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ARTIFICIAL KIDNEY*

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In ancient times it was thought that the kidneys were linked closely with the temperament of the individual, and physicians of old practised largely on physic and examination of the urine. With modern pathology, much more has been learned about the kidneys in many respects, but their detailed function is still a mystery.

Our interest in an artificial kidney came only as a sideline to the work being done with heparin, and fundamentally a good anticoagulant is paramount when blood is to be circulated through any system of artificial tubes.

There were other reasons which made such an investigation more or less logical. The ever-present patient with anuria, for whom so little could be done unless the kidneys themselves decided to go to work, also offered a real challenge. The persistence of anuria in a patient who may look and feel well induces in the doctor in charge a series of changing moods ending in desperation and an admission of helplessness from ignorance of the disease of uraemia, its cause, how it acts, and its cure.

With heparin as an anticoagulant, attempts were made to clear the blood stream of toxic substances by transplantation of a kidney from one animal to another and from one species to another. This work was done in 1933-5 with moderate success (Murray, Delorme, and Thomas, 1947). The objective in this present investigation was to produce similar effects by preventing a patient from dying of acute toxæmia in such conditions as acute mercury and phenol poisoning, in the toxæmias of acute infections such as nephritis or pneumonia, etc., with oliguria or anuria, as well as in acute anurias following blood transfusions, crush, excessive sulpha-drug administration, eclampsia and toxæmia of pregnancy, severe skin burns, induced abortions, acute injury to ureters and kidneys from calculus obstructions, reflex or otherwise, or following operation. This thesis is supported by Trueta's (1947) work, in which it was shown that the cortex of the kidney may be put out of action by various reflex or other means, and that it may regain its function provided the patient survives long enough.

It therefore seemed possible, if the patient could be protected from death from toxæmia in such conditions, that after a time a number of the kidneys affected might recover enough to resume function, and such has been the case in several instances.

It was with satisfaction, therefore, that experimental results to justify this thesis were noted and also that clinical

evidence has supported the claim. Also, it has been demonstrated repeatedly that the apparatus works smoothly for long periods, and that it performs the functions for which it was developed.

Many workers, including Abel, Rowntree, and Turner (1913, 1914), Thalheimer (1938), and numerous others, have embarked on similar investigations, but the work has not to our knowledge been developed to a point where it was a proved effective clinical method of treatment. The one exception is that of Kolff and Van Noordwijk (1946), in Holland. We were not aware of their investigations, and not until after the war did we hear of their results. Their excellent monograph gives evidence of the treatment of an extensive series of patients, with some good clinical results. Apparently our efforts have been carried on simultaneously, and they were quite independent. It was interesting, therefore, to compare the methods and the material used, and to note the different avenues followed, which evidently converged fairly closely towards the same goal of end-results.

Development of the Apparatus

The principles of our artificial kidney are: (1) a dialysing membrane which is selective in allowing the passage of some substances and not of others from the blood stream—namely, non-protein nitrogen and other toxic substances; (2) a method of circulating the blood through this extrinsic system; (3) protection from removal of necessary substances from the blood stream.

It was not until very extensive and arduous trials and experiments had been made that we finally arrived at the present set-up (see Diagram), which works satisfactorily both experimentally and in clinical patients.

Schematic diagram of artificial kidney (not drawn to scale). V_1 and V_2 = valves. C = condom. S = syringe. E = eccentric. T = rubber tubing. A = air trap. R = inlet control. D = dialysing membrane. G = Bath jar.

*Based on the Alexander Simpson-Smith Lecture delivered at the Hospital for Sick Children, Great Ormond Street, on July 11 by Dr. Gordon Murray.

The following is a summary of some of the series of events which led to the development of the apparatus and of what might be termed the evolution of this instrument.

1. The first method was the circulation of arterial blood with return through the venous side through several coils of cellulose acetate tubing (sausage-casing) bathed in warm tap-water. This tubing was 1 in. (2.5 cm.) in diameter and presented the primary disadvantage of the volume/surface-area ratio. Also, the size of the tubing allowed escape of too much of the animal's blood before there was sufficient return, if a reasonable length of it was used. In this way the animal really had haemorrhage into the tubing. Filling this with blood beforehand overcame the difficulty.

2. Later on, with considerable effort, tubing $\frac{1}{4}$ -in. (1.25 cm.) in diameter was obtained, with somewhat better results. Then $\frac{1}{8}$ -in. (0.6-cm.) tubing was obtained from the Visking Corporation, of Chicago, and this gave fairly satisfactory results.

3. With sufficiently long sections of this tubing *in vitro* we were able to demonstrate that there was some passage of N.P.N. substances through this membrane and that the larger protein molecules did not pass (Chart 1).

4. To diminish the volume of these tubes it was attempted at first to pass the tubing through a series of wire cells containing the dialysing tubes.

5. Next, concentric wire cylinders between which the tubes were partly compressed were used.

6. Then we tried a wooden reel on which the coils could be assembled fairly quickly. This did not control the volume satisfactorily.

7. Next it was decided to coil the tube round a small platform, when plastic perforated sheets were applied on each side and bolted together to compress the tubing in the coil. These were found to be unsuitable because of the bulging under the pressure of the fluid in the coil.

8. Then sheets of the plastic plates were replaced by wood, and these were found to warp.

9. The latter were replaced by aluminium-steel plates, which were bolted together with a thin definite spacing between them. This worked moderately well, but was finally discarded for

10. A vertical wire-mesh cylinder around which the tube was wound in spiral fashion and held in place by cross-pieces of wood. This method finally gave the best result with the $\frac{1}{8}$ -in. tubing, and lengths up to 150 ft. (45.72 metres) of tubing could be used quite satisfactorily, giving a fairly high rate of dialysis.

Sources of the Blood for Dialysis

The next problem to be solved was that of a method of circulating the blood. Early on it was decided that using an artery as the propelling force had many disadvantages: (1) The artery could be used only once; if further attempts were to be made another vessel would be required. (2) The pressure in the system was such that there was not a satisfactory return of the venous blood by this type of pressure. Moreover, the animal tended to act as from the result of haemorrhage from the arterial bleeding.

In all these methods, of course, it is quite obvious that the animal was highly heparinized to make sure that there was no clotting or thrombosis either in the system or at the points of intake or output or in the animal itself.

It was decided to attempt to develop a method by which the blood could be taken from the venous system and then returned to it through another point. On this basis, blood

was taken first from femoral veins, then from external jugular veins, but it was found that with any pump system which produced suction the vessel collapsed and acted as a valve over the tube. To overcome this difficulty a catheter of fairly large diameter was finally passed through the femoral vessels and into the inferior vena cava or into the right heart region. From this any quantity of blood could be removed by aspiration without any interference or obstruction, and it could be returned quite readily to a vein on the opposite side. This seemed to have many advantages: (1) there was no ill effect on the animal's pressure simulating haemorrhage; (2) the quantity of blood removed could be controlled accurately, which was not the case when an artery was used; (3) the venous blood, unoxygenated, was circulated through the system, and therefore more impurities were available for dialysis by this method; (4) the blood was not oxygenated, and, as well as dialysing it, it was easy to add oxygen during the circulation through the system of tubes.

Pump System

The next problem was one of providing a circulating pump system which would not damage or crush the blood corpuscles, would not produce haemolysis, would work smoothly, and would not become plugged and clotted with fibrin. At first the blood was drawn into a flask, circulated through the dialyser, and then returned to the venous system by gravity.

Next a piston syringe was used as a pump, with intake and outlet valves on glass seats, but it was early demonstrated that in spite of high heparinization the spinning of these valves and the passage of the blood through the small apertures tended to cause some collection of fibrin and to interfere with the functioning of the system. In place of this a rotary-pump effect was used, but it was only moderately satisfactory. Finally, a pump system was used whereby a rubber tambour was inflated and deflated by the action of the piston syringe attached to an electric motor. Rubber intake and outlet valves gave good results, so that a smooth circulation, without injury to blood and without clotting and deposit of fibrin or platelets, could be ensured for many hours at a stretch.

Experiments on Increasing Dialysis

Many efforts were made to increase the rate of dialysis through the membrane.

1. The best and most obvious means was by increasing the length of the tubing used. Lengths up to 35 ft. (10.67 metres) were employed quite satisfactorily, and it is possible that this length could be considerably increased with still more beneficial effect. Recently lengths of 150 ft. (45.72 metres) have been used.

2. It was thought that by attempting to reduce the atmospheric pressure surrounding the tubing an improvement in dialysis might be obtained, but the results were not very satisfactory.

3. By increasing the pressure within the dialysing tubing it was hoped that there might be some increase in the dialysis, but again this requires further study to be certain of the effect.

4. Some investigation was carried out to see if the work described by McBain and Kistler (1928, 1929, 1930, 1931) would apply under these conditions. These authors indicated that the use of 64% zinc chloride solution would stabilize the apertures in the membrane and increase the rate of dialysis. Extensive tests, covering several months, were done with this. It was our conclusion that, while there was some benefit in the rate of dialysis early in the exchange, in the final results there was not a very great difference. The difference did not seem to be great enough to justify the effort and trouble of treating the tubing, and for that reason the method was discarded and the untreated tubing was used. It was noted in our experiments

CHART 1.—Showing dialysis of N.P.N. from human blood *in vitro*. 2.3 g. of N.P.N. was removed in two hours. No proteins came through.

that the use of zinc chloride, with adequate washing afterwards, did not seem to produce any toxic effects in the animal.

The Dialysate

The next problem, related to the protection of the animal against the removal of substances which are necessary for life, involved a great deal of work and was the most difficult to solve.

If an animal's blood was dialysed through this instrument with a surrounding bath of tap-water it was found that within five to seven minutes the animal showed very striking clinical changes. The rate of breathing was accelerated until this became very violent. There was shock and collapse, and the animal died within a period of seven to fifteen minutes.

At this stage we were not certain whether important substances such as adrenaline, "pituitrin," insulin, heparin, and so on were being removed and whether the animals were going into shock on this account. As the chemical tests for some of these substances are exceedingly difficult and uncertain, we were not convinced by chemical analysis whether such was the case or not. However, we arrived at our final conclusions by the following methods:

During dialysis it was demonstrated that the animal had an increasing concentration of haemoglobin, and that it showed evidence of water loss. It was therefore decided to balance the dialysate surrounding the tubing with some of the normal substances in blood as indicated in Ringer's solution. It was found that by an addition serially of each one of these substances we could overcome one or other of the difficulties and could carry on a dialysis without producing these disastrous effects on the animal. When the chlorides, the calcium, the magnesium, the potassium, the sodium, the phosphate, the carbonate, and the sugar were balanced in turn these disastrous effects did not occur. In the preparation of our dialysate it was found that with the potassium left out the animal suffered ill effects and when potassium was added it was protected against these effects, and similarly with the other salts and sugar. Variations in the pH also caused alarming results. It was necessary to add bicarbonate to the solution so as to maintain the pH at a level of about 7.3. With the dialysate at this level there was no change in the blood pH during or following dialysis.

However, as both quantitative and qualitative tests for some of these chemicals are difficult and unreliable, we found it difficult or impossible to prove the specific effect of the lack of potassium, calcium, etc., although the experimental proof of this seemed to be adequate. Finally, a bath solution similar to that used by Seligman, Fine, and Frank (1946) was used. It contained sodium chloride, calcium chloride, magnesium chloride, potassium chloride, sodium hypophosphate, sodium bicarbonate, and dextrose in physiological amounts. This solution was well buffered, but a certain care in mixing and autoclaving was required to prevent precipitation of insoluble salts.

Transfusion of Blood

The next problem was the fact that in a smallish or medium-sized animal there was so much loss of blood into this machine before any was returned that the animal was left with saline in its circulating system and all its blood out in the apparatus. However, this was overcome by filling the machine with suitable blood for the animal. When this was done the circulation could be carried on indefinitely without ill effects.

Many of our earlier experiments were carried out *in vitro* by circulating blood and other solutions through the instrument and by placing substances in the circulating fluid which could be detected in the surrounding dialysate. Next, in a normal animal, with the circulation going, 5 g. of urea was injected and the rate of removal of this was

determined. With the tendency of urea to form a closer relation in the blood of the dog, it was probably not as fair a test of dialysis as might occur in the human being, in whom the urea is separated more readily and is more easily dialysable. However, this did demonstrate the rate of removal of N.P.N. substances from a normal animal.

Uraemia in Animals

The next problem was to produce azotaemia in an animal so that the effectiveness of the apparatus could be assessed under these conditions. Bilateral nephrectomy was found to involve a number of uncontrollable factors, and the uraemia so produced was so severe and was associated with such a poor resistance in the animal that it did not lend itself to these experiments. A more gradual onset of uraemia was desirable, and was thought to be more comparable to the clinical condition in patients.

The chemical production of oliguria and anuria was investigated, but no completely selective uncomplicating poison which seemed suitable was encountered. Most of the work done on specific kidney damage involved the perfusion of the kidney by exposure and cannulization of renal vessels.

Ligation of ureters was performed on a series of animals, but sudden death, presumably from cardiac arrest, as has been described in the literature, was so frequent before dialysis could be carried out that many of the animals succumbed. Finally, an interesting method of producing uraemia was employed. The ureters were transplanted into the small bowel in the hope that there would be enough resorption of non-protein-nitrogen bodies to produce uraemia. This took place in a surprisingly short time, and high levels were reached in three or four days, associated with lethargy and diarrhoea. The animals, however, maintained their food and fluid intake, which was not the case with nephrectomized animals or in those with ligated ureters.

The study showed that blood may be circulated outside the body, and that with a reasonable length of dialysing tubing moderate amounts of N.P.N. can be removed in short periods from normal and uraemic animals, provided these animals are not moribund or in a state of severe circulatory depression. The N.P.N. level in the blood varies greatly in the above state and is a less reliable guide to the efficiency of the dialysis than is the N.P.N. measurable in the dialysate removed during the test run.

It seemed obvious from the experiments as well as from the effects on patients clinically that the level of N.P.N. substances measured in the blood gave only a poor indication of the effect of such dialysis. Obviously the N.P.N. substances in the blood stream are not produced there, but are the waste products delivered to this circulating medium from the tissues in which they are formed. This circulating medium, the blood, has the function of carrying these substances to points where they are detoxified and prepared for excretion, and finally are carried to the kidney, where they are excreted from the system. While the level of N.P.N. substances in the blood may be reduced somewhat, the essential point in treatment is to reduce these and other toxic substances in the vital centres and other fixed tissues. During many of the experiments and in the clinical runs more N.P.N. was removed than was contained in the total volume of blood in the animal and still the level in the blood stream was lowered only slightly. Thus it was obvious that there is a constant drainage of these substances from fixed tissues into the blood stream, one of whose functions is to transport the substances for disposal.

It seemed of interest to investigate this aspect of the problem. For that purpose animals were nephrectomized and the N.P.N. of the blood and spinal fluid was followed as the animal developed uraemia. When the N.P.N. had reached a high level in these two fluids the animal was sacrificed and blocks of tissue were immediately frozen, ground up, and N.P.N. estimations done on these by Dr. Gornall. Chart 2 indicates the state of affairs here. When

CHART 2.—N.P.N. levels in a male dog weighing 12 kg. after left nephrectomy and ligation of right ureter.

the blood N.P.N. reaches a certain level the spinal fluid level is above this, and the level of the N.P.N. substances in the tissue examined was above that level again. This would tend to bear out the point already made that the blood is only a medium for the collection of these substances and washing away of them for disposal.

When, therefore, in a clinical patient it was reported that 12.97 g. of N.P.N. substance was removed and readings of the blood showed only a slight depression of the N.P.N. level it was obvious that the N.P.N. substance removed was bringing down the level of these toxic substances in the vital fixed tissues of the patient, and the proof of this was the clinical improvement, with diminishing signs of toxæmia, even though the blood N.P.N. was still at a fairly high level.

From the events observed in animals and clinically, we think it can be assumed with fair certainty that, while N.P.N. substances can be removed, there are other substances that are also removed by this dialysing system. These substances are probably responsible in large part for the severe toxæmia and ultimately for death. Proof of this is the fact that in a normal animal from four to ten times the amount of urea necessary to place the N.P.N. at a high level can be given without much injurious effect. Probably, therefore, another substance is responsible for the toxæmia. This substance has not yet been separated and has not been described or analysed, but this system offers an excellent method of approach to the study of such substances, as suggested by Abel, Rowntree, and Turner (1913, 1914).

This work represents some early excursions into a field which offers great prospects for expansion. The method might be used therapeutically to remove toxic substances as well as

to administer substances which may be beneficial for the individual.

Several tests have been made on patients to assess the functioning of the apparatus. The cases reported illustrate the ability of this apparatus to perform what was intended.

Case 1

The patient, a woman aged 26, had anuria for a period of nine days after an attempt at induced abortion. During these nine days she was passing about 35 ml. of urine daily, and when first seen was in a state of uraemia. She was comatose, was having mild uraemic convulsions, was severely oedematous, and was not passing urine. She was seen by the physicians, the gynaecologists and the genito-urologists, all of whom agreed that her case was utterly hopeless; in fact, they had given up treatment except for some diathermy which was being applied through the loins.

On the ninth day the patient was attached to this artificial kidney by passing a catheter through the saphenous vein into the inferior vena cava on the right side, and another into the femoral vein on the left. With the machine running for one hour she was moderately improved. The results of the run are shown in Chart 3.

Towards the end of the hour the patient showed some discomfort. She developed a fairly severe chill. Because of this and not knowing just what the effects were, and because of difficulty in following the chemistry accurately, the dialysis was discontinued at the end of an hour. It was shown fairly conclusively on subsequent runs without any similar ill effects that the probable trouble was inadequate washing of the tubing. On all occasions we used new tubing throughout, including rubber tubing, the tambour in the pump, and the dialysing membrane. On the subsequent occasions this was thoroughly washed through with distilled water for an adequate period of time and then washed for a short time with blood solution to remove any remaining substances either in the dialysing membrane or in the tubing. On subsequent runs lasting up to eight hours there were no ill effects whatever in the form of thermal reactions, changes in respiration, pulse rate, blood pressure, or otherwise.

Following the treatment the patient was considerably improved clinically. The next day her condition was fair.

CHART 3.—Case 1. The shaded columns on the sixth, eighth, and eleventh days show the period of dialysis with the artificial kidney. The fall to normal of the blood N.P.N. on February 3 is indicated.

The day after that she was much worse again and another run of eight hours was given on the machine. The results of this are shown in Chart 3. Her condition was very greatly improved. There was still only 45 ml. of urine. Three days later the patient's condition was again serious and another run of six hours was given. The clinical improvement of the patient was very striking. She was comatose at the beginning of each one of these runs on the machine; at the end she was quite bright. The delirium and coma had disappeared. The patient would drink small quantities of fluid, would respond to questions and conversation, and stated that she felt much better. In spite of the pronounced oedema there was some appearance of intelligence in her face.

During the runs on the machine samples of blood, ascitic fluid from the peritoneal cavity, and spinal fluid were removed, and N.P.N. and other tests done on these.

After the last dialysis there was a moderate secretion of urine, and next day there was an enormous secretion of 4,000 ml. of urine. Subsequently the patient made a progressive and uninterrupted recovery and returned to normal health. During the next two weeks samples of both blood and spinal fluid showed a progressive fall of N.P.N., until on the twenty-fifth day these had both reached normal. The oedema had entirely disappeared. The patient was up and about, and was in normal health. At this stage the gynaecologists reported that the foetus was not present in the uterus. While there was no record of its escape, I think one cannot assume that the dialysing apparatus removed it by this means. The patient was in hospital 33 days.

The only remaining abnormality was a lack of concentration on the two-hour test. The urinalysis otherwise was quite normal and the two-hour test showed a concentration only up to 1012. However, as shown on the final point on Chart 4,

CHART 4.—Case 1. Showing later stages of recovery. N.P.N. and water balance returned to normal.

on the sixty-first day the blood N.P.N. was 28 mg. per 100 ml. The spinal fluid N.P.N. was also 28 mg. per 100 ml., and the two-hour test showed considerable improvement. Here the concentration went up to 1018, and the day and night quantities were fairly normal. The patient has gone back to her regular work and is in normal health. She has since married and given birth to a normal child. Kidney function was watched closely throughout pregnancy, and at no time was there evidence of toxæmia or impaired function.

Case 2

A married woman aged 40 was seen by the courtesy of Dr. J. Crosbie. After caesarean section, when a blood transfusion was given, there was oliguria, and the urine contained haemoglobin and haematin. She passed only 3 to 5 ml. of urine daily for eight days, at which time the blood N.P.N. was 179 mg. per 100 ml. and the patient was showing signs of uraemia.

She was then treated for 26 hours with the artificial kidney. Fifty-four feet (16.5 metres) of tubing was used and 70 g. of N.P.N. was removed from the blood. The following day the urinary secretion increased to 210 ml., rising to 6,730 ml. on

the fifth day. The patient gradually improved, and has made an excellent recovery. Renal function has returned to normal and she is in normal health.

There has been survival in about 50% of the patients treated. Those who succumbed were found on the whole to have had chronic kidney disease, and even though the purification of the blood was accomplished satisfactorily they relapsed into a uraemic state.

We wish to thank Professor Van Wyke and Professor J. McClelland for providing some of the patients. We acknowledge with thanks the privilege of laboratory space and the use of some chemicals provided by Professor Andrew Hunter. The assistance of Dr. Allan G. Gornall in doing N.P.N. assays of tissues is acknowledged with thanks. Otherwise the work was carried on independently of the University or other assistance.

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MALARIA

WITH SPECIAL REFERENCE TO CERTAIN EXPERIMENTAL, CLINICAL, AND CHEMOTHERAPEUTIC INVESTIGATIONS*

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LECTURE II: CHEMOTHERAPY

The factors which may modify the results obtained by treatment with antimalarial drugs include not only the species of the malaria parasite but the variety or strain of the particular plasmodium implicated. The presence or absence of immunity or partial immunity in the patient is very important, and racial considerations may be relevant. Those of negroid stock are sometimes relatively refractory to infection, while Caucasians show maximum susceptibility.

Regarding strains of parasite, James (1931) reported that the Rome strain required eight times as much quinine as the Indian strain of *P. falciparum* to elicit a satisfactory therapeutic response; both strains were equally susceptible to "atebrin" (mepacrine). The Madagascar strain of *P. vivax* was twice as susceptible to "neosalvarsan" (neoarsphenamine) as the local Dutch strain.

Variations in the sensitivity of different strains of the same species of parasite to a given antimalarial drug illustrate the inadvisability of assuming that because a drug in a certain dosage is effective in one geographical area it will necessarily be equally so in another. This point will be specifically illustrated later with reference to mepacrine and proguanil in New Guinea strains of *P. falciparum*.

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