

The Artificial Kidney: a dialyser with a great area.

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Purpose of the artificial kidney.

In the treatment of patients suffering from uremia resulting from renal insufficiency our first attempt will be, where we cannot remove the cause of this insufficiency, to restrict the formation of endproducts that have to be excreted by the kidney by giving a diet containing little albumen. Next we make all extrarenal factors influencing the secretion of urine as favourable as possible. We regulate the absorption of water, we control the composition of the blood and supply sodiumchloride as this is lost by vomiting. We give alkali in the case of acidosis, and so on. Furthermore we try to aid the circulation as much as possible by removing troublesome exudates, etc.

If in spite of all these efforts the secretion of urine should remain insufficient, so that the endproducts of metabolism accumulate more and more in the organism, the urea percentage of the blood rises and the uremia gets more and more serious, we have come to the end of our resources.

Urea and other substances leave the body with the sweat, vomit and with the feces, and several ways of removing the toxic products responsible for the uremia without using the kidneys have been tried. However, all attempts at finding a satisfactory method have proved a failure.

All substances excreted by the normal kidneys can be dialysed, and as all these substances accumulate in the blood in uremia, one might try to remove these substances from the blood by dialysis. For this purpose the blood must be dialysed against a certain liquid through a system of tubes or membranes outside the body, and then brought back again into the patient's body. The blood must be kept liquid by means of a substance preventing clotting. If all substances accumulating in uremia could be successfully removed, a person would be able to live without kidneys, in some cases so long till his own kidneys would resume their activity.

In 1912 and 1913 vividialysis was performed on animals by Abel, Rowntree and Turner (1, 2). The blood was pressed through a system of collodion tubes and subsequently brought back into the animal, clotting being prevented by hirudine.

Necheles (1924) (4, 5) and Haas (1928) (3) used other apparatus; the latter has applied vividialysis to human beings as well. The capacity was, however, much too small; in the course of a whole day of bloodwashing, he could remove only 2 grams of urea.

In 1938 W. Thalhimer took up the problem again, armed with heparine and cellophane tubes. To our regret we do not know whether he has achieved a practical solution.



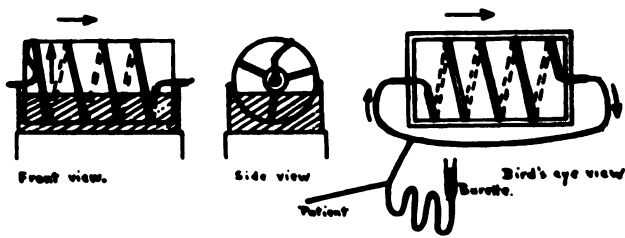


Fig. 1. A cellophane tube has been wound spirally round an aluminum cylinder. The blood within the cellophane always sinks to the lowest point. When the drum is rotating the blood moves from left to right.

The apparatus.

Contrary to previous investigators we can prevent clotting by heparine, and we have excellent dialysing membranes, i.e. cellophane tube. The next step was the construction of a dialysing-apparatus with a small blood volume and a membrane large enough to rival the human kidney. We calculated that by using a cellophane tube 25 mm wide, we should need a length of at least 25 to 30 metres.

A principal difference between our apparatus and all previous ones results from the fact that we have not filled the tube system entirely, but that we cause a small quantity of blood to pass through a tube which is for the rest empty, so that the ratio area: volume gets much more favourable.

We pass over the various apparatus built in the last few years and shall describe only the artificial kidney in use at present.

The apparatus (fig. 3 and fig. 4) consists of a large horizontal cylinder, revolving with its undermost segment in a tank of rinsing liquid.

30 metres of cellophane tube have been wound spirally round the cylinder. The blood is in the cellophane tube, which has been for the rest evacuated and in which it sinks to the lowest point. With the cylinder rotating in the direction of the arrow in figure 1 the blood moves from left to right, continually seeking the lowest point. It leaves the cellophane tube by a rubber tube, carried through the hollow axle to the right (fig. 4), and it enters by flowing through the hollow axle on the left. In the hollow axles the rubber tube is interrupted by a rotating coupling (fig. 5).

Methods of dialysis:

1. *Continuously.* The blood may be let out of one bloodvessel, pass through the kidneys and after dialysis be brought back into another vessel.

2. *Fractionated.* The process is shown schematically in figure 2. A side tube has been attached to the circuit branching in two: one branch to the patient and the other to a burette. By raising or lowering the burette blood may be let into or out of the patient and into or

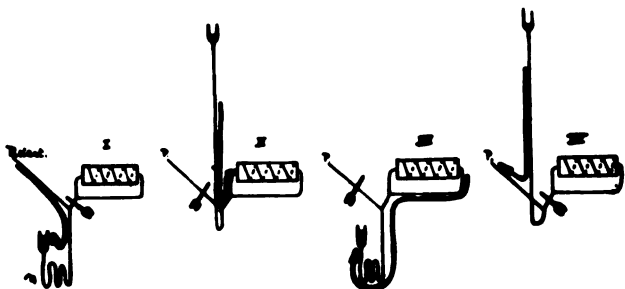
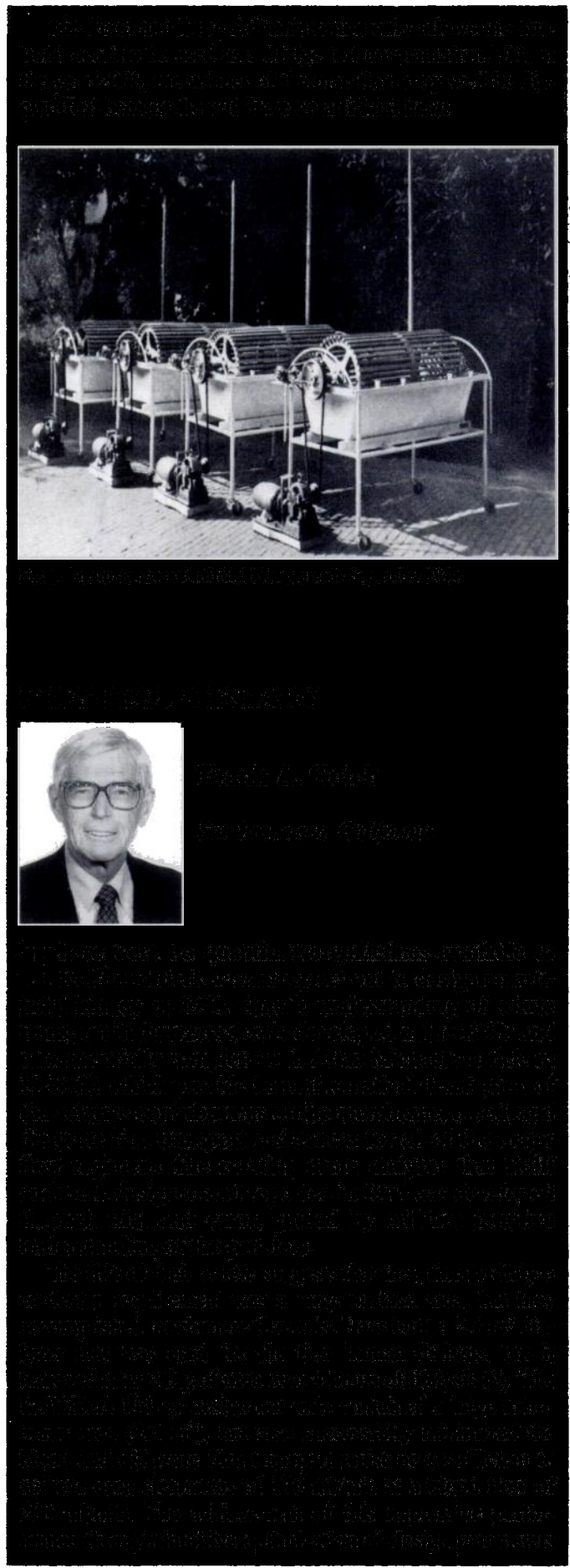


Fig. 2. I. Connection with dialyser shut off. Burette down: impure blood is flowing from the patient's body into the burette. II. Tube to patient shut off. Burette high: impure blood is flowing from the burette into the dialyser. III. Tube to patient shut off. Burette low: purified blood is flowing from the dialyser into the burette. IV. Connection with dialyser shut off. Burette high: purified blood is flowing from the burette into the patient's body.



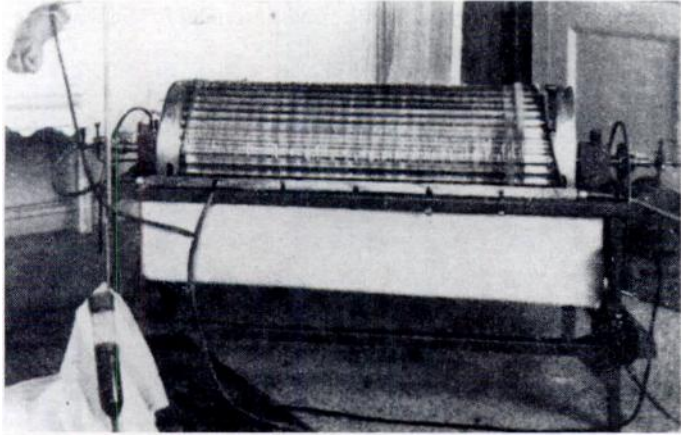


Fig. 3. Front view of the dialyser. The blood, contained in the 30 windings of cellophane tube which are plainly visible, covers the aluminum cylinder with a thin film. The cylinder has been provided with ridges.

out of the dialyser. In following this method only one single venapunction is necessary.

In the tube passing to the patient there is a cellophane window, through which may be seen directly whether there exists positive or negative pressure and by means of which one may check if blood is flowing.

Rinsing liquid. We use 70 to 100 litres of rinsing liquid warmed by a heating element to 37°-39°C, and clean though not sterile, as cellophane is impermeable to bacteria. To avoid hemolysis the addition of glucose was necessary. At present we use the following composition:

NaCl	0.7%
glucose	1.5%
tapwater	97.8%

Cleaning and sterilising. All parts coming in contact with blood, i.e. tubes, couplings and the cellophane are cleaned thoroughly and sterilised. They may be subsequently put together and kept filled with a solution of superol. Before use the superol is washed out with a pyrogenic saline solution and all air is expelled from the tube.

Heparinising. At present we apply the following doses:
At the beginning: 400 mg of heparine in the »kidneys»
400 mg » » » » patient (intravenously)
During dialysis: every half hour 100 mg.

Results of an experimental dialysis. When dialysing 500 cm³ of a 4.17% solution of urea 1.68% proves to be still present after 5 minutes; 2.49% or 1.24 grams have therefore been excreted by dialysis in

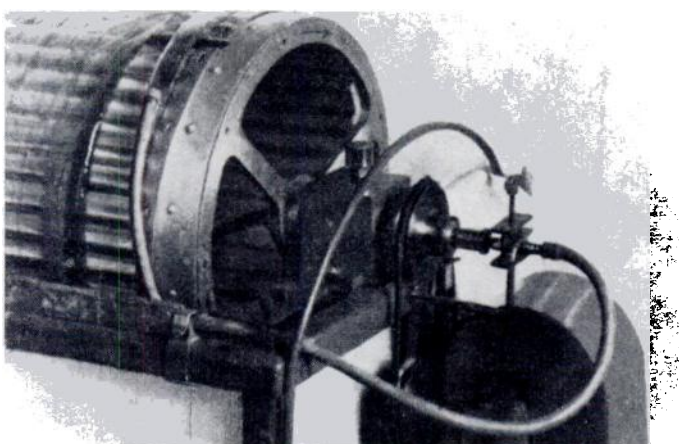


Fig. 4. Half lateral view. The cellophane tube passes into a rubber tube leaving the cylinder by the hollow axle, inside which the coupling is fixed after having been sterilised together with the tubes.

[The following text is extremely faint and illegible in the original scan. It appears to be a detailed scientific or medical description of the dialyser, covering its components, operation, and experimental results. Due to the low resolution of the scan, the specific words and sentences cannot be transcribed accurately.]

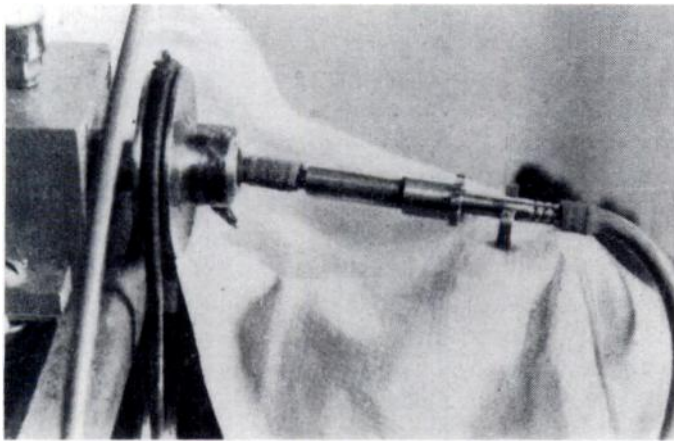


Fig. 5. A rotating coupling. The blood-light joint is formed by a cotton packing being pressed on to the inner tube by means of a screw socket. Later on a counter nut has been fixed on the screw socket as well.

these first 5 minutes. After continuing the dialysis for another 5 minutes 0.57% proves to be still present.

The dialysing area of our first kidney amounts to 17,000 square cms, and our second one to 23,000 sq. cms, the total area of the human glomerular being 20,00 sq. cms.

Patient.

Miss S., single, 29 years of age, consulted the ophthalmologist (Dr. Keiner) in December 1942 because her sight grew steadily worse. There was extensive edema of both papillae with hemorrhages and white foci in the retina. Dr. Dhont, specialist for internal diseases in Zwolle, found symptoms of a chronic nephritis with uremia; Tension 245/150. Urine: isosthenuria, hematuria, 2-3% of albumen. Urea percentage of the blood 110 mg%.

Under general treatment the urea percentage of the blood sank to 75 mg%, but on the 1st of March she had to be taken to hospital again. She vomited almost daily and her state grew worse, so that Dr. Dhont decided to give the artificial kidney a chance, well knowing there was nothing to lose, but perhaps a temporary improvement to gain.

On arrival at the Kampen hospital on the 16th of March 1943, her state was as follows:

By bleeding from the nose her Hb. had sunk to 35% and was still going down rapidly. Pulse 100. Tension 220/140. Urea percentage 164 mg%. The breath smelt strongly of urine. The heart was enlarged towards the left, the ictus

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almost reached the axillary line, a gallop and a systolic murmur were audible. The patient sat up in bed and complained of palpitation and oppression of the chest. All over the lungs moist rhonchi were audible on the following days. All these symptoms have improved after we brought the Hb percentage to a normal level by transfusions of syrup of erythrocytes, during which each time we let an equal volume of the patient's blood escape for fear of causing pulmonary edema. During the subsequent course of the treatment the heart gave no more trouble.

As we did not know at all how our first patient would react to the dialysis we started with repeatedly dialysing small portions of blood. In the end we succeeded in keeping the percentage of urea at the same level for 26 days, after that no more serviceable veins were available.

Various complications have stood in the way of a clinical improvement. First of all the alarming bleedings from the nose, which necessitated repeated transfusions (totaling 14.5 litres), but which were subdued after reiterated cauterisations (Dr. Hinnen). On the 10th day a pericarditis became evident. Next, an angina, a painful parotitis and after that a very serious otitis media of both ears. The copious purulent secretion ran through the tube Eustachii into the throat and excited the vomiting again which had just decreased a little. After treatment with sulfanilamides this too improved.

When a preparation of arteries (Dr. Kehrer) was necessary (all veins being ruined) very persistent hemorrhages arose from the subcutaneous connective tissue owing to the heparine.

After the 12th dialysis had become a failure, the artery being damaged, the urea percentage of the blood rapidly rose to 640 mg%, whereupon death followed.

At necropsy the following appeared:

Prof. Dr. J. J. Th. Vos was kind enough to examine the organs microscopically. The kidneys were very small, their weight was 80 and 67 grams respectively. The glomeruli showed all stages of degenerative changes up to perfect hyalinisation. The arterioles and capillaries showed serious sclerotic changes. The heart was very strongly enlarged with a mighty wall of the left ventricle. There was a purulent pericarditis without the signs of specific inflammation.

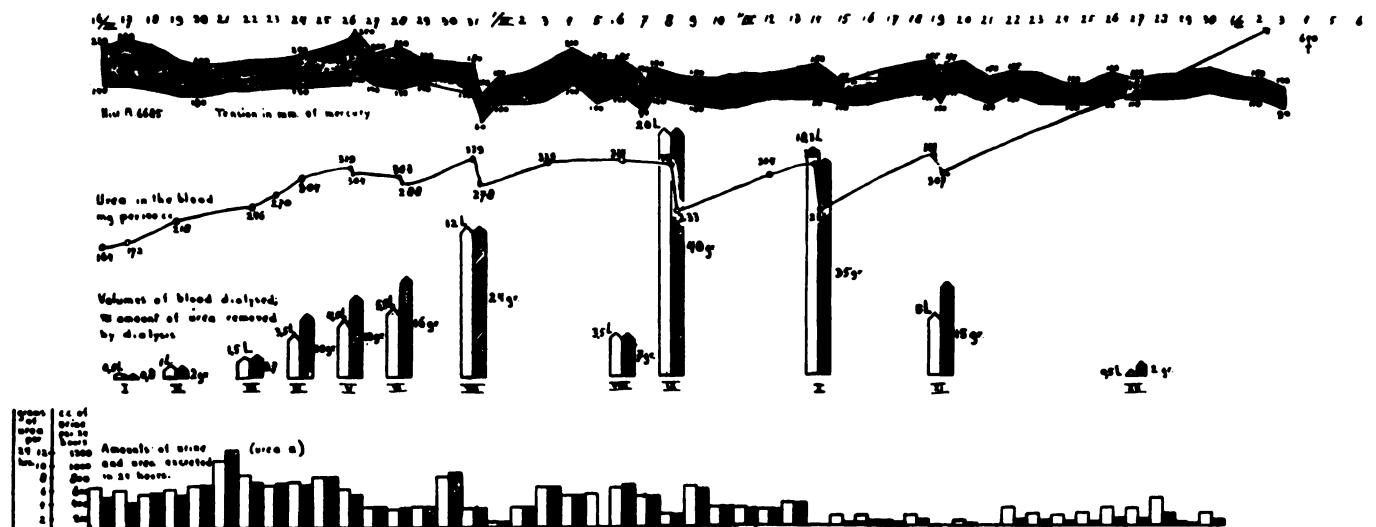


Fig. 6. Graph of patient S., treated with the artificial kidney. In the top of the figure the systolic and diastolic blood-pressures have been indicated, the difference between them being blackened.

The percentage of urea of the blood has been indicated by a drawn line. It is shown to sink each time after a large dialysis, e.g. from 339 to 278 mg per 100 cm³ etc. The dialyses are reproduced by columns. The white column indicates the quantity of blood dialysed; the shaded one the quantity of urea removed by the dialysis. Right at the bottom the quantities of urine passed per 24 hours are found represented by white blocks. The quantities of urea excreted with this urine are indicated by shaded blocks.

The lungs showed small cuneiform foci, reminding of old hemorrhagic infarcts. Prof. Vos however did not find necrosis in the centre, so he is inclined to look on them as old hemorrhages. Clinically they gave no symptoms. Possibly they may be accounted for by hemorrhages (heparine) around small emboli (clots), so that in the future the blood will pass through a filter before returning to the patient's vein.

In this patient we could not effect more than a slight prolongation of her life, but we have been able to collect valuable data.

Clinical symptoms of the uremia during treatment.

Miss S. did not make that deadly indolent and dull impression usually made by uremic patients. For the first four days after the greater dialysis she was often strikingly well and her mind was perfectly clear. The vomiting was temporarily less violent after the 5th to 9th dialysis.

Eyes. The ophthalmologist Rochat found on the 16th of March: strongly prominent papillae; veins widely dilated, many hemorrhages, and a small number of white foci radiating from the papillary region. The sight was very bad. During treatment the edema of the papillae disappeared nearly entirely and returned later. The hemorrhages were totally resorbed, and no fresh ones appeared. The white foci improved temporarily, increasing again later on. The sight improved so much that she could read the paper without any difficulty; this improvement remained until the last days of her life.

Bloodpressure. During the dialysis a sinking of the bloodpressure through shock could often be observed. Secondary effects of the heparine used probably accounted for this. Even when the shock was entirely overcome after dialysis by giving extra saline and blood, the bloodpressure remained at a lower level for the first few days after dialysis. On the graph (see figure 6) the dialyses are shown as columns: the white column indicates the quantity of blood dialysed, the shaded one the quantity of urea removed by dialysis. In the top of the graph the bloodpressure has been reproduced; here one sees that each time after a larger dialysis a lasting decrease of the bloodpressure occurs, e.g. from 180/110 to 145/100. After four or six days the blood pressure returns to its former level. Possible causes are: 1. the removal of a tension-increasing substance from the blood by dialysis? 2. insufficiency of the left ventricle, or chronic shock. This was not in accordance with the clinical picture.

Urine. The hope that the patient's urine production would suffice to maintain a certain balance has not been fulfilled. One gets the impression that the urine production suddenly slackened off after the larger dialysis (see figure 6). This may be connected with the temporarily lowered blood pressure and the lowered percentage of urea in the blood after dialysis. Besides the amount of urine passed per 24 hours decreased gradually during her stay in hospital, and the concentration of urea in the urine sank till it equalled the concentration of urea in the blood. This must be seen as a consequence of the progressive renal degeneration.

Never has there been a trace of hemoglobine in the urine after the dialyses. The sediment only seldom contained some leucocytes and erythrocytes.

Research on substances removed by the artificial kidney.

We are fully aware that urea is at the utmost only partly co-responsible for the clinical symptoms of uremia, but nevertheless we chose it as a measure for the results of the dialyses. Smaller molecules will dialyse more rapidly and bigger ones less so.

Urea: in the larger dialyses 24, 40, and 35 grams of urea were dialysed out respectively. The largest quantity of urea excreted by the patient per 24 hours with the urine amounted to 12 grams.

Figure 6 shows how the percentage of urea after having risen rapidly in the beginning could be kept at the same level for 26 days, to rise again very rapidly after the treatment was discontinued.

In table 1 one finds the results concerning urea summarized once more. With fractionated dialysis, where the blood circulates a few times through the kidney, the percentage of urea in the blood sinks to the concentration in the bath water. In continuous dialysis the blood flows only once through the kidney. It is therefore most often not being washed out so completely. Besides, the concentration of urea in the bath rises after prolonged dialyses, in future we shall change the water in the bath.

From this table one sees that uric acid, creatinine, rest nitrogen and urea are being removed from the blood by dialysis. The fact must be taken into account that the blood was flowing through the kidney only once before being infused again. In the rinsing bath, which was not changed, large amounts of these substances had accumulated towards the end of the dialysis (51 mg per 100 cm³ for urea).

The percentage of *xanthoproteine* in heparinised blood could not be read accurately.

From table 3 we may gather that indoxyl too is being removed from the blood by dialysis.

Percentage of potassium: we found it impossible to determine the percentage of potassium in heparinised blood plasma. One cannot but presume that the ionised potassium dialyses very rapidly, so that blood flowing through the kidney only once will probably lose its potassium entirely. This is important as in patients suffering from uremia an intoxication by potassium often seems to be the direct cause of death.

Dialysing into the blood of substances added to the bath water.

Through the dialysing membrane molecules go in and out. If it is e.g. desired to compensate the loss out of NaCl or glucose from the blood these substances are added to the rinsing bath.

From table 5 it is evident that Cl' has always entered the patient's body from the kidney, especially when the patient's percentage of salt was too low. In taking a retrospective view of the treatment we must admit that we did not always supply enough salt, although we gave it repeatedly. The loss of Cl' must be attributed to the vomiting.

In the dialyses N^os, IV and V no glucose had been added to the bath. The bloodglucose sank to very low values. In the dialyses N^o. VII and X (and other ones) glucose was being resorbed from the bath.

From the table printed above one sees that, given a well-chosen rinsing bath, a normal sodium percentage of the blood may remain unchanged. If necessary, other substances which are as yet removed e.g. Ca, Mg, K, etc. may be added to the bath water.

The dialysable constituents of the blood will be regulated according to those of the fluid in the bath, a surplus being washed out, a deficit replenished.

Oxygen is resorbed very rapidly: already after a few windings one sees the blue blood get red.

Table 1.

Percentages of urea in the blood and in the rinsing bath in mg per 100 cm³.

Dialysis N ^o .	I	II	IV	V	VI	VII	IX	X
Blood of patient before dialysis	172	217	303	319	288	339	324	324
Blood from kidney after dialysis	5	10	20	10	48	92	76	56
Percentage of urea in rinsing bath				10		30	58	51
Blood of patient after dialysis						278	233	333
	Fractionated dialysis					Continuous dial.		

Table 2.

Data concerning diverse retention products, Sulfamethylthiazol and Calcium in mg per 100 cm³ in dialysis N° X.

	Uric acid	Creatinine	Rest N	Urea	Sulfamethylthiazol	Ca
Blood of patient before dialysis	9.3 10	5.44	188	324	15.3	9.4 9.4
Blood of patient during dialysis	8.2	4.8		253		
Blood of patient after dialysis	7.4	4.7		233		
Blood from kidney during dialysis	4.7	2.2	51 50	45		
Blood from kidney after dialysis	4.1 4.8	2.3	49	58	8.3	6.7 6.5
Rinsing bath after treatment				51		

Table 3

Indoxylreaction after Jolles (most intense colour taken as 100).

Date Dialysis N°.	19/III II	21/III —	22/III III	23/III —	14/I X	4/V
Blood of patient		55		50		100
Blood from kidney	39		33			
Bathwater before treatment					0	
Bathwater after treatment ..					+	+

Table 4

Percentage of potassium in mg per 100 cm³ of the patient's blood serum (without a trace of hemolysis).

Date	16/III	23/III	12/IV	4/V
Potassium	18.8 and 19.6	18.8	17.8 and 18.1	85 and 92 Blood from heart 8 hours after death

Table 5.

Percentage of NaCl in the blood plasm in mg per 100 cm³ (calculated from the (Cl⁻)).

Date Dialysis N°.	17/3 I	22/3 III	24/3 IV	26/3 V	28/3 IV	31/3 VII	6/4 VIII	8/4 IX	12/4	19/4 XI	4/5
Blood of patient ..	590 588	533 534	556 564	533 530	612?	500 506	600 600		633 623	474 494	640
Blood of patient after dialysis ...				535 530		590 605		644 636			
Blood from kidney	658 652	642 649	633 632	575 585	560 562	639 638	748 750				
Bath water	650	650	650	570	570	700	700	700		700	

Table 6

Percentage of glucose in mg per 100 cm³ of blood and bath water.

Dialysis N°.	IV	V	VII	X
Blood of patient before dialysis	95 95	98 107	114 114	104 106
Blood from kidney after dialysis	2	20 0	450 454	550 568
Bath water	0	0	1500	1500
Blood of patient after dialysis		80 85	301 301	189 200
	Bath water without glucose		Bath water with glucose	

Table 7

The sodium percentage of the blood serum in mg per 100 cm³.

Date Dialysis N°.	16/III	26/III V	31/III VII
Blood of patient before dialysis	329 330	312 309	305 292
Blood of patient after dialysis		328 312	
Blood from kidney			309 308

Water.

It is not easy to form an opinion concerning the question what the water is doing. On both sides of the dialysing membrane osmotic forces are active. From the blood a mechanic force is acting as well. Towards the blood: the colloid-osmotic action of the blood-plasm. By adding glucose to the bath the retraction of water may probably be augmented.

Cultures of the blood both from the patient as well as from the kidney after dialysis remained sterile.

Summary.

The artificial kidney is a dialysing-apparatus with a small blood volume and a dialysing area of about 20,000 sq. cms., in which the blood of a patient is cleared of retention products.

With one patient 24, 40, and 35 grams of urea could be dialysed out in 1.5, 4, and 6 hours respectively. Other retention products were removed by dialysis as well. This could be demonstrated for: rest N, urea, uric acid, creatinine and indoxyl.

We believe to be able to keep patients suffering from uremia and anuria alive so long as bloodvessels for puncture are available.

In the case of acute uremia the possibility exists for the kidneys to regenerate in the meantime. Sulfamethylthiazol and other substances with small molecules (poisons!) may be removed by dialysis as well.

Post Scriptum at the time of correction, January the 15th, 1944.

In table 5 the high value of 748 (check 750) mg% of NaCl is probably caused by infusion of saline a short time before the sample for determination was taken. Further analysis of the rinsing fluid after dialysis no. X gave the following results:

70 litres of bath water contained 42 mg of magnesium, 25 mg of phosphorus and 210 mg of potassium.

Two more patients have been treated with the artificial kidney, both were from a clinical point of view hopeless cases;

1. a man suffering from cachexia and uremia due to bilateral renal tuberculosis. 32 grams of urea were removed by one dialysis; on the next day he passed more urine than before the dialysis.

2. a man with an acute glomerulo-nephritis and oliguria, one of whose kidneys had been decapsulated without success. He passed into collapse and coma a few hours before the dialysis, from which he did not awake. 100 grams of urea were removed in 6 hours, the urea contents of the patient's blood showing a decline from 460 to 290 mg%.

In order to prevent thrombosis in the needles it proved advisable to start heparinisation 2 or 3 hours before the dialysis, by giving 200, 100 and 100 mg of heparine at hourly intervals.

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