THE USE OF THE ARTIFICIAL KIDNEY IN THE TREATMENT OF UREMIA *

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The use of an apparatus which employed an artificial membrane for the dialysis of blood outside of the body was first suggested in 1913 by Abel, Rowntree, and Turner¹ who employed a device which utilized, for its dialyzing membrane, collodion which these workers extruded themselves. Employing hirudin, the anticoagulant principle of the leech, they successfully performed a number of dialyses in animals. Because of the many technical difficulties involved, attempts to reproduce such a device were sporadic until the generalized use of a better dialyzing membrane in the form of cellophane and an improved anticoagulant, heparin. Kolff in 1944² developed what must be considered the first clinically successful apparatus. Other workers in Europe and in Canada shortly published their results with dialyzers of different construction conceived independently. Within the last few years, in this country particularly, the use of the so-called "artificial kidney" has increased, and its potentialities as well as its limitations have begun to be realized through larger experience. All of these devices, though they vary somewhat in design, function by causing blood from the animal or patient to course through a cellophane tube or between two cellophane sheets. On either side of the cellophane membrane is opposed a dialyzing bath appropriately formed with regard to its electrolyte and osmolar composition. The cellophane

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membrane is impermeable to molecules with molecular weights of about 20,000 or over so that the serum proteins are retained and larger amino acids pass slowly, if at all. The smaller molecules including metabolites such as urea, phosphates, sulfate, and potassium diffuse easily through the pores of the cellophane and are removed in the rinsing fluid on the other side. Since the concentration of essential electrolytes in the bath is such as to affect no gradient for these across the membrane, there is no net exchange of these substances and thus no change in the serum concentration. It is possible, however, if one wishes to remove potassium, for instance, to eliminate potassium from the dialyzing bath, thus creating a marked diffusion gradient from blood to bath, and causing a rapid passage of potassium into the bath where it can be removed, with the resultant depletion of the potassium content of the plasma. On the other hand, if the plasma level of sodium is lower than that in the bath fluid, an influx of sodium into the plasma occurs from the bath as a result of this gradient, and this may occur at the same time that potassium is moving in the opposite direction. Since the individual diffusion gradient for each of these ions determines the direction of its movement and the rate of its exchange, sodium may be added to plasma at the same time that metabolites are removed (Table I). The fact that such transfers may be effected across an inert membrane and in accord with relatively simple physical chemical laws gives the artificial kidney an advantage over techniques such as intestinal irrigation in which the membrane involved is governed by more complicated metabolic processes involving selective resorption and transfer.

Progress in construction of artificial kidneys has involved primarily the use of non-wettable and disposable plastics which have obviated the previous difficul-

TABLE I

H.M. ♀ 30	Acute Anuria	
	0 HOUR	6 HOUR
BUN	313	65
Na	135	145
K	9.0	5.2
Co ₂	13.5	16.5
Cl	97	115
P	3.13	1.20
SUGAR	145	135
Hct.	32	31
BATH UREA NITROGEN		87 GMS.

ties of clotting and pyrogen reactions, and have made the procedure of hemodialysis in proper hands a relatively safe and, certainly, effective technique. It should be emphasized, however, that the apparatus itself is only one, and perhaps the smaller part of the technique, the other being the experience, skill, and plain common sense of the operator. These requirements have been adequately fulfilled in a number of laboratories employing this technique, and the experience accumulated to date in the use of the artificial kidney in the treatment of uremia has been uniform and satisfactory enough so that its role as a therapeutic device may perhaps be delineated. Technique of procedure and construction of various apparatus has been recently reviewed.³

CLINICAL USE

1) *Acute renal insufficiency*: As early as 1923 it was first suggested that an artificial kidney might be used to maintain life and reasonable well-being during periods of acute renal insufficiency where the underlying lesion was reversible.⁴ This view was entertained when the apparatus was first developed at the clinical level, and certain points may now be made with regard to its employment in such cases. There can be no question but that the conservative management of acute renal insufficiency has progressed with recent knowledge to the point where the unwarranted mortality in this syndrome has been reduced to a minimum.⁵⁻⁷ A young, previously healthy individual without concomitant trauma, sepsis, or vascular disease may survive periods of complete urinary suppression as long as three to four weeks. Our experience with acute renal failure includes a series of 112 patients about half of whom have been treated with conservative measures. The experience with the undialyzed patients fits well with the figures given by advocates of conservative therapy alone. It cannot be too strongly stressed, however, that provided the criteria mentioned for its use above are fulfilled, the artificial kidney is an effective adjunct to such forms of conservative therapy. To argue whether dialysis is "necessary" in the treatment of acute renal insufficiency or whether it changes the mortality rate is pointless in this view. If one considers the case of a 22-year-old man, previously in good health, who became suddenly anuric as the result of intravascular hemolysis, the reason for this statement is perceived. This patient who had no concomitant disease would undoubtedly have survived his ordeal with or without dialysis; however, on the ninth day of his anuria, he was semicomatose, apathetic, and vomited frequently. The required fluid and calories had to be administered carefully by vein. Dialysis with the artificial kidney was accomplished on this day, and the following morning the patient was able to sit up in a chair, was alert, and responsive, and in spite

of continued anuria for another five days, was able to take his entire caloric and fluid requirement by mouth. Diuresis supervened, and he went on to get well as, indeed, he would have with or without the artificial kidney. There can be no question but that the procedure was not "necessary" in this case. There can be no question either, however, but that the conservative management of this problem was greatly facilitated by the procedure. This patient's morbid state was entirely due to retention of normally excreted metabolites. In such a situation, the artificial removal of these metabolites, if it can be accomplished safely and effectively, is a rational approach to treatment. Let us now translate this man's illness into terms of an elderly, obese, hypertensive, arteriosclerotic woman who had become anuric during the course of an operation for the removal of an infected gall-bladder. On the fifth day of her anuria, in part as a result of increased protein catabolism secondary to operative trauma and sepsis, and in part due to the susceptibility of an elderly patient to the toxic effect of these metabolites, the picture was entirely different. The patient was comatose, immobile and heir to all the postoperative complications that an elderly, obese patient with vascular disease may incur if immobilized for too long. Under such circumstances, we have seen dialysis with the artificial kidney improve the clinical state to the point where mobilization is possible, and where the patient can eat and be out of bed. Granting that even in this case survival is possible without the use of artificial means, common sense dictates that where facilities for its employment exist, they should be utilized.

Even with the best conservative measures, however, one can often not predict when diuresis will occur. Equally important, one cannot predict, particularly in the case of the postoperative or the septic patient, when lethal complications, such as acute spontaneous potassium intoxication, may supervene. The syndrome of potassium intoxication which may result from the accumulation of potassium liberated in the course of protein catabolism or shifted from the normal intracellular position under the influence of severe uremia or acidosis is not a universal complication of acute renal insufficiency. It is, however, one which is frequently overlooked, and one which may be lethal during the course of an otherwise reversible disease process. Many methods have been proposed to decrease the extracellular levels of potassium in the anuric patient. These include the use of glucose and insulin solutions⁸ and the use of ion exchange resins.⁹ The former is a temporary measure whose duration is short and whose clinical application involves the infusion of extra fluid which may be unwise. The latter, while more effective and highly successful in some cases, in our hands has been variable and unpredictable in its results. Lavage of the various portions of the gastroin-

testinal tract and of the peritoneal cavity are perhaps more effective in removing potassium but certainly more cumbersome than the previously mentioned methods. The artificial kidney which is certainly as cumbersome has, however, the advantage of not only removing potassium rapidly but of also effectively correcting the underlying chemical disorder which unquestionably facilitates a syndrome of which a high extracellular level of potassium is only one part. In such cases, the use of hemodialysis may perhaps be truly "necessary."

2) *Chronic renal insufficiency*: Recent experience with hemodialysis has indicated that the artificial kidney may be of pronounced therapeutic benefit in selected cases of chronic uremia. It should be emphasized that such cases, however, must be carefully selected. In many cases of chronic renal insufficiency, the clinical picture is complicated by hypertensive cardiovascular disease. Hemodialysis corrects only chemical abnormalities, and if the patient's situation depends largely upon derangement of his cardiovascular apparatus, the restitution to normal values of serum metabolite concentrations will affect the clinical picture very little. On the other hand, a prominent feature of most advanced cases of uremia, both chronic and acute, is anorexia, apathy, and, particularly, nausea and vomiting. These appear in large part to be due to retention of metabolite, and the removal of metabolite by hemodialysis effects a decided improvement in these symptoms. At the present time, the therapeutic objective of any form of treatment of chronic uremia is aimed at the amelioration of such symptoms, and if an adequate trial of conservative therapy fails to achieve this result, dialysis may be employed. At first glance, the results obtained might seem to defeat the purpose for which the procedure is employed. In the patient with chronic renal insufficiency, obviously no change in the functional status of the kidneys is accomplished. Thus, removal of non-protein nitrogen is followed at the termination of dialysis by a progressive increase in plasma concentrations to predialysis levels. If this were all that might be accomplished, there would be very little rationale in employing the procedure for the treatment of chronic uremia. It is of interest, however, that the clinical improvement effected may outlast by weeks and months the return of abnormal serum concentrations of metabolite and electrolyte to predialysis levels. Of even more interest is the fact that unlike the patient with acute renal insufficiency, in whom dialysis may effect marked clinical improvement within hours, the patient with chronic uremia shows little or no effect from the procedure for a period of one to three days. This clinical improvement may then begin in spite of return of abnormal plasma concentrations of non-protein nitrogen, and the sense of well-being may persist far beyond the re-establishment of predialysis values for these concentrations. Teleologically one

might suppose that the compensatory mechanisms which adjust for increasing uremia must be reset following the rapid changes in this essentially chemical illness, and that these compensatory mechanisms, set for a new internal milieu, might reasonably be expected in chronic illness to require days rather than hours to adjust. Whether or not such arguments are valid, in many cases this delayed therapeutic response may be compatible with months and in a few cases, years of relatively comfortable and productive existence. It should also be emphasized that a metabolic state, however abnormal, which has been attained slowly over a period of years may entail some degree of risk if it is corrected within a matter of hours. Thus, although the literature tends to emphasize the efficacy of apparatus for hemodialysis, it may well be that the correction of the chronic uremic state should be achieved with an apparatus less effective over a period of days rather than hours.

In general, the polyuric normotensive patient responds better and for a longer period of time than does the relatively oliguric hypertensive uremic patient, and at the present time it can be stated with some degree of surety that the chronic uremic patient with a urine volume of better than 1500 ml./day who has no hypertension and whose nausea, vomiting, anorexia, and weakness fail to respond to conservative measurements may expect a good response to hemodialysis. Responses to successive procedures, unfortunately, tend to be less successful. This may be in part due to the advent of the hypertensive phase of the disease or to the general clinical deterioration. The oliguric response which followed hemodialysis in the chronic uremic with hypertension has been largely abolished by the expedient of dialyzing such a patient against an isourea bath. In such cases, the fact that failure to change the level of the blood urea nitrogen has made little or no difference in the clinical improvement is a fact of some physiologic significance.

Not the least important responsibility of the physician in the use of the artificial kidney for the treatment of chronic uremia is the necessity for carefully explaining to the patient's family the limitations of the procedure and exactly what is to be expected. It is of paramount importance that the responsible member of the family be fully cognizant of the ends to be attained and the results to be expected. A tragic by-product of this technique is the raising of false hopes with subsequent disappointment and disillusionment.

The clinical improvement, however temporary, may be of importance in preparing a patient with chronic renal insufficiency for surgery aimed at the improvement of his underlying disease. In such cases, pre-operative dialysis may enable him to tolerate a major operative procedure which might otherwise carry consid-

erable risk. In the post-operative procedure, too, once the danger of bleeding with heparin administration is passed, convalescence of the uremic patient may be facilitated. In the same manner, patients with exacerbations of chronic glomerulonephritis or of chronic pyelonephritis may be tided over these periods of crisis, and enough renal function remain to permit reasonably comfortable existence.

CONTRAINDICATIONS TO HEMODIALYSIS

The recognition of lack of indication for hemodialysis is equally important as the knowledge of indications for the procedure. Uremia, per se, that is, abnormality of plasma concentrations, is not an indication for the procedure unless accompanied by clinical symptoms. Indeed, there is some evidence that disturbing a patient nicely compensated in the chronic uremic state may be a definite form of mistreatment. Similarly, as has been mentioned above, if the clinical state cannot be closely related to the chemical imbalance, the use of the artificial kidney has no value. At the present stage of our knowledge, hypertensive cardiovascular disease or nephrotic edema cannot be treated by hemodialysis. Anuria per se is obviously not an indication for the use of the artificial kidney. If marked symptoms appear or if the medical management becomes difficult because of deterioration of the clinical state, the procedure may be used with some justification. It does nothing, however, for the anuric state in itself and should not be used unless these criteria apply. Similarly, elevation of blood urea nitrogen, the occurrence of acidosis or hyponatremia in a surgical patient with generalized peritonitis or acute pancreatitis do not entitle one to expect that correction of the chemical abnormalities by dialysis will markedly alter the clinical problem. Although in over 270 clinical trials to date, we have not seen a death attributable to the procedure itself, there are definite contraindications to its application. The first of these stems from the necessity for heparinizing the patient in order to prevent coagulation of the blood during its circuit outside the body. Oozing or bleeding particularly from the gastrointestinal tract may become aggravated during the procedure and fail to cease following its termination, even though the clotting time is restored to normal with protamine. Similarly, subarachnoid hemorrhage or intracranial bleeding of other etiology may be considered probable contraindications to the procedure. Patients with acute glomerulonephritis, particularly with severe hypertension, do not respond well to hemodialysis. The hypertension may be aggravated and convulsions ensue following the procedure, and in such cases, it should be reserved until such time as the chemical deterioration appears to outweigh these considerations. In one case in which anuria followed shock incident to myocardial infarction, dialysis with the artificial kidney resulted in

return of the shock-like state. This experience has led us to believe that anuria following acute myocardial infarction should not be treated with the artificial kidney.

SUMMARY

Certain of the uremic states respond with gratifying clinical improvement to dialysis with the artificial kidney. In acute renal insufficiency, the procedure, if properly employed, may be a valuable adjunct to conservative management and occasionally in acute spontaneous potassium intoxication have a distinct advantage over other methods of treatment. The chronic uremic patient whose debility is due primarily to retention of metabolite may improve dramatically though temporarily following the procedure. Where the clinical situation is not in large part due to these derangements, hemodialysis should be expected to have very little effect upon the clinical course. In any consideration of the benefits to be achieved by this procedure, an understanding of the lack of indication and the contraindications are of utmost importance.

REFERENCES

1. Abel, J. J., Rowntree, L. G. and Turner, B. B. On removal of diffusible substances from circulating blood by means of dialysis, *Trans. Assoc. Amer. Phys.* 28:51-54, 1913.
2. Kolff, W. J. and Berk, H. T. J. Artificial kidney; dialyzer with great area, *Acta med. scand.* 117:121-34, 1944.
3. Merrill, J. P. Medical progress; the artificial kidney, *New Engl. J. Med.* 246:17-27, 1952.
4. Necheles, H. Über Dialysieren den strömenden Blutes am Lebenden, *Klin. Wschr.* 2: 1257, 1923.
5. Stock, R. J. Acute urinary suppression; observations in 22 patients, *Amer. J. Med.* 7:45-55, 1949.
6. Strauss, M. B. Acute renal insufficiency due to lower-nephron nephrosis, *New Engl. J. Med.* 239:693-700, 1948.
7. Muirhead, E. E., Vanatta, J. and Grollman, A. Acute renal insufficiency, *Arch. intern. Med.* 83:528-38, 1949.
8. Merrill, J. P., Levine, H. D., Somerville, W. and Smith, S., III. Clinical recognition and treatment of acute potassium intoxication, *Ann. intern. Med.* 33:797-830, 1950.
9. Elkington, J. R. *et al.* Treatment of potassium retention in anuria with cation exchange resin, *Amer. J. med. Sci.* 220:547-52, 1950.