patient in contact with the bath solution on the other side of the cellophane membrane. The bath solution consists of a physiologically balanced electrolyte solution plus glucose to adjust the osmolarity. The volume of blood necessary to fill the dialyzer and thereby give 0.9 M^2 of dialyzing surface is only 350 ml. This small volume eliminates the necessity of transfusions when using the Kiil dialyzer. When the patient is placed on dialysis, the A-V shunt is cross-clamped and the continuity of the shunt disrupted. The arterial line of the shunt is connected to the dialyzer inlet and the patient is bled into the dialyzer, replacing the heparinized saline and filling the dialyzer blood compartment. When blood begins to appear in the dialyzer outlet line, it is connected to the venous side of the shunt. Blood then flows continuously from the patient through the dialyzer and back to the patient. At the end of the procedure, the blood in the dialyzer is returned to the patient by flushing it back in with saline. The net loss of blood per dialysis is 30 to 50 ml. Blood pumping is not necessary, but it is done in some centers to speed up the rate of dialysis and reduce the time spent on the kidney. Without blood pumping, it usually requires two 12 hour periods of dialysis per week to maintain an anephric patient asymptomatic of uremia. The rate of blood flow through the dialyzer without pumping is approximately 100 to 150 ml per minute. The bath solution flows at the rate of approximately 500 ml per minute and is then discarded. By running the bath solution through the dialyzer only once and then discarding it, several patients can be run from a single bath source, providing they can all tolerate the same bath composition. This entire procedure is executed by especially trained nurses and technicians, thereby freeing the physician completely. The major role of the physician in a dialysis center is to care for the patients off dialysis, and to decide when dialysis should be carried out. The physician must also occasionally modify the bath formula as deemed necessary according to the patient's individual needs. There is no reason to feel that any physician who has taken the time to make himself aware of the benefits of dialysis and what can be expected of the procedure, should not be able to order this service when indicated.

Results and Discussion

Dialysis with Transplants

During 1962, 15 dialysis were done. Six of these were done in conjunction with the transplant program on 3 patients and the remaining 9 were for acute tubular necrosis and barbituate intoxication on 6 patients. In 1963, there were 195 dialysis done, and in 1964, 507. The great majority of the dialyses in 1963 and 1964 were for the transplant program, using primarily the Kiil kidney.

Between August 1962 and April 1965, 63 renal homotransplants were carried out in 57 patients. Four patients were transplanted twice and one patient had 3 transplants. In order to support this program, 760 hemodialyses were done. The distribution of these dialyses is shown in Table 1.

Most pertinent to this discussion are the data on patients that were never transplanted. These 61 dialyses were done in 11 patients, all of whom are now dead. Five of the first ten admissions to the transplant program died before they could be transplanted. We attribute this to inadequate dialysis facilities. Peritoneal dialysis was used in four of these five patients and these four had significant peritonitis that

TABLE 1
Hemodialysis with Transplantation

	Number of Dialyses	Average dialyses per transplant
Pre-transplant	614	11.6
Post-transplant <2 weeks	39	2.6
Post-transplant >2 weeks	30	6.0
Patient never transplanted	61	5.5
Patients awaiting transplant	16	4.0
Total	760	

contributed to their demise in uremia. For this reason, it is felt that peritoneal dialysis is not adequate to support a transplant program. The remaining 6 deaths occurred evenly distributed over the subsequent 58 admissions. Therefore, by instituting an active dialysis program, the mortality rate prior to transplantation was reduced from 50% to 10.3%. Looking now at the six deaths that occurred after dialysis facilities were adequate, we find that one of these was preventable. This occurred in a six year old male who was being dialyzed for the first time. He was in congestive heart failure and was receiving digitalis. When his serum potassium was lowered by the artificial kidney to normal levels he developed digitalis intoxication and died of ventricular fibrillation. The remaining five deaths pre-transplant were attributable to septicemia in two, brain stem hemorrhage in one, and gastrointestinal hemorrhage in one. One patient refused further dialysis and transplantation.

Dialysis for Acute Renal Failure, Chronic Renal Disease and Poisoning

Since the development of our existing artificial kidney unit, the volume of acute dialysis has likewise increased. As stated earlier in 1962 only 6 patients other than transplant patients received dialysis. This number increased to 9 in 1963 and 15 in 1964. The 24 patients that were dialyzed between Jan. 1, 1963, and Dec. 31, 1964 are divided into three groups. The first group was made up of eleven patients who had acute renal failure with otherwise normal kidneys (table 2). The second group, comprising 10 patients, included those with known chronic renal disease, but with superimposed reversible features (table 3). The third group consisted of three patients with attempted suicide, who were dialyzed to remove the ingested toxin (table 4).

The results of dialysis are most rewarding in acute renal failure. In our own series of eleven patients, seven regained sufficient function to bring their BUN and creatinine back to normal, and in five of these that were

TABLE 2
Dialysis for Acute Renal Failure

	Patient	Etiology	Number of Dialyses	Results†
1	K.S.	Cortical Necrosis, Post-partum Hemorrhage	14	Transplanted, Died.
2	J.C.	A.T.N.*, Gunshot	3	B
3	C.H.	A.T.N., Septicemia	3	A
4	Z.T.	A.T.N., Septicemia	5	A
5	R.J.	A.T.N., Abruptio	1	A
6	C.B.	A.T.N., CCl_4	2	A
7	G.S.	A.T.N., Pancreatitis	1	B
8	W.C.	A.T.N., Ethylene glycol	4	A
9	J.B.	A.T.N., Septicemia	6	Died
10	J.R.	Acute Vasculitis	2	Died
11	M.B.	A.T.N., Hemorrhage	2	Died

** A.T.N.—Acute Tubular Necrosis;† Classification of results: A, GFR > 75 cc/min, B, patient alive BUN and creatinine normal, but no evaluation of G.F.R. available.*

TABLE 3
Dialysis for Chronic Renal Disease with Reversible Features

	Patient	Etiology of Acute failure	Number of Dialyses	Results*
1	E.D.	Iatrogenic Acidosis	1	Lived 6 months
2	J.W.	Pyelonephritis	1	Lived 2 weeks
3	J.P.	Accelerated Hypertension	6	Lived 1 week
4	B.C.	Pyelonephritis	4	Transplanted, Died
5	S.C.	Pyelonephritis	3	Lived 2 months
6	E.L.	Pyelonephritis	2	Lived 3 weeks
7	R.D.	Dehydration	2	Lived 3 weeks
8	A.S.	Pyelonephritis	4	Lived 1 month
9	A.C.	Pyelonephritis, A.T.N.	1	Lived 1 day
10	N.J.	Heart failure due to rheumatic disease	2	Lived 1 month

* Duration of life after last dialysis.

TABLE 4
Dialysis for Attempted Suicide and Intoxications

	Patient	Drug or Toxin	Number of Dialyses	Results
1	E.S.	Combination of Drugs	1	Living and well
2	W.G.	Barbiturates	1	Living and well
3	J.C.	CCl_4	1	Died

checked with creatinine clearance studies, all were found to have a clearance of greater than 75 ml per minute. There were four deaths in this group. Of these, two were probably not dialyzed long enough or frequently enough, as borne out by the fact that they died in uremia. One patient (J.R.) with an acute vasculitis of unknown etiology died with azotemia of a significant degree, but it is not felt that renal failure was the cause of death. The fourth death occurred in a patient with renal cortical necrosis following a complicated delivery. The patient was maintained on the artificial kidney for eight weeks. At the end of this period, an open biopsy of the kidney revealed cortical necrosis. The patient was then bilaterally nephrectomized and transplanted.

In our present state of knowledge, it appears that the prognosis for a patient living through an episode of acute tubular necrosis is more dependent on the prognosis of the underlying disease than on the tubular necrosis itself. In our own experience, we have maintained a bilaterally nephrectomized patient on dialysis in a reasonable state of good health for over 14 months. Scribner et al. now have some essentially anephric patients that are doing quite well after 5 years on dialysis.

In those patients with chronic renal disease who suddenly become decompensated due to a superimposed acute insult, the results are not as good. Here again the prognosis is determined by the underlying chronic renal disease and the availability of chronic dialysis facilities.

Dialysis is very useful in the management of drug intoxication and attempted suicides. First, it promptly removes the offending agent from the blood, and secondly, it shortens the period of unconsciousness, thereby reducing the complications of coma.

Summary

Hemodialysis is a safe acceptable method of treatment for drug intoxication, and acute renal failure. It is also useful in the management of patients with chronic renal disease either on a periodic basis or, intermittantly, for acute exacerbations superimposed on chronic renal insufficiency. The great majority of dialysis at MCV has been done in conjunction with the ongoing renal homotransplantation program. Here dialysis has proven to be an innocuous procedure and has contributed significantly to the success of this program.

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Panel on the Maintenance of Life in Uremia*

DAVID M. HUME, Moderator

Dr. David M. Hume (Stuart McGuire Professor, and chairman, department of surgery, Medical College of Virginia, Richmond): I'd like to begin by asking Dr. Doolan a question. Do you have any special technique or criterion, Dr. Doolan, for determining the reversibility of disease in a patient that is being dialyzed for acute renal shutdown? That is to say, how do you decide whether to turn the dialysis off after several days?

Dr. Paul D. Doolan (director, clinical investigation department, Naval Medical Research Institute, Bethesda, Maryland): I don't know if I understand this question.

Dr. Hume: Well, suppose you've got a patient with acute shutdown and you have dialyzed him, because you had to keep him going. How do you decide whether this patient is going to "open up" sometime on his own; how long do you keep dialyzing him if you don't have a chronic program, and when do you decide that the shutdown is irreversible?

Dr. Doolan: If he's got acute renal failure, I don't know whether you can ever say it's irreversible. This question seems to emerge when you have shutdowns of unknown origin, and you are wondering about whether the person doesn't have acute glomerulonephritis, for example. If they don't open up in less than 30 days, then the likelihood of their opening up is very remote.

Dr. Hume: How do you decide they have got acute glomerulonephritis?

Dr. Doolan: Well, I think history and clinical appraisal is all I know of.

* Held at the Second Annual Kidney Symposium, Virginia Chapter of the National Kidney Disease Foundation, Richmond, October 16, 1964. Transcript of the symposium was edited as little as possible to keep the informality and spontaneity of the discussion. I am indebted to Dr. John Bower for help in preparing this material for publication.—Ed.

If an adult is shutdown with acute glomerulonephritis, the prognosis is poor. I think it varies among different people as to when you feel justified in doing renal biopsy to see whether or not this will help you with making the decision of whether to continue dialysis. I would say that, in my own experience, renal biopsies have not helped.

Dr. Hume: Anybody else on the panel want to comment on this question?

Dr. John E. Kiley (professor of medicine, Albany Medical College, Albany, New York): I think when you see a patient with acute renal failure that does not open up after two or three weeks, you begin to see a somewhat characteristic behavior on the part of the physician handling the case. What we tend to do, first, is to support the patient by dialytic means, hoping that diuresis will ensue. But once you go into the second or third week, one certainly begins to feel pushed. After having eliminated any obstructive uropathy (by cystoscopic examination, etc.), we then do a renal biopsy. And, although there are some contraindications to doing a biopsy, it has been helpful in revealing a disease condition that we had not suspected, e.g., glomerulonephritis, overwhelming pyelonephritis, and infarction of the kidney. These conditions tend to make one turn off the dialyzer, because this is not acute tubular necrosis, and the kidney will not regenerate. The other thing to do would be to put a catheter up by way of the femoral artery to the level of the renal artery and inject a radioopaque dye. In this way, one can study the vascularity of the kidney. In some instances we have discovered that there has been bilateral infarction which we didn't suspect. This usually occurs when the patient has infarcted one kidney, say a year or two earlier, without its being clearly diagnosed, and later the patient has infarcted the other kidney. So, renal biopsy and pyelography can be helpful, when, after a month of dialysis you're beginning to wonder whether you are not rapidly going into chronic dialysis, inadvertently. Perhaps someone else on the panel has had more experience than I with the use of the newer diagnostic techniques of infusion pyelography.

Dr. Hume: Some patients don't "open up" for 60 days. The question is, at the end of 30 days, what do you do?

Dr. Belding H. Scribner (chief, division of kidney disease, department of medicine, University of Washington, Seattle): We're obviously confronted with this problem continually, because we do have a chronic program that is full. But at the same time, we are in a very serious dilemma in this kind of situation. I underscore completely what John Kiley says about the use of the biopsy at the 30-day point, so to speak. The other side of the coin here is, if you do find normal glomeruli and tubular necrosis at 30 days, then you are committed to keep the patient going on dialysis indefinitely. I know of one patient from Stanley Sheldon's group in England that went 90 days with tubular necrosis and then opened up. So, on the hopeful side, if you do come up with this diagnosis on renal biopsy, even in the presence of anuria, then you are obliged to go on. If you are worried about the vasculature, I think the aortogram may be done in 60 days or 90 days, if you are still "sitting" on the case. I can not elucidate the question Dr. Kiley raised about the newer radiographic techniques.

Dr. Joseph H. Magee (director of renal section, department of medicine, Medical College of Virginia)[1]. I want to allude to what Dr. Scribner just said. One of the abstracting journals had reported two cases of cortical infarction, where dialysis was carried out for 70 to 80 days before recovery. The authors believed that some one-sixth or one-fifth of nephrons, which are juxtamedullary, will come back and function if you dialyze them long enough. So I wonder if you aren't on the griddle for about two to three months, where shock or cortical infarction might have been the cause of shutdown.

Dr. Hume: Would anybody on the panel like to tell about his experience with the use of large quantities of contrast material, or would anybody like to comment on the use of radioactive materials, renal scans or radiorenograms, as assists in determining whether renal artery thrombosis has occurred—Dr. Kiley?

Dr. Kiley: Well, of course, I can't see how the use of radioactive substances is going to help you, because they don't really reflect the blood flow, but rather the ability of the tubular cells to concentrate and excrete the isotope. These patients may have neither blood flow nor secreting cells, so I would not be enthusiastic about these procedures.

Dr. Hume: If you have neither blood flow nor kidney cells, you wouldn't get any uptake, but if you have got some uptake, then that would be some evidence of vascularity.

Dr. Kiley: If you're looking for vascularity, I still think that renal angiography would be beter than isotopes.

Dr. Hume: Dr. Kiley, in your earlier discussion (paper on artificial dialysis in adults), you talked about using dialysis for hypercalcemia. I am wondering if you would advocate this form of therapy in hypercalcemic crisis, rather than operating on a patient who has hyperparathyroidism and hypercalcemic crisis, and removing his parathyroid adenoma. Another condition I noticed on your list was ammonia intoxication, and I wonder how your results have been with this.

Dr. Kiley: Well, first, I'll put my guard up by saying that at that time I was showing a list of situations which have been recorded as successfully treated by dialysis. Now, with hypercalcemia, we have an interesting situation there. I have not personally treated a hypercalcemic crisis by dialysis, so I am in no position to disagree with Dr. Glenn's[2] statement that parathyroidectomy is preferable. However, as

[1] At present, assistant professor of medicine, Jefferson Medical College, Philadelphia.

[2] Dr. James F. Glenn, professor and chairman, department of urologic surgery, Duke University, had spoken earlier on surgery in the prevention of uremia.

a surgeon, I would like to strike back by asking you if this would not be an extremely difficult type of emergency operation. The hypercalcemia may be due to hyperactivity of the parathyroid, which is deeply situated within the body. I think the complexity and difficulty of this surgery is at least a factor suggesting that dialytic therapy might be more efficacious; it is certainly more straightforward. How do you feel about this operation itself?

Dr. Hume: We have not had much experience with this. We had one patient who we thought had this problem. He certainly had a hypercalcemic crisis, and we dialyzed him for a short while, with some fall in calcium, although its level did not fall strikingly. We then took the patient to the operating room, explored the neck and then made the diagnosis of widespread metastatic disease, which hadn't shown up in x-rays. The patient ultimately died of malignant disease. Dr. Magee, do you recall that patient? I've forgotten exactly what the results of dialysis were.

Dr. Magee: I think we got calcium down from about 20 to 18. We just dialyzed for minimum number of hours and weren't getting anywhere and proceded with the operation. Thomas and co-workers[3] in a review of about 14 such cases, said they believed the thing to do was to get them right up to the operating table, because you just can't dialyze fast enough.

Dr. Kiley: Well, I would disagree with that. I think that if you are equating a good operation with relatively poor therapy, that certainly is true, but I also think that there are better medical ways of managing this disorder than by dialysis. As a matter of fact, I think dialysis may be weak, because you are dealing with a double equilibrium caused by abnormal parathyroid hormone, so you will have calcium coming out of the skeleton just about as rapidly as you can dialyze it out. On the other hand, by the use of sulphate and citrate, and, at least theoretically, EDTA, you can cut down considerably on the amount of ionized calcium that is present. This kind of medical therapy, although a temporary measure, can give you a good deal of time, even in the middle of the night, to prepare the patient and the operating room for surgery. And it can forestall the disaster that sometimes occurs with sudden death. So, I wouldn't minimize the usefulness of the right kind of medical therapy.

Dr. Doolan: I don't know whether it was a tribute to Dr. Kyle, my old boss, but I never saw a hypercalcemic crisis with hyperparathyroidism, and he had only a few cases. I have seen hypercalcemic crises with metastatic bone disease. This is the case in which you are not worried about operating. You can lower calcium by giving these people steroids, or you can lower it by doing peritoneal lavage, and, if you want to, you can put EDTA in the peritoneal lavage solution and remove even more calcium that way.

Dr. Hume: That's a good thought. Actually, there have been about 40 of these reported in the literature and the mortality is about 50%.

Dr. Doolan: With the hyperparathyroid?

Dr. Doolan: Yes.

Dr. Magee: And there are a lot more now.

Dr. Doolan: Well, my only point was, they're not all surgical.

Dr. Hume: No, not right away. We get them in the end, though, because there is no medical cure for hyperparathyroidism.

Dr. Doolan: The discussion has spun around how fast the patient with hypercalcemia should get to the operating room. But, what about the hypercalcemia that is not due to hyperparathyroid?

Dr. Hume: Well, we don't take those to the operating room.

Dr. Doolan: This is why I mentioned peritoneal lavage, steroids, and EDTA in the peritoneal lavage solution.

Dr. Hume: It is true that the majority of the hypercalcemic crises that we have seen here have been due to carcinoma of the breast, and we usually treat those with steroids to get them off the hook. Now, Dr. Kiley, I would like to ask you about dialysis in ammonia intoxication.

Dr. Kiley: We demonstrated quite a few years ago that the ammonia ion is very efficiently removed by a dialyzer, and we have used this with some gratifying results in about half a dozen patients. The thing I want to emphasize is that I don't believe at all that this is effective clinical use of dialysis. Ammonia toxication is almost invariably handled better by other approaches.

Dr. Hume: Were these people in hepatic coma, or were they people who had ingested some household detergent?

Dr. Kiley: The patients who were successfully treated were patients with portal cirrhosis who were getting along quite well, who then had a massive gastrointestinal hemorrhage. The hemorrhage was then stopped one way or another, but they went into ammonia intoxication from digestion of the blood in the gastrointestinal tract, and they were benefited by the removal of this excess ammonia. But I think this has very little practical general clinical worth.

Dr. Hume: Dr. Kiley, when I was an intern and resident, we used to see patients with various types of renal shutdown and potassium intoxication. In those days, a major indication for dialyzing a patient was potassium intoxication. We used to go scurrying around trying to get the patient just on the razor's edge, watching for EKG changes of potassium intoxication. And we were in sort of a sweat to see whether he was going to survive, and to judge the right moment to put him on the kidney. Now you suggest in your talk that we ought to get an EEG instead of an EKG, to decide when to put the patient on the kidney. This is harder to get than an EKG, and it is somewhat more difficult to interpret. Do you really feel that this is the way to decide when to put a patient on the kidney?

Dr. Kiley: Well, first of all, let us be clear that the EEG has nothing to do with potassium intoxication. Although I was possibly skipping along to catch up a little time, I did preface my slide of the EEG with the statement that

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[3] Thomas, W. C., Jr., J. G. Wiswell, T. B. Connor, and J. E. Howard. Hypercalcemic crisis due to hyperparathyroidism. *Am. J. Med.* 24: 229–239, 1958.

it was not generally available. And I would agree with your comment that, were this to be efficiently used, it must become more available clinically, and I think we must work more to that end. We have it fairly available now because this is a particular interest of ours. We have a portable EEG machine which can be taken to the ward, and you can count the frequency of the waves per second as they come off the machine. So, the EEG can become clinically useful, and I think it is something we must progress with. Really, what we are striving for here is a relatively simple electronic counter which will sort the seconds into two stacks; those in which the wave frequency of the EEG is above six and those in which the wave frequency is below six. The latter is a clearly abnormal situation. I do think that all of us are now using the EKG for potassium intoxication, particularly since the cardioscope has become generally available. If we have a potassium problem, we move the cardioscope into the room and turn it on and monitor the EKG continuously.

Dr. Hume: I was wondering, since Dr. Scribner has demonstrated that dialysis is so easy to do in the basement, why don't you simply dialyze the patients repeatedly when they have uremia, rather than rely on some particular danger signal to put them on dialysis?

Dr. Kiley: I think you're quite right, and I think that this is where we should be going. And, we should be using the artificial kidney and other dialyzers more as the human kidney, to preserve normalcy, rather than to correct a very abnormal situation. But I think that, in the present state of our knowledge, the main question is just how much dialysis is ideal. We just don't know that, because we have not yet correlated the changes in metabolism, particularly nitrogen metabolism, with these physiological changes. The thing I like about the EEG is that for the first time, we have something reasonably objective in altered physiology which we can use in clinical uremia. I was all sort of up-in-the-air in clinical uremia because we usually stood at the foot of the bed and looked at the patient, and wondered how sick he was, and that is hard to go on.

Dr. Hume: Dr. Finberg, I wonder if in the course of dialysis for poisons of one sort or another you ever see a rebound phenomenon after the dialysis is done. That is, the patient wakes up from dialysis and then, sometime later, he lapses back into coma. Has this ever been a problem?

Dr. Laurence Finberg (chief, division of pediatrics, Montefiore Hospital, and professor of pediatrics, Albert Einstein College of Medicine, New York): In most of the common poisonings that we see that is not a problem. There are some poisonings in which that has been notoriously reported to be the case. Then, you have to go back and dialyze again.

Dr. Hume: Dr. Finberg, supposing you have a problem, as occasionally comes up, that a child is born without kidney function. Is there any effective way to dialyze the newborn baby, or otherwise to manage the problem?

Dr. Finberg: Yes, I think there are two comments pertinent to this question. One is that the infant is probably the only living organism that can survive without any renal function at all, and without any artificial aid, for long periods of time. The record is up to six weeks. This is because the infant is so rapidly growing that if the absence of urine formation is not a consequence of some kind of disease which in itself induces katabolism, he will grow, and will so expand his body fluid compartments that they can actually hold the toxic substances in them in so dilute a form as to permit growth. This will be true if the infant is on the proper feed, and the ideal feed for this is human-breast milk. And that is how the record was set. The mother took her baby home, who subsequently turned out to have no renal mass at all. She didn't bring him to the hospital, not thinking it was terribly important that he hadn't put out any urine, until he was almost six weeks old. As for dialysis in infants, you can dialyze small infants if they have an abdominal cavity that is approachable. You can do it with peritoneal dialysis, of course, and this is what we talked about before. I am told the McNeal-Collins kidney can be adapted for small infants, but I haven't actually seen it in action myself. The other, larger devices are almost impossible to use on a small infant, even with trying to cut down the coil area and exteriorized blood volume.

Dr. Hume: Has anybody on the panel dialyzed a child under two years of age?

Dr. Scribner: Dr. Robert Hickman, in the department of pediatrics in Seattle, has been working on the problem. It seems to me the number-one requirement for infant dialysis is a small stable external circuit. I think Dr. Hickman has dialyzed a child only four weeks old, and he is using the Kiil half-length, one-layer unit, with a completely rigid external circuit, and no blood pumps. It is about a quarter the size of the unit we use for adults. If you fully prime the external circuit, the infant's vasculature cannot tell when he is on or off the dialyzer. The big problem in dialysis is to shift the blood from the equipment to the small child and back again. With a small rigid external circuit, we've had good luck in infant dialysis.

Dr. Hume: Do you put the child on a set of scales to be sure how much weight he is gaining or losing?

Dr. Scribner: It isn't necessary unless you're filtering large amounts of salt solution and then, of course, it's very helpful to have him on a scale. As far as the blood shift is concerned, if you have a rigid external circuit that is small and fully primed, there's no problem with bloodshift.

Dr. Hume: Dr. Magee, I wonder if you want to comment on some of the things Dr. Scribner has mentioned briefly, that is, the medical management of a patient with chronic uremia who is not yet ready for dialysis?

Dr. Magee: Picking out some of the things the speakers have brought up today, the common situation now is that practically no uremic patient comes in on the ward about whom you are not asked whether there is some reversible feature. Twenty-five years ago there were no nephrologists because there was nothing for them to do. Most people didn't believe for 100 years after Bright's description of

uremia that there was any such thing as reversible uremia. The things that seem to have come along to have changed all this were: 1) Weiss and Parker[4] showed that pyelonephritis was a common cause of chronic uremia. They picked out, retrospectively, a lot of reversible cases that came in with a pericardial friction rub or uremic frost, and then left the hospital. Some of the older physicians didn't think they'd ever seen this but here there were some cases. 2) The salt-losing nephritis emphasized by Thorne and colleagues[5]; when the patients went into shock, instead of giving them adrenocortical hormones you only had to give salt. 3) Then along came the exponential growth of blood banks and non-exponential growth of technicians and we had a large number of transfusion reactions. A lot of younger fellows really got going from the encouraging experience of bringing some of these patients through. These easy ones are not seen any more, but they just reinforced the concept of reversible uremia. 4) W. J. Kolff's book, *New Ways of Treating Uremia,*[6] which had the artificial kidney in it, but most importantly, it had the high-caloric, low-protein feedings and the protein-sparing feeding, and the necessity of restricting water, to avoid pulmonary edema. 5) And then came the electrocardiogram and the flame photometer, which helped tell us when the potassium is elevated.

Dr. Hume: I would like to make a couple of comments relative to Dr. Scribner's talk comparing chronic dialysis and transplantation, and then ask him to comment on my remarks. In the first place, I think we all ought to admit right off the bat that some form of chronic dialysis is essential to any transplant program. That is, without Dr. Scribner's help, and without the use of his device, our own program might never have gotten off the ground. Secondly, transplantation is not a therapeutic program at the present time; it is an investigative program. It's difficult to talk to Dr. Scribner without being challenged by him, because he regards chronic dialysis as a therapeutic program. This immediately puts you on the defensive. So, I'd like to point out the insufficiencies of chronic dialysis, and correct a few figures that have been given about transplantation. 1) The patients who were cared for by him for chronic dialysis were a highly select group of intelligent people. It is not everybody who can go down in his basement and dialyze himself. At least ¾ of the patients we have done transplants on, not only couldn't dialyze themselves, they barely had the intelligence to void! Our overall objective has not been to see what percentage of survival we can get, but what we can learn about transplantation. 2) Chronic dialysis is pretty much out with respect to children because it does interfere with growth and sexual maturity, as Dr. Scribner has said. 3) The number of patients who can be benefited by chronic dialysis is very small. Suppose for a moment that you were to take the point of view that the present objective of either of these two methods is to keep the greatest number of people alive. (Although this is not the point of view that we take, it is the point of view that Dr. Scribner takes.) In his own setup in Seattle, Washington, he has had six patients on hemodialysis in a five-year period; five of the six patients are still living. He's done six patients on peritoneal dialysis; five of these patients are still living. And he's got two patients in their basements. That's a total of 12 patients in five years, who are living who would otherwise have died. Our own program of transplantation has been going only two years. We have 28 patients living who would otherwise have died. None of Dr. Scribner's patients is cured; they all still have their disease. None of his patients is really well, but this is not true of any of the transplant patients either. 4) Hypertension does occur in patients with chronic renal disease, even in those on a low-salt diet. We have seen this in two instances out of the 50 patients we've had on chronic dialysis. Dr. Scribner hasn't seen it in his six patients, but it does occur, and it is a problem and one that you cannot solve with dialysis but you can solve with transplantation. 5) The degrees of independence of the two types of patients, that is, the patient with kidney transplant and the patient on dialysis, are quite different. Even if dialysis is done in the basement, and even if you can dialyze yourself at night while you sleep, it does encroach upon your independence to a greater extent than does the normally functioning kidney transplant in a well patient. 6) None of the patients on chronic dialysis really ever regain their pre-sickness weight. They do regain some weight, but they never are as healthy as the patients with good transplants, although not all patients with transplants have good ones. 7) Almost all of the patients on chronic dialysis require blood transfusions which are expensive and dangerous. 8) Neuropathy is almost never corrected by chronic dialysis—hemodialysis, that is. 9) The mortality figures are somewhat misleading. If you take Dr. Scribner's figures and show them on a slide today, 71% of the patients on chronic dialysis are now surviving. This figure is not too different from the figure for the larger series of transplant patients. Sixty-two per cent of all the patients we have done from the very first one are surviving. Of all transplants from related donors in the three largest groups in the country, 73% are surviving. Of our own cadaver transplants, 70% are surviving; and if we took only our last eight months' cases—93% of those are surviving. Even if we took all the patients we did in the first year, all of whom are now one or two years post-transplant, 46% are still living. Four of the first six patients we did are still living, and the two that died, died of total body radiation, which we no longer use. Virtually all of our patients have been on chronic dialysis before transplantation, and all of them prefer the transplant to chronic dialysis. The

[4] Weiss, S., and F. Parker, Jr. Pyelonephritis: its relation to vascular lesions and to arterial hypertension. *Medicine* 18: 221–315, 1939.

[5] Thorn, G. W., G. F. Koepf, and M. Clinton, Jr. Renal failure simulating adrenocortical insufficiency. *New Engl. J. Med.* 231: 76–85, 1944.

[6] Kolff, W. J. *New Ways of Treating Uremia.* London: J. and A. Churchill, Ltd.

figures which Dr. Scribner quoted, i.e., that 70% of identical twins who could have lived five years had died of the disease of the host, are figures that were reproduced in a recent editorial,[7] and are incorrect. The facts are 80% of all twins done in the last 10 years are living at present. Although it has been reported that occasionally either the twin kidney or a homografted kidney has developed the disease of the host, this has not happened as a rule, and it has not happened in any of our homotransplants or any of those in Denver. There's something more than 100 cases in this combined series, so, I think it must be extremely rare. He quoted Dr. Don Thomas' thoughts, namely, that he figures that 5 to 20% of patients who were transplanted had a chance of living two years, and that less one percent of them had a chance of living for four years. Dr. Thomas has recently moved to Seattle and it is understandable that he would have these thoughts. Dr. Scribner is a very convincing fellow. Had Dr. Thomas thought otherwise he might be carried away in the middle of the night. The actual figures from the largest series in the country are that, of those patients who could have lived from one to two years, 40 to 45% are living. Of our own patients who could have lived for two years, which is a very small group, 50% are still living. Dr. Scribner also says that the dialysis program works without doctors. But the patient with basement kidney must have about $1,500 a year in professional fees. Furthermore, in our own dialysis unit, which is modeled after Dr. Scribner's, Dr. Bower hasn't had a vacation in a year. Even though our program is run by nurses and technicians, Dr. Bower doesn't leave town for any length of time. I would like to conclude these remarks by saying there is really no competition between chronic dialysis and transplantation because the goals of the two are vastly different. But, I think if there is going to be an ultimate solution to the problem, that the patient with a normally functioning kidney, urinating in a normal fashion, with a completely normal life, who feels perfectly well, and has regained his pre-sickness weight, is in a little better situation than the fellow with a home kidney in the basement. Dr. Scribner, would you like to comment on this?

Dr. Scribner: I guess we could stay around a couple of hours and really have at it, but time is over already. I'll just make one or two brief remarks. We only had 12 patients at the University of Washington because it was not our job to take all the patients that could come our way. Our job was to demonstrate the feasibility of the method, to get on with the job of doing research to improve the method, and to learn all we could about the biochemistry of what's going on. Actually, unless we have had a new research project, such as the home program, we have not added a patient to our program in over two years. In contrast, of course, the new center downtown now carries 13 patients and is about to go up to 30, so the statement that there are fewer patients being benefited by chronic dialysis is simply a function of economics. If we had the money, we could take everybody in King County and we think we are going to be able to do this soon with the combination of the center and the home program. One or two other points. To say that 80% of all twins done are now alive is not necessarily contradicting the statement that 70% of the twins who could have survived five years are now dead.

Dr. Hume: This statement is incorrect.

Dr. Scribner: This was the statement that Don Thomas got from the group in Boston about two weeks ago. I do believe that chronic dialysis, based on our experience, is an accepted method of treatment. This is borne out by the world survey that we have just conducted. In this survey we asked, "can any well-trained internist, if he wants to, maintain a patient on chronic dialysis?", and all 20 investigators said yes. So, chronic dialysis is no longer an experimental technique; it is a therapeutic technique available to anyone who wants to get in, roll up his sleeves, and go to work. The problem is that we need time to activate the units, we need money, and proper facilities. And, incidentally, with all due respect to the excellent program here (at the Medical College of Virginia), they do not have proper facilities for chronic dialysis on an outpatient basis. The chronic dialysis program here is solely for the support of the excellent transplant research program that is going on.

Dr. Doolan (to Dr. Hume): You mentioned something about someone overpowering someone. I would find it hard for anybody to overpower you, Dave. There really wasn't any argument the way you wound it up, in that nobody argues with the ultimate desirability of having an intact kidney in you. But, let me ask you, how many transplants with non-maternal donors have survived over a year?

Dr. Hume: Of the patients that started off with a non-maternal kidney that could have survived more than a year, there were two, and they are both alive. Of the patients that have received cadaver kidneys, an unrelated group, 70% are still alive.

Dr. Doolan: After one year?

Dr. Hume: No, because they haven't all been a year.

Dr. Doolan: Dave, will you make the statement here and now that you, a surgeon, can guarantee a more than one-year survival of 50 or 70% in unrelated homotransplants?

Dr. Hume: Of course not, that would be a ridiculous statement to make.

Dr. Doolan: Well, boy, you threw around an awful lot of statistics. I don't know whether you are talking about two weeks, two months, or what.

Dr. Hume: Well, I think the most important figures in this regard are that if you take the patients who have been done more than a year ago, who are still living at the present time, so that all of these patients are from one to two years, and are patients who couldn't have lived more than a year, 46% of them are living.

Dr. Doolan: Would you give me that once more? I'm a little slow.

[7] Elkinton, T. Russell. Moral problems in the use of borrowed organs, artificial and transplanted. Annals int. Med. *60:* 309–313, 1964.

Dr. Hume: Yes. Take the patients done in the first year of our program. Our program began August, 1962. All those patients are now from one to two years from their transplant. Now take all the patients who could have lived during that time—there were 13 such cases who were done during that year —six of those patients are now living, which is 46% of the group. If you take those patients who have now been one year, which is not quite the first year, all told, 44% of patients who could have lived during that year are now living.

Dr. Doolan: I would only say that, as far as I know, unrelated transplants is strictly an investigative technique and if you select your patients well, from what I know of the Seattle group, it's a therapeutic technique. So, the only position I'm left with here is wondering why you have the sensitivity you do in the first place.

Dr. Hume: I have no particular sensitivity. I think that the figures do represent the facts as they are now. I think it's important to feel that transplantation results are good enough to justify any investigation on this program. And I think it's good that the results of hemodialysis are not so good that one should settle for this type of therapeutic regimen at the present time. That's all.

Dr. Scribner: I don't wish to give up keeping score here, but could I take advantage of this situation to ask you to comment on what the fundamental improvements have been in the technique of transplantation in the past year or two. I have a feeling that things are improving.

Dr. Hume: I think the thing we've perhaps observed better than before are, first of all, that at the first indication of rejection, immunosuppressive therapy is increased. Secondly, I think the use of local radiation has helped and I think this may be one of the reasons that our cadaver transplants are coming along better than some. This is something that has come out of the laboratory that seems to help clinically. Thirdly, the use of prednisone has been extremely valuable in preventing rejection. Fourthly, the preparation of patients for surgery by the types of chronic dialysis now available is vastly better. We started off with peritoneal dialysis and now we use the Scribner technique. Fifthly, I think that keeping the patients on hand longer has given us the time to observe them and manage them better after transplant.

Dr. Doolan: May I make one more comment in a different vein, Dave, and that touches on statistics. I recommended for the military section of the AMA that the treatment of post-traumatic renal insufficiency should be prophylactic hemodialysis à la Seattle group technique, which I think is the finest available. The way I justify this statistically is that Scribner and Bob Hagstrom are the only ones that have lowered mortality rate in acute renal insufficiency in the post-traumatic group. To the best of my knowledge, that's where the issue stands statistically at the moment.

Dr. Scribner: I'm terribly biased in this regard, but I feel that the prophylactic approach to acute renal failure just makes eminent good sense as Paul just very well stated, and since dialysis in a properly-run center such as you have here in Richmond is virtually without risk, and uremia is dangerous to a person with fractures and so on, it just is the only way to do it.

Dr. Hume: Thank you very much for your kind attendance.

"The basic texture of research consists of dreams into which the threads of reasoning, measurement, and calculation are woven".

Albert Szent-Györgyi, *Introduction to a Submolecular Biology*. New York and London: Academic Press, 1960, p 1.

Ethics in New Medicine: Tissue Transplants*

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Conservatism in medicine is a posture of comfort. The physician who lets a patient go his way with little more than a squeeze of the hand, a pain pill, or a knowing look to the relatives, can console himself that it has been this way before. It is also the easiest way. Then when another physician comes along to state that a certain disease can indeed be removed, but by a new and difficult procedure after careful study by new biochemical discriminants, the conservative is disturbed. He sees his authority challenged. He feels a deep uneasiness that many of his ways may soon become outmoded, particularly if he is inexperienced in, or unable to understand or perform, the new procedure. He becomes outraged when he discovers that several of the new operations have resulted in fatality rather than cure. Therefore, with the strong conviction that he is protecting the welfare of his patient, he claims that this new departure is still only experimental, and therefore unethical.

Postgraduate education in medicine is devoted to surmounting this innate conservatism. It is a tribute to the medical profession that each year thousands of doctors return to sources of learning to refresh their sense of the "tried," if not always the "true" in the sense of widely proven. Practitioners who return periodically to hospitals, where challenge of the old is a way of life, find that they overcome this human tendency to entrench, crystallize and defend an unchanging art.

Nevertheless, the history of such positions against advance, positions taken on the ground of ethics, is long and illustrious. It ranges all the way from the use of ether in childbirth to the use of aseptic techniques in the operating room, from the prevention of puerperal sepsis by isolation to the removal of brain tumors, and finally includes even the repair of valvular diseases of the heart! An older and more conservative generation has each time looked askance at these new ideas and new procedures and, at some point in heated controversy, has declared them unethical.

And yet, some are! Some "innovations" are indeed quite unethical and unacceptable! How should we consider the transplantation of goat glands to restore the waning virility of the elderly male? Or the treatment of arthritis by irradiation from outer space? Or the administration of small doses of creatinine diluted in water, to raise the hopes of cancer patients . . . at a price?

How can the lay person, the legislator or the newspaper writer steer his way through such controversy? What values provide guideposts, what criteria are standards for acceptability in medical innovation? How is one to regard the newest entry in this field, an entirely new kind of surgery: the transplantation of organs from one person to another?

As new fields of clinical science emerge, they come under fire from many directions. The commonest criticism is that new procedures are experimental and therefore their employment in the care of patients is

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immoral. It accomplishes little to point out that all of medicine is in a sense experimental, and that most of the daily tasks in practice—large or small—are in a very real sense tentative, insecure. No one can ever take for granted his mastery over nature. One must always approach his conquest of natural forces with a high sense of risk, of uncertainty and of experiment. One must seek the same clever skill employed by the glider pilot who rides air currents that at one moment support him upward, and the next—if miscalculated—dash him against the hillside. This simple idea, that applied human biology involves the hazard of repeated experiment, applies to all of medicine and surgery. A few examples will suffice.

A surgical operation employs bacteriology in just this way. An open incision bares large areas of sterile human tissue to the invasive bacteria of the surrounding world. Cutting, sewing, dissecting the tissue, an operation becomes an experiment employing techniques of bacteriology to avoid bacterial infection. If performed properly, the tissues will heal without infection; if faults and breaks occur, there is infection. Soon after Pasteur and Lister showed the bacterial nature of infection, it became obvious that "every surgical operation is an experiment in bacteriology."

When a physician gives his patient digitalis for the first time, he is carrying out an experiment in pharmacology. If he has misjudged the dose because of some unforeseen abnormality in his patient, he must readjust his prescription on the basis of the electrocardiogram and the heartbeat, working just as carefully as the scientist who manipulates a highly controlled system of variables in the laboratory.

Even such a commonplace operation as exploratory laparotomy for acute appendicitis, undertaken as an emergency in the midnight hours, harbors an element of experiment. "We are not sure what's the matter with Johnny, but we better have a look. If it *is* acute appendicitis, we can remove the appendix; if it is not, we are running little risk."

Each patient and each patient's disease is different from the last or the next. Each necessitates a rigorous approach to the phenomena of nature, of humanity and of illness. These in themselves are reasons enough for the continuing emphasis on biological science in medical education.

When we turn from these everyday uncertainties of medicine and surgery to the more troublesome aspects of entirely new treatments for critical illness, we pass from smooth sailing into choppy waters. The same experimental aspects are there, but now uncertainty is accentuated. The doctor can no longer tell his patient the chances of success or failure because he does not know them himself—nor can he minimize the risk.

At the present time, the patient dying of kidney failure has but two things to look forward to, other than a lingering and unpleasant death. One is a program of repeated dialyses or "blood washings" (on the artificial kidney) at high cost, bringing no possibility of release from the shackles of repeated procedures, sensations of waste accumulation, and reattachment to the machine. The artificial kidney has brought new hope to many patients with short-term kidney disease capable of healing and recovery. But for highly destructive kidney diseases, such as chronic glomerulonephritis, chronic pyelonephritis and chronic polycystic disease, these repeated dialyses are but a series of temporary makeshifts—a way of staying alive but hardly a way of life.

The other choice is to have a kidney transplantation. This carries many uncertainties and several risks, both at the operation and later on, as well as hazards for the donor if a living donor is used. But despite these factors, kidney transplantation has reached the point where many patients are now alive and well, up and about, and at home and at work, free of repeated dialyses, but still on medication, with their transplants working well. To arrive at its present station, however insecure, this work has taken fifty years of gradual evolution and fifteen years of intensive research in America and Europe.

The first long-term survival after homotransplant of a kidney (a homotransplant is a transplant between nontwin members of the same species) was in the spring of 1962, eight years after the first identical-twin transplantation. Up to the autumn of 1964, almost 500 kidney transplantations had been carried out in this country and abroad, involving many different relationships between donor and recipient. Of these, the large majority have been done since March, 1963; for these, no one can possibly claim "long-term survivors!" It is now, as this procedure is gradually emerging from a small and tightly controlled research study to more widespread use, that the ethical question is being raised: is it ethical to offer a kidney transplant to a patient dying of kidney failure?

"Good science is ethical science." Applied human biology finds meaning only in assistance for human suffering. In viewing any new therapy as an experiment in human biology, it is possible to draw up certain guidelines that will support its ethical and moral climate. These guidelines are much the same for any medical advance or clinical research, but for each there are special problems and details to be served to meet the humane standards that all must seek.

The *first guideline* requires that the patient and his family be brought to an understanding of the alternatives through conversation and education. It is asking too much of a suffering patient to expect from him a final decision; he has neither the dispassionate view nor the background in biology required for such a decision. Yet he must be enabled to understand what lies ahead, what the possibilities are, and to enter the procedure of his own free will and clear assent. Even more important, this gives him a positive motivation to aid and assist his doctors. It is never possible to impose good surgical care on the unwilling; there is tangible gain in the confidence and cooperation that comes from education and understanding.

This education will tell the patient and his family what a transplant really is, how it is done, how it is sutured in place, the meaning of urine output, the use of immuno-suppressive drugs

and many other details. He should understand the risks, the question of timing, the utility of repeated dialyses, the various donor possibilities and the experience of the hospital group. Any patient with a good background in high school biology soon comes to understand a remarkable amount about any new medical procedure.

The newest operation needs the most ancient clinical judgment for its success; the *second guideline* is, therefore, that each patient must receive the best and most experienced medical care available. No operation or medical procedure can stand alone. It succeeds only with the assistance of all the rest of modern medicine and surgery, the help of many doctors, nurses, blood bankers, laboratory technicians, and the participation of that whole constellation of human activities encompassed in the modern hospital. While an isolated research institute may contribute much to the idea, its most effective implementation is in the skilled environment of a busy hospital service. Consultation among doctors provides the checks and balances that avoid excess of one view, or a one-sided bias in interpretation. When four or five keenly interested persons are concerned with the patient's care, under the guidance of one of their number, there is a healthy openness of view that exemplifies the freedom of communication and sharing of knowledge so essential to the care of complex illness.

Work on man must be the culmination of an effort, not its initiation; the *third guideline* is that preliminary study in the laboratory by the doctors doing the work (not someone else!) must yield enough skill in performance and likelihood of success to justify the attempt. The so-called "great advances" of modern medicine, no matter what their nature, have had a sound basis in laboratory work before they were moved to the clinic. This basic laboratory groundwork makes their clinical application not a mere adventure, but the establishment of a new routine. When this important guideline has been neglected, with an attempt to make the "great leap" straight from the test tube to the patient, tragedy has resulted. The one example in the transplant field wherein the boundaries of ethical acceptance appear to have been crossed shows up at this point. The initial transplantation from chimpanzee to man was well based in laboratory work on blood grouping; but the subsequent series of attempts to place baboon kidneys (and even other organs, some of them obviously too small to do the job) in man, represented a premature step based on inadequate laboratory work. It is quite possible to set up experimental interprimate heterografts (such as monkey to baboon, or monkey to anthropoid apes) which could have tested this fundamental hypothesis that immunogenetic acceptance might somehow be achieved more readily than with homografts.

The exact locus of the laboratory in any advance of applied human biology depends on the nature of the work to be done. No dogma is effective for all. In cancer chemotherapy, for example, the only available animal model is the small laboratory rodent—rat or mouse. Spontaneous or transplantable tumors in larger vertebrates (permitting study and care resembling that in man) are but rarely available. In other fields, such as active immunization against poliomyelitis or measles, the final step somehow has to be made, and it is still a big one. It involves considerable hazard even though the circumstances are less spectacular than a surgical operation. The initial test with vaccines is made cautiously and with small doses. It should never be done on captive or primitive populations who cannot understand the risk.

In transplantation research this long step from test tube to man was taken only after a decade with the dog. The size of the dog, the size of his blood vessels, the ease of his care, the frequency with which blood and urine tests can be made, and the ability to judge fine gradations in his clinical status by physical appearance alone, have all made study in the dog basic not only to the science but also to the ethics of transplantation in man. Antivivisectionists please take note: there could be nothing more shocking than moving straight from the rat to man with the transplantation of organs!

And finally, as a *fourth guideline* of the utmost importance, each patient's case must be studied, documented as carefully as possible, and made available to the general view. The study and documentation of each case must be so complete and accurate that any interested person can come to the hospital and spend a few days or weeks reviewing and challenging the procedure or the data—and learning from them. There can be no toleration of secrecy. Every compound used, every procedure employed, must be fully known and made clear. When the time comes, the collected experience must be published with everything displayed, results both good and bad, so that the openness of modern science can be satisfied. There have been no breaches of this faith in the transplant field. Several transplant centers have now banded together to place data on computers for complete analysis. Any doctor in the world may join this project, so that his statistics, his failures and his successes are freely made available for all to see.

But helpful as these guidelines are, no one of them fully answers the question unique to transplantation—what about the donor? For the first time in the history of medicine a perfectly normal, healthy person has now been subjected to the rigors of a major surgical procedure and the removal of an organ, to help another.

The principle of injury to one so as to help another is common throughout nature and is basic to the Christian ethic. Examples are not to be found in the protection of its young by hazard to the mother, or when one person has sacrificed himself to help another, in war or peace. But in these natural phenomena and altruistic events, there has never been a third party—the physician—*advising* the individual to take this risk. It has been an emotional rather than an intellectual decision, and a matter of personal choice.

Medical science began to invade this field about 1915, with the development of blood donation for transfusion. Here the injury appeared to be minor and the body had methods to

compensate. The hazard in blood donation lies not in any threat to the donor but in the threat to the recipient by the transmission of disease.

The initial step in organ transfer was taken in 1954, with the first of the identical-twin transplants. Up to September, 1963, thirty-three identical-twin transplants have been carried out in the world, of which twenty-two are still alive with kidneys functioning well. The success of identical-twin transplantation has become sufficiently assured so that it scarcely arouses a question of morality with regard to the recipient—who is dying from terminal kidney disease. But as it bears on the donor, the ethical problem is as pressing and urgent now as it ever was, and is just as severe for the identical-twin donor as it is for the unrelated person, or for the father, mother or brother who seeks to be a kidney donor.

There is no simple unitary ethical solution for kidney donation from a living person today. Nephrectomy (removal of a kidney) carries a risk and a mortality. When enough have been done, it will be found that one has resulted in fatality. When enough have been done, it will likewise be found that a subsequent injury to the opposite kidney has resulted in significant loss of function, shortening life. The likelihood of a donor's losing the use of his remaining kidney is very small, and has been estimated as being in the same range as an automobile fatality, yet probabilities and statistics are inescapable. Such a major procedure as nephrectomy will surely exact its price when finally enough have been done.

It is clear that the first priority in donor development lies in better methods for preserving kidneys from recently deceased persons—a situation that completely side-steps the use of the living donor. This is still a research problem (though many cadaver kidneys have functioned well), but it is a research problem with an ethical overtone. Until cadaver kidneys can be used for all, the living donor (closely related to the recipient) still yields the best chance for success. Some important principles appear to be as follows:

First, every effort should be made to assure the maximum donor-recipient tissue compatibility. Despite advances in this area during the past year or two, the most reliable criterion is still that of close family relationship.

Second, one must be assured that both kidneys of the donor are quite normal, that there is no disease of the upper or lower urinary tract, and that kidney donation will involve only the risk of nephrectomy itself.

Third, the donor, just as the recipient, must understand the risks, the alternatives, the hazards, the discomforts, and most especially the uncertainties in the enterprise. If the donor is an identical twin, the prospects for success can be described with reasonable optimism. If any other relationship, then the prospects in all their uncertainty must be outlined clearly.

But surely the most important thing, as mentioned above, is to move away from the living donor entirely. This requires intensive study of cadaver organ procurement, and the definition of those factors in the recently deceased that bias the health of the remaining tissues. When the brain and heart are dead, then the patient is said to be "dead," even though many of his tissues are still alive, respiring in a blood stream increasingly devoid of oxygen, accumulating acid, but still alive for a few more minutes and salvageable for life in a new host. The care of the dying patient must never be compromised by impending tissue donation. The finest tissue bank in the world is the body of a person recently deceased from causes not damaging the health of transplantable tissues. Death from certain types of injuries, heart disease or brain tumors has provided many useful tissues. If cancer, infection, chronic vascular disease or just plain old age enter the picture, then the organs are of little use or actually dangerous to another. Herein lies a whole new field of endeavor in which we, as doctors, need the help of lawyers and legislators to give us legal guidelines to steer us through the uncertainties.

It is ironical to find that while tissue transplantation itself is being called into ethical question, in point of fact it is giving an entirely new meaning to human generosity as living persons or families of those recently dead make free donations of tissue for the assistance of others. The ethical lesson of kidney transplantation may turn out to be on the side of the Good Samaritan rather than the Evil Scientist!

It is a curious fact that although the general questions of ethics are not appropriate for examination by the methods of science, nonetheless a strong ethical flavor runs through all of science—"good science is ethical science." What are these features within science which give it ethical stature?

"Experiment is perilous and decision difficult." In that well-worn phrase, "perilous" and "difficult" indicate two of the ethical values in scientific experiment: courage and persistence. Other values have to do with rigorous personal honesty in viewing and displaying the results of scientific research, without prejudice, with a dispassionate discrimination, and with the selfdiscipline required to make a judgement valid. Those who enjoy the privilege of science must spend many years acquiring an education so as to make their work meaningful. Ethical values in science include also such things as openness of communication, exchange of information, avoidance of secrecy, willingness to educate the young and the avoidance of selfish gain.

Every few years the public is affronted by some spectacular example wherein a self-styled scientist has kicked over these traces, and sought a quick victory over nature by disobeying these inner ethics of science. But science is a stern taskmaster; transgressors are brought to a bitter judgment.

Examples are to be found in those goat-gland transplants. Though hardly science in any term, they were most assuredly devoid of the ethical content of careful study, openness of method, documentation, and analysis of results. The Nuremberg trials showed us another failure of ethics in experimentation. When a so-called "scientific experiment" was conducted wholly at the expense of the welfare of human beings, nothing good came of it. Even

the experimenter himself was finally debased and prostituted.

Most recently in the public press there has been described a flagrant example, where in science has shown that its own inner ethic must indeed be obeyed and respected. A person of previous scientific achievement has evidently tried to convince the public of the effectiveness in cancer treatment of a compound the identity of which he kept a secret—and indeed it truly was a secret, because as it now turns out, he himself did not know what it was! Instead of education and openness, careful trial, clear publication, controlled results, documentation of good and bad clearly shown for all to see, advocacy here was on the basis of hearsay about a secret and unknown compound, based on testimonials from random patients. A travesty on all the guidelines we have discussed! And then, with a fitting irony, downfall came through the study of a scientist working in the laboratory and obeying the basic ethic of honesty and rigorous examination. While examining this highly publicized "cancer cure" by infrared spectroscopy, he found it to be creatine—a commonplace material present in large amounts in the bodies of all cancer patients.

The study of patients is always more difficult and complicated than the study of controlled experiments in the laboratory. Sick people can be difficult, demanding, biased and fickle; controls are hard to conceive and devise. The patient's own emotional involvement and that of the doctor himself often provide false evidences of success. Persons working in clinical research (research in patient care) are as much in need of special education for this complex work as is the physiologist working under highly controlled conditions in the quiet of his laboratory. Five years ago, the field of tissue transplantation was in a very difficult phase of clinical research. Then came the demonstration of immunosuppressive pharmacology by scientists working with the New Zealand white rabbit. There was then a period of advance clear for all to see as studies in the dog confirmed their findings and were moved to man. But now again the field of tissue transplantation has been advancing more slowly, awaiting its next stepwise upward progression. As this is written, several new modifications are coming along, any one of which might make tissue transplantation safer and more effective. Until then, the toilers in this vineyard must work with the methods they have, respecting some such guidelines as these, for ethics in the pursuit of *veritas*.

It is most appropriate to raise ethical questions at a time like this, not only to strengthen and shore up the procedures of each group working in the field of transplantation but also to challenge the critic and put him on his mettle to show cause why this particular advance of medical science should be any more suspect than another. The laboratory scientist tends to be critical of the clinician, the physician of the surgeon; these petty chauvinistic antagonisms should never cloud the real issues of ethics and acceptability in applied human biology.

Tissue transplantation, like other advances of the past, will react to the welfare of mankind if explored and exploited within the ethical bounds of science itself. Honesty and self-discipline must be held as values of the same importance as the very essence of all medical ethics: the welfare of the patient.

The Frequency and Natural History of Urinary Tract Infection in School Children*

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This presentation reviews briefly investigations of the epidemiology and natural history of urinary tract infections in school children conducted during the past four years in Central Virginia. The results of this work will be summarized and their implications discussed.

Urine Culture Methods

The clean-voided, quantitative pour-plate urine culture was performed throughout. Cases were defined as children with three consecutive positive cultures (criterion 1×10^5 bacteria per ml). Almost all cases were confirmed by culture of urine obtained by catheter at the time of the urologic study. *E. coli* were serotyped according to their O and H antigens.

The Population

Following a pilot study of 3,057 children in Waynesboro, Virginia, in 1959, full scale surveys of school children in Charlottesville-Albemarle County, Virginia, were conducted in 1960–61 and 1962–63. Participation was 85% in the pilot study and 90% of all children enrolled in school in the full scale surveys. Altogether, more than 20,000 cultures have been performed on specimens from 16,000 persons. A prospective study of a cohort of girls begun when they first enrolled in school is still underway.

Frequency of Bacteriuria

The prevalence of bacteriuria was 1.2% in school-aged girls and 0.04% in school-aged boys. Prevalence was about the same in Negro and white girls, equally distributed in urban and rural areas and constant in all three studies. The prevalence of silent bacteriuria was significantly higher in older Negro girls (15–19) than in white girls or younger Negro girls. Incidence of silent bacteriuria over a two-year period was 0.7% and the same in whites and Negroes. Incidence of overt urinary tract infection in school girls during the same period was 3.6% and higher in white than Negroes (5.3% and 1.1% respectively).

Characteristics of Cases

One hundred and twenty two bacteriuric children were discovered in these surveys. Pyuria (four or more WBC/hpf) was present in almost 50%; past history of overt infection was reported by almost one third; and 40% had symptoms, usually referable to the lower urinary tract. Urologic studies (IVP and cystogram) were performed in 107 cases. Intravenous pyelograms revealed some abnormality in 22; caliectasis was present in 14; and 4 had reduplication of the collecting system. Cystograms revealed some abnormality in 40 children including reflux in 20, large bladder in 11, small bladder in 5 and trabeculation in 13. Lesions detected on IVP and cystogram were significantly ($P < .05$) more frequent in white than Negroes. Pyuria, past history of infection and symptoms were not reliable indicators of the presence or absence of abnormalities later found on urologic study.

Therapy and Recurrence

Most cases were initially treated with sulfonamides for a period of two weeks. Recurrences were first treated with a second course of sulfonamide and, if frequent, with tetracycline, nitrofurantoin or other appropriate drugs. Recurrences were frequent. For example, at the end of one year, 65% of white girls had at least one recurrence. The recurrence rate in Negro girls (18.2%) was significantly lower than in whites ($P < .01$) at one year. Recurrences were analysed as being due to endogenous relapse (recurrence of the same *E. coli* serotype or same bacterial species other than *E. coli*) or to reinfection (appearance of a new *E. coli* serotype or a new species in the urine). Most recurrences (about 80%) were thought to be due to reinfection rather than to endogenous relapse, and possibly related to inadequate therapy. This indicates that this population with cases of bacteriuria is distinctly different from the general population of school children in which bacteriuria is

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relatively rare. One possible implication is that females who develop pyelonephritis during the reproductive years emerge from this group of children with frequently recurrent bacteriuria.

Frequency of recurrences could not be related to the previous findings of caliectasis, reflux or trabeculation on urologic study, suggesting that the entrance and persistance of bacteria in the urine is not related to these abnormalities. This does not necessarily indicate that structural abnormalities may not be important in the genesis of infection of the upper urinary tract once bacteriuria is established.

Antibody Response to Infection

All children studied over the age of two had circulating antibodies to a wide variety of *E. coli* O antigens including those most commonly found in children (reported by us) and adults (reported by others). The common types of *E. coli* are 0, 1, 2, 4, 6, 7, and 75. Enteropathic *E. coli* were not found in urinary tract infections. A rise of antibody titer in association with bacteriuria was rarely observed in the current series of cases and persistence of constant antibody titers for many months was commonly observed.

Summary

This brief summary of our studies of urinary tract infection in school children indicates that bacteriuria is frequent enough among girls to make surveys of this type quite practical both as a community effort and an office practice. The ultimate significance of bacteriuria is unknown, but about 10% of the cases found had important urologic lesions (including the megacystis syndrome) which would not have been detected if these studies had not been conducted. Long term follow-up of cases, now underway, may help to determine the true significance of bacteriuria.

Acknowledgement

The studies reported were conducted in coöperation with Dr. Albert Paquin, Jr., professor of urology, University of Virginia School of Medicine.

The Scholar as a Teacher

"... I hold that no teacher—no matter how skilled—can so well present a subject as when he himself is working in that field. It is a truism that a member of a university community of scholars must himself be engaged in scholarly work. There is nothing like the combination of clinical problems at the bedside and dirty hands in the laboratory to teach the teacher. A prime prerequisite for scholarly work is a curious and inquiring mind. Attempting to answer any single question in depth soon disciplines omnivorous curiosity. Many problems can be approached only by carefully planned and slowly developed data, and no problem is solved until it is formulated and worked out and the data analyzed and published. 'Publish or perish' is more than a scoffer's jibe. The investigator who does not publish his results has not completed his research problem, made full use of his data, or justified the financial support intended to increase available human knowledge. 'Reading maketh a full man; conference a ready man; and writing an exact man.' And I mean writing for professional journals—not for the lay press. It is also true that when a problem presents itself on the ward or in the clinic, nothing is more apt than Claude Bernard's aphorism, now 99 years old, that 'chance favors the prepared mind' (Bernard, C. *Introduction a l'Étude de la Médicine Expérimentale*. Paris: Baillière, 1865).

"The exact influence of research on teaching is, of course, hard to assess. Certainly enthusiasm is an important teaching instrument, and the person intensely engaged in work on a subject about which he is teaching is the best possible person to create an enthusiastic reception on the part of the student. To my mind, a scholar who is himself working on the subject which he teaches is also the person most aware of the pitfalls, dubieties, uncertainties and qualifications involved. Such caution should contrast greatly with the glib veneer of the nonscholar. Glib oversimplification may sell soap, but it should not be the tool of the scholar. In the academic community, teaching is not a popularity contest and the teacher must aim at clarification rather than simplification. Who knows better the limitations of knowledge than the man who is himself striving to extend the frontiers of that knowledge?"

Gilbert S. Gordon, M.D., Credo, *Postgraduate Medicine* 36: 630–633, 1964.

γ-Globulin Administration and Anti-Globulin Antibodies in Children*

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The etiology of the rheumatoid factors in patients with rheumatoid arthritis and of anti-globulin antibodies in normal individuals remains obscure despite recently documented observations. Allen and Kunkel (1963) and Vierucci (1965) have reported an increased incidence of anti-globulin antibodies in children who received multiple transfusions for chronic anemia. Fudenberg et al. (1964) and Stiehm (1965) found that children who had been receiving repeated γ-globulin injections were more prone to produce anti-globulin antibodies than children not exposed to γ-globulin. These data furnish indirect evidence of the isoantigenicity of genetic determinants in human γ-globulin. From the clinical standpoint, the observations are of interest to pediatricians administering γ-globulin to children whose sera show low levels of γ-globulin, and whose clinical courses are characterized by repeated or chronic infections.

This study was undertaken to determine the incidence of anti-globulin antibodies in non-hospitalized children with chronic or recurrent upper respiratory infections, only some of whom had received γ-globulin injections.

Materials and Methods

The 185 children studied were under the care of their private physicians or attended the pediatric clinic. Hospital patients were not included. With the coöperation of the participating physicians, history forms were completed on each child, recording age, race, sex, the amount and duration of globulin therapy, reason for administering γ-globulin, transfusion history, and whether or not joint symptoms were present. All children with a transfusion history were excluded from this study in order to obtain a more uniform population.

The 44 children who had received γ-globulin injections had γ-globulin levels less than 500 mg per 100 ml. The duration of γ-globulin therapy reflected to some degree the course and duration of their respiratory infections. The 141 children who had "never" re-received any γ-globulin comprised the largest group. Although these children were recorded as "never" having had γ-globulin, it has been customary for some physicians to give a small amount of γ-globulin with measles vaccine. Some of these 141 children were tested before the initiation of γ-globulin therapy. Thus, these children do not necessarily represent a group of children with normal levels of γ-globulin.

All sera were tested at a 1:20 dilution by: the slide latex test (Hyland), the sensitized human cell test, and the sensitized sheep cell test. These tests have been described previously (Waller et al., 1961). In addition, most of the sera were tested at a 1:5 dilution with selected sensitized cells known to detect anti-Gm^a, Gm^b, Gm^x and Gm^f activity.

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Results

Anti-globulin Antibodies

Of the 185 children studied, only 44 had received injections of γ-globulin at the time of testing. All of these children were tested at a 1:20 dilution of their serum with the slide latex test and the sensitized human cell test. The latex test was strongly reactive in only one child and weakly reactive in 12 children. Only one of these 13 children had received γ-globulin injections. The human cell test was positive in eight children (4.3%), only one of whom had received γ-globulin. This incidence does not differ significantly from that characteristic of the normal adult population (Waller et al., 1964). The sensitized sheep cell test (Waaler-Rose Test) was performed on 135 children, including all children found to be positive by any of the other tests. In no instance was a positive sheep cell test observed.

Since the titers of anti-globulin antibodies in normal individuals may often fall below 1:20, 140 of the original 185 children were tested at 1:5 dilution of their serum with Ripley sensitized cells. Eighteen children (12.9%) gave positive tests at this dilution. However, of these 18 children with positive tests, only three had received injections of γ-globulin.

Thus, to look at the results in another way, of the 108 children who had not received injections of γ-globulin and whose sera were tested at a 1:5 dilution, 15 (13.9%) gave positive tests. However, of the 32 children who had received γ-globulin and whose sera were tested at a 1:5 dilution, only three (9.4%) gave positive tests. These differences are probably not statistically significant ($p > .4$).

Figure 1 compares the titers of anti-globulin antibodies in children who had received γ-globulin injections with those who had not received any γ-globulin. The left bars, 1:5, represent the negative group in our study, since the children were not tested at a level below 1:5. Ten children gave titers of 1:5, but only two of these had had γ-globulin. Eight children had titers above 1:5, but only one child had had γ-globulin. Thus, among the 44 children who had received injections of γ-globulin, only three children gave positive tests for anti-globulin antibodies. There was no correlation between the amount of γ-globulin administered, the duration of globulin therapy, and the presence of a positive test for anti-globulin antibodies. Three children had had in excess of 100 ml of γ-globulin over a period from one to three years, and all gave negative tests at 1:20 dilution of their serum. Two of the three were also negative at 1:5 dilution of their serum.

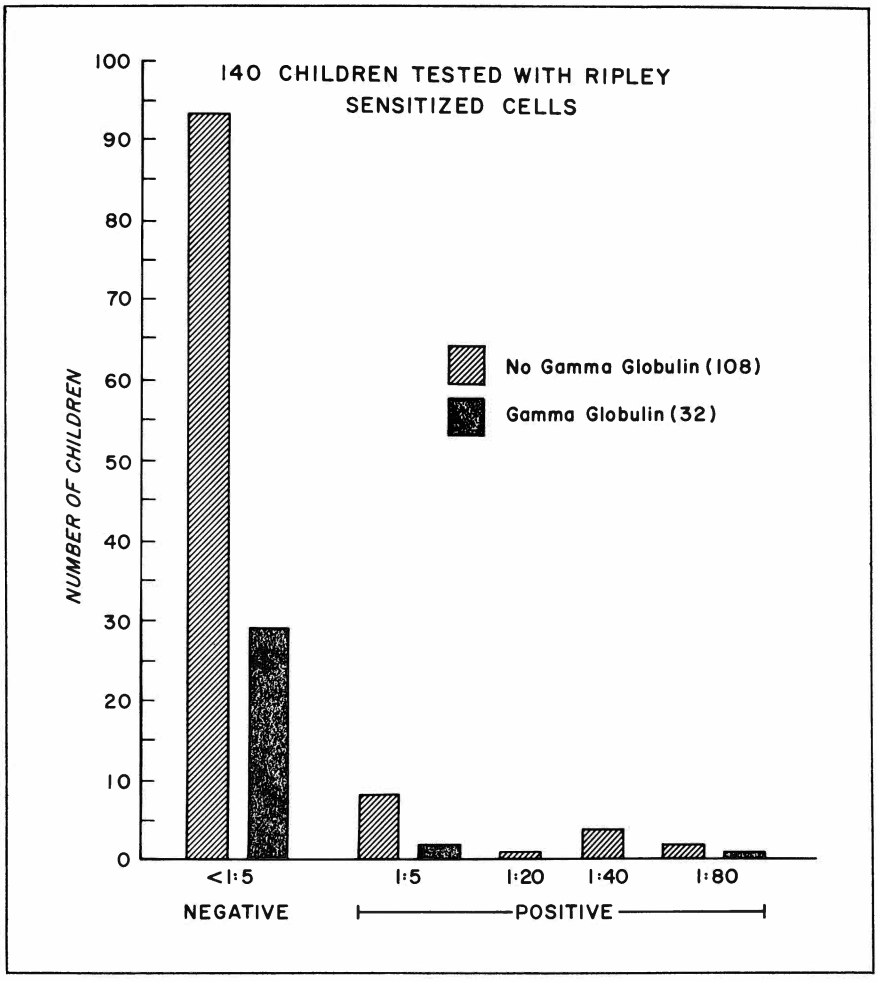

Fig. 1—Titers of anti-globulin antibodies in 32 children who had received γ-globulin injections, and 108 who had not.

Gm Specificity of Anti-globulin Antibodies

In addition to the sensitized human cell test (Ripley), four other anti-D sera were used to sensitize cells for Gm specificity of the children's sera. Ninety children were tested for Gm specificity. Of these 90 children, 10 agglutinated the Ripley sensitized cells and five of the 10 agglutinated one or more of the other sensitized cells. Of these 10 children, five gave specific anti-Gm activity, one anti-Gm(f), one anti-Gm(x), and three anti-Gm(a). The sera of the other five children agglu-

tinated only the Ripley sensitized cells, and it was not possible to obtain Gm specificity. Of the five children whose sera showed specific anti-Gm activity, only one had received γ-globulin.

Lack of Correlation between Presence of Anti-globulin Antibodies and Level of γ-globulin or Age of Children

There was no apparent correlation between the presence of hypogammaglobulinemia (<500 mg per 100 ml) and the presence of anti-globulin antibody. There was also no correlation between the ages of the children and the presence of anti-globulin antibody. Among the children up to three years of age, 12% gave positive tests for anti-globulin antibody at a 1:5 dilution of their sera. Among the children over three years of age, 13.7% gave positive tests. Of the 185 children studied, four children gave history of joint complaints, none had had γ-globulin at the time of the study, and none had anti-globulin antibodies demonstrable in their sera.

Injection of γ-Globulin into Adults

We have studied the effects of subcutaneous injections of pooled γ-globulin in four young healthy male volunteers. These men were all Gm(a—) and received (.5 ml) injections of pooled γ-globulin weekly. In addition to tests for anti-globulin antibodies, slide latex tests, and sensitized sheep cell tests, the following tests were performed: serum electrophoretic pattern, sedimentation rate, hemoglobin, and total protein.

Two of the volunteers received a total of eight injections of γ-globulin over a period of three months and two received 16 injections over a period of one year. In no instance did these four individuals produce anti-globulin antibodies, nor were any changes noted in the other tests performed.

Discussion

Although the incidence of anti-globulin antibodies in children receiving multiple transfusions is markedly increased, we were not able to demonstrate this increased incidence in the children receiving pooled γ-globulin. There are several possible explanations for these observed differences. The children receiving multiple transfusions had a definite disease entity while the children that we studied were "normal" except for chronic or recurrent upper respiratory infections. The evaluation of just how chronic, recurrent, or severe the infection rested with the individual physician; however, all of the children studied had electrophoretic patterns of their serum performed as a consequence of the degree or duration of their infection. No attempt was made in this study to separate the children according to degree or duration of their illnesses. Certainly, the children were not ill enough to require hospitalization during the period of this study.

It is possible that plasma is more antigenic than pooled γ-globulin or that the globulin administered intravenously is a better antigen than when it is administered intramuscularly. In addition, the children receiving multiple transfusions received more plasma for a longer period of time than did the children receiving pooled γ-globulin.

Stiehm and Fudenberg (1965) studied 14 hypogammaglobulinemic children who had received many γ-globulin injections and found that nine of these children (64.3%) had developed anti-globulin antibodies. Among the 24 untreated siblings of these children, only two agglutinators were found (8.3%). We are not able to explain the discrepancies in these results other than by the fact that we did not use as controls the siblings of the hypogammaglobulinemic children. However, in addition, one may presume that the untreated siblings were untreated because they were not hypogammaglobulinemic or that they were not subject to chronic or recurrent infection. Some of our untreated children were hypogammaglobulinemic and most were subject to chronic infection. After the testing of their sera, some children were started on γ-globulin therapy.

Since an equal number of our children who had not received γ-globulin produced anti-globulin antibodies, pre-

sumably other, as yet unknown, agents are as likely to stimulate the production of these antibodies as is the administration of pooled γ-globulin.

Steinberg and Wilson (1963) studied eight non-transfused donors of γ-globulin antibodies and found that in each instance the donor's mother had the globulin factor that the donor lacked. They assumed that the donor's antibody was formed as a result of transplacental isoimmunization. However, we have been unsuccessful in our attempts to elicit anti-globulin antibodies in normal adult Gm(a—) volunteers by the injection of pooled γ-globulin.

There is no definitive evidence that the serological reactions called rheumatoid factors in patients with rheumatoid arthritis and anti-globulin antibodies in normal individuals, differ except in strength of reaction (titer) and possibly in specificity. Not all investigators are convinced that the idea of an antigen-antibody relationship for γ-globulin (Gm) and anti-globulin reagents (anti-Gm) in man is firmly established (Grubb, 1961). Certainly, the deleterious effects of the serological reactions called "rheumatoid factors" have not been proven at the present time. Regardless of these unresolved questions, it is not established that the isoantigenicity of γ-globulin is such as to override its therapeutic potential in infection.

Summary

1. We examined sera from 185 non-hospitalized children, 44 of whom had received repeated injections of γ-globulin for upper respiratory infections.

2. There was no significant difference in the incidence of anti-globulin antibodies in the two groups.

3. The presence of anti-globulin antibodies could not be correlated with the level of γ-globulin in the children's sera or with the age of the children.

Acknowledgements

This work would not have been possible without the coöperation of the 33 pediatricians who so kindly filled out the history forms. We are especially indebted to Dr. L. Anthony Austin for sending us some of his young patients who had been on long-term γ-globulin therapy. We also thank Miss Jane Atkinson for providing us with most of the sera used in this study.

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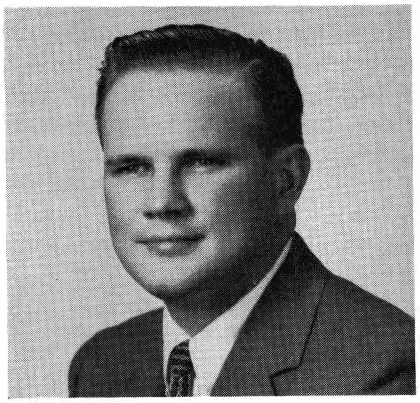

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Panelists at the Second Annual Kidney Symposium; from left, Drs. Kiley, Doolan, Scribner, Finberg, Magee, and Hume.

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