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METHODS OF ACTIVE THERAPY OF PATIENTS WITH
ACUTE TOXICOSES

USSR

[Translation]

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FOREWORD

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METHODS OF
THERAPY OF PATIENTS WITH ACUTE TOXICOSES.

(USSR)

Sovremennyye Metody Aktivnoy Terapii
Ostrykh Toksikozov

[Modern Methods of Active Therapy of
Acute Toxicoses]

1959, Moscow
Pages 233-245
Russian, book

O. S. Glozman

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It can be seen from the description above that, at present, science puts at the doctor's disposal a series of different very active methods for combating endo and exotoxicozes. In choosing a method of treatment, it is necessary to consider in each specific case the character of toxicosis; the original condition of the patient and the peculiarities of the intervention selected; that is, whether the intervention is easy or difficult to apply and whether a special apparatus is needed; how effective it is, and what is the expected effect; how it generally reacts on the patient; how the patient's condition is controlled; and whether it holds possible complications and dangers. Therefore it appears advisable to make a comparative evaluation of the new forms of active intervention in a pathological process.

We shall first of all speak of the principles lying at the basis of these methods. All the methods described aim at removing from the organism toxic substances circulating in the blood regardless of their origin. In cases of anuria they are called upon for replacing the function of the affected kidneys. All these methods can to a greater or lesser degree fulfill this role for a certain time. But in fact they cannot fully or permanently (nor for too long a time) replace the kidneys. This depends not only on the fact that all "temporary kidney substitutes" replace only one excretory function of just one part of the nephron, which is the glomerulus, but also because they cannot replace the function of the whole organ. Also these methods

represent in themselves technically and essentially such serious nonphysiological interventions that they are not indifferent to the organism and cannot be applied for a very extended time.

Moreau (1954) has well said that all methods based on the principle of dialysis just "imitate" the function of the kidneys but do not replace it. Inasmuch as the kidneys function continuously and all the dialytic apparatus in practice function intermittently, it would be necessary for the latter, in order to obtain equivalent results, to be more productive than the kidneys. In addition, the function of the kidneys is selective and varies under the effect of neurohumoral reactions, whereas it is necessary to adapt extrarenal methods of clearance to each individual case. It is evident that these methods have a decisive significance in temporary anurias which develop in reversible kidney affections (or in those affections of the urinary tract which can be eliminated). In chronic uremias due to irreversible changes in the kidneys, these methods are palliative, delaying only for a short time the fatal outcome. The transplantation of kidneys is the sole method which could help to solve radically this problem in cases of chronic uremia. But, at present, this operation still is a clinical experiment and will remain such until the problem of homoplastic transplantations can be solved. In acute reversible anurias when urgent temporary measures are needed, the transplantation of kidney is of no help.

The other method of combating the symptoms of acute anuria are far from equivalent in their effectiveness.

The artificial kidney undoubtedly takes first place in its capacity for liberating the organism from unnecessary and injurious substances. This apparatus (the latest models being of the type of Alwall's ultra-filter dialyzer, Bartrina's apparatus, or the latest Meller's artificial kidney) is highly capable of removing all dialyzable products of albuminolysis, which play such an important role in starting the symptoms of the uremic autointoxication. Depending on its construction, an artificial kidney can remove from 10 to 20 g of urea per hour. At the same time (and this is very important), this apparatus is capable of correcting the water and salt balance in the organism. Also depending on the composition of the external dialytic solution, it can either remove the water (in general edema) and mineral substances (particularly potassium), which accumulate in the organism, or supply the organism with water (in dehydration) and mineral substances (such as calcium) if the organism needs them.

Thus, the field of application of the artificial kidney is wide, as it is also suitable for combating acute edemas of different origin. However, the artificial kidney is particularly important in the treatment of patients with acute uremia. Can all the substances producing

clinical symptoms of uremia be removed by the method of hemodialysis? Kolff answers this question in the following way: "We do not know any definite substances which determine uremic intoxication; the latter is caused by all the substances not removed by the kidneys and accumulating in the organism.

Finally, the third field of application of the artificial kidney lies in preventing acute exogenous poisoning if toxin has circulated in the blood for a certain time and is capable of dialysis. However, the use of the artificial kidney for this purpose still is not well developed. It is only known that in poisoning with the preparations of salicylic acid, barbituric acid and bromides, it has been possible to dialyze these substances from the blood with the help of an artificial kidney.

But even substances of related origin have different capacities for dialysis; this can be seen from the studies of Sunshine and Leonards (1954). In their experiments, they intoxicated animals with sodium amytal, sodium pentobarbital and phenobarbital; then they passed their blood through an artificial kidney. With a surface of 20,000 cm² of cellophane, blood flow at a rate of 200 ml per minute, and 200 to 300 l of dialyzing solution, the dialyzer eliminated, during 4 to 8 hours of dialysis, 15-25% of sodium pentobarbital introduced into the vein, 35% of sodium amytal introduced into the vein and 40-70% of phenobarbital introduced intraperitoneally. In phenobarbital intoxication, they were able to save the lives of animals by the hemodialytic method; they observed some effect in using an artificial kidney for sodium amytal intoxication, but the results of this treatment in sodium pentobarbital intoxication were very doubtful.

It is evident from the above that many more experiments are still needed for determining in which cases of exogenous intoxication the artificial kidney can be used and what effect can be expected from it.

Although the use of the artificial kidney in acute uremias is undoubtedly beneficial, there are still many factors limiting the possibility of applying this very effective method of treatment. The complicated construction, the high cost of the apparatus and the necessity of having a well-trained staff permit its application only in large medical centers. Moreover, the lack of standardization, the large number of designs proposed and the absence of mass production of the apparatus oblige us to use only a unique apparatus serving in the majority of cases as experimental models and needing approval. Under these conditions it is difficult to compare the results obtained by different authors using various apparatus, especially since in many cases, the artificial kidney was used for very sick patients frequently in critical condition. But this is not the only thing that limits the

use of the artificial kidney. While the apparatus is in operation, it is necessary to check the patient's condition constantly and very carefully. In addition to a general clinical detailed examination of the patient, his preliminary examination must include the determination of the blood urea, of the residual nitrogen, of the time of blood coagulation and of prothrombin, of the hematocritic index, of the content of protein, potassium, calcium and chlorides of the blood, etc. It is also necessary to determine the patient's reaction to heparin. Naturally all this requires a good laboratory for special analyses and additional personnel.

The necessity for such extensive investigations is dictated by two factors. On the one hand, the patient's blood composition determines the composition of the dialytic solution which, to a certain degree, must be prepared individually. On the other hand, the patient's condition must be checked to prevent possible complications. Complications may take place as it is far from possible to take into consideration all the factors which may affect the course of an operation, all the more so since the experience of using the artificial kidney is still very limited. The following complications may arise: the rise of body temperature, intravascular hemolysis, oscillation of the arterial pressure, cerebral hemorrhages, hemorrhages (in an overdose of heparin) and shock. For this reason, we think that the statement of Z. S. Vaynberg (1955) in his report on the artificial kidney is incorrect. He states that "the use of the artificial kidney is safe". It is more correct to say that this method is relatively safe when it is used by experienced doctors and the basic technical rules of operation are maintained. At the same time, it is necessary to point out that Merrill, who is greatly experienced in the use of the artificial kidney, considers that the great hopes pinned on this method are not justified and warns against too much enthusiasm concerning it.

In the fight against acute uremia, the second place after the artificial kidney must be given to the method of peritoneal dialysis in its effectiveness of the degree of clearing the blood from the products of nitrous disintegration, of correcting the water and salt balance and of removing from the blood certain endogenous toxins. At best in using peritoneal dialysis up to 4 g of urea were removed in one hour from the organism. Peritoneal dialysis is based on the same principle as the artificial kidney but, at the same time, it is different:

- 1) With the artificial kidney dialysis occurs outside the organism, in vitro, whereas with peritoneal dialysis it occurs in the organism, in vivo.

- 2) There is a direct arteriovenous anastomosis in the artificial kidney; the blood circulation is not directly disturbed in peritoneal dialysis.

3) A supplementary blood circulation forms in the artificial kidney, which may require in some cases an additional power for displacing the blood; this does not occur in peritoneal dialysis.

4) In the artificial kidney dialysis is accomplished through an artificial lifeless membrane; in peritoneal irrigation it is accomplished through a living complex membrane.

5) The rate of dialysis depends on the construction of the artificial kidney and can be voluntarily modified and by enlarging the surface of the membrane, it may be increased; in peritoneal dialysis the size of the membrane remains constant and cannot be controlled by us. The rate of diffusion depends almost entirely on the rate of perfusion of dialytic solution and; in part, on its composition; it also has a threshold value.

6) When using an artificial kidney it is absolutely necessary to introduce into the vascular canal of the patient an anticoagulin; "hemophilia" created artificially may produce hemorrhages. It is not necessary to introduce anticoagulins into the vascular canal in peritoneal dialysis; anticoagulins used in dialytic solution do not cause artificial hemophilia.

7) With the use of the artificial kidney, the operative intervention is very small; it is limited to the arterio and venosection with the insertion of cannulae into the vessels. With peritoneal dialysis, it is necessary to introduce catheters into the peritoneal cavity; these catheters must remain there for a long time, thus creating the danger of peritonitis.

8) A still greater danger of peritonitis may be due to the dialytic solution washing out the peritoneum; it may introduce an exogenous infection to the intestinal walls with an increased permeability; also, an endogenous infection of the peritoneum may occur. With the artificial kidney the danger of infection is almost excluded since the dialytic solution is in contact with an artificial membrane which is impermeable to microbes.

The greatest advantage of peritoneal dialysis over the artificial kidney is that this operation is technically simple and does not require any special apparatus. In both methods it is generally necessary to check constantly the blood composition and the patient's condition (to avoid the disturbance of the water and salt balance) and to individualize to a certain degree the composition of the dialytic solution. Also it is possible in both methods for complications to develop which are not connected with the technique of the operation

but are due to the process of dialysis (edema of the lungs, hypopotassium and other). Grollman (1948) in his experiment on nephrectomized dogs (and later in uremia in children) discovered that an intermittent peritoneal lavage is more effective than the artificial kidney.

Kolff reproduced the comparative evaluation of these methods in the following Table (Table 9). It is given with slight modifications.

Table 9

	Peritoneal Lavage	Artificial Kidney
Contraindications		
Recent abdominal operation	+	-
Infection of the abdominal wall or skin	+	-
Marked colitis	+	Hemorrhage danger
Abdominal symptoms unrelated to anuria	+	-
Old adhesive peritonitis	+	-
Hemorrhages	-	+
Dangers		
Infection	Peritonitis	-
Perforated intestine	Possible; more probable in the introduction of a trocar	-
Invagination of the intestine	Has been described in dogs	-
Hemorrhages	-	Possible as a result of heparinization

(continued)

Table 9 continued

	Peritoneal Lavage	Artificial Kidney
Shock	Possible and has been observed	Probable
Edema of the lungs	Possible and has been observed	Possible and has been observed
Chill	Possible unmarked chill	Can be very strong
Unpleasant sensations	Intermittent strong abdominal pains and colic. Possible distention and vomiting. Frequently none	None except a possible sensation of chill

In applying an artificial kidney, Edwards and coworkers observed an intestinal invagination in 3 dogs out of 10, causing their death (Edwards A, *oth. Arch. Surg.*, 1958, 76, 5, 754).

Without question in cases of reversible acute anuria, peritoneal dialysis should be introduced into medical practice when suitable conditions exist (sterility) and when it is impossible to perform an extrarenal clearance with the artificial kidney. The effectiveness of this method is evident (it has been demonstrated in experiments and in clinic) and, in cases where the patient suffers from a prolonged anuria, the threat of his death must move aside the fear of possible severe complications.

The data available on the use of peritoneal dialysis in combating exogenous intoxications are very limited and important experimental research is needed in this field. It is quite probable that toxins which can be removed with the artificial kidney can also be removed with peritoneal dialysis.

Different forms of gastrointestinal dialysis are unequal in their effectiveness of combating uremia but all of them are considerably inferior to the first two methods described. In principle they also slightly differ from the artificial kidney and peritoneal dialysis. In the two methods described the removal of impurities from the organism is accomplished by an extraordinary non-physiological to the organism

way. In gastrointestinal dialysis or, in other words, gastrointestinal irrigation, it is accomplished by strengthening the physiological process of separating waste matter from the organism and of helping the organism to utilize its supplementary elimination apparatus which begin operating in an emergency. Also the intestinal endothelium differs still more than the peritoneal endothelium from a simple semipermeable membrane and, being a living membrane, is capable of adsorption and secretion almost independent of the concentration of various substances of the solution in the lumen of the intestine. This explains the fact that in gastrointestinal lavage the separation of various substances and, primarily, of urea from the blood into dialytic solution is small.

The mucous membrane of the stomach is the least capable of removing nitrous waste. Consequently, gastric irrigation can be of interest only in the strength of its technical simplicity and in cases where the use of other methods proves to be impossible. Not many people speak in favor of lavage of the large intestine through the appendicular stump. It is not very effective in removing nitrous wastes and, besides, it requires an operative intervention. The operation is not very serious but it may aggravate the patient's critical condition.

Intestinal dialysis in one or another form (pergastral lavage, intestinal lavage with a two- or three-way catheter) should always be used in cases of uremia (for several hours daily) when other more active methods are not available. Although this method is comparatively less effective than other, it still permits us to separate from the organism nitrous wastes in quantities sufficient for improving the patient's general condition. In view of the fact that this method is technically simple and practically safe, and can be applied under any conditions, it should always be kept in mind and its application should become usual in every hospital. Tuns (1950) and others recommend the use of intestinal dialysis in acute anuria; Derot and coworkers (1951) do not apply this method for acute cases, preferring its application for cases of chronic uremia. Naturally, it is necessary to check the general condition of patients during the treatment with intestinal dialysis because in uncontrolled conditions surplus fluid can be absorbed from the intestines and cause edema of the lungs. One of the simplest ways of control is the weighing of patients during the given operation.

Hamburger and collaborators (1950) experimented on dogs and conducted research on persons in good health and on those sick with general edema. They succeeded in demonstrating to what extent the effect of intestinal irrigation can vary depending on the composition of the perfusion and on the rate of its flow. A sucrose solution with a freezing point of -0.8° used for perfusion in the men investigated, caused

dehydration in them; a solution including 0.2% of sodium carbonate and 0.2% of sodium chloride and sucrose flowing at the rate of less than 2.5 l per hour produced hyperhydration in the men; the same perfusion flowing at the rate of more than 2.5 l per hour produced dehydration.

Taking into consideration the gravity of the operation needed to isolate an intestinal loop for the lavage, one should hardly recommend the use of this method. It can be used as an "operation of despair" in cases of chronic uremia to prolong somewhat the patient's life but without hope of saving him.

All that we described above concerning intestinal irrigation through catheters can be fully related to the method of "bile-letting", which is not identical with intestinal lavage but has much in common with it in the technique and essence. But additional research is needed to determine its effectiveness. We do not know of any new works in this field except for the reports of Auguste and V. V. Gubst given above. Also it is very regrettable that there is no data available on the use of intestinal dialysis for the removal of exogenous toxins from the organism in different intoxications.

In our opinion, the method of parabiotic connection of two organisms can hardly be applied in the near future for the treatment of uremia or of acute intoxication. It seems fantastic to imagine two adults living together as an innate "Doppelmenschen", and who have voluntarily doomed themselves to an eternal connection by an operative concrecence.

The possibility of using temporary parabiosis in the form of cross circulation for the treatment of uremia and of acute intoxication appears more real to us. Cross circulation is probably the most effective of all the methods we know for combating acute exo and endotoxicoses. Thanks to it the sick organism has temporarily at its disposal all the strength and compensation abilities of the healthy organism as far as it is possible to accomplish common circulation between two organisms. The mutual effect of both partners on each other needs to be carefully studied with a view to using this method to the maximum with the least danger to the healthy partner and the most benefit to the patient. Also the indications and contraindication for using this method must be determined. Then we shall be more confident in proposing this operation to be included in the store of methods of fighting for human life. A shortage in volunteer donors can hardly be expected, particularly among close relatives of the patient. We are confident that in the near future cross circulation can become one of the most human and effective methods of treatment in acute toxicoses.

Plasmapheresis or "lavage of the blood" stands somewhat apart although it is included among the methods of treatment of acute toxicoses. Plasmapheresis can be applied as an intermittent operation when portions of blood taken in succession are washed out from the plasma or as a continuous process of removing the plasma with a separator. It has its positive and negative sides. It has not been tested (or at least we have not come across any studies on the subject in medical literature) for treating uremia and very few experiments demonstrate its effectiveness in exogenous intoxications. A partial (intermittent) plasmapheresis with repeated blood letting, centrifugation, lavage of erythrocytes and return of the erythrocyte suspension is fraught with the danger of possible infection of the blood but it does not require any apparatus other than a large centrifuge. Continuous plasmapheresis requires the use of special apparatus and, besides, an intensive blood letting at the start of the operation drops sharply the arterial pressure; this should be considered as a negative factor. The removal of large quantities of plasma and its replacement with crystalloid solution remains unclear in its effect on the organism although, apparently, it is not particularly negative. The question concerning the significance of returning the patient's own erythrocytes in the blood stream remains unexplored. This is all the more so since the degree of adsorption of different toxins in the erythrocytes is unknown as is also the degree of detoxication of the organism in removing the plasma.

Since related experimental data are lacking it is difficult to decide whether this method is effective for treating acute cases of exotoxicosis although, in principle, it may prove to be so for some intoxications.

The operation of substituting the recipient's blood with that of a donor differs from all the other methods not only in its principle but also in its universality. It can be applied in acute and chronic uraemias, and in different endogenous and exogenous toxicoses accompanied by the circulation of toxin in the blood, and not only for the purpose of detoxication but also for the correction of technical and morphological composition of the blood.

Exchange transfusion used as a method of extrarenal clearance of the organism is inferior to dialysis in its effectiveness; for this reason, it must be repeated at short intervals. Thus, if the artificial kidney removes from the blood up to 100 g of urea or more in a few hours, and peritoneal dialysis up to 45 g of urea in 12 to 15 hours then a complete exchange transfusion eliminates only 20 to 25 g of urea. But there is reason to believe that in acute uremia, the therapeutic effect of exchange transfusion does not consist only of the removal from the organism retained impurities but also of producing a diuretic effect. The cause of this phenomenon still remains to be

explored but we may assume that the process of exchange transfusion and perhaps the decrease in the concentration of nitrous wastes retained in the blood relieves the spasm in the interlobular arteries of the cortical layer of the kidney (A. Ya. Pytel', 1955) and, in this way, improves the process of glomerular filtration. At the same time, there is reason to believe that the diuretic effect of exchange transfusion is not something specific to this operation. Evidently it is not the type of intervention that is responsible but the intensive reaction on the dynamics of the life processes of the organism. A similar diuretic effect has been observed by a number of scientists after artificial kidney or peritoneal dialysis treatment of patients with anuria.

Concerning the relatively small effect of exchange transfusion in uremia on the level of residual nitrogen in the blood, this should be explained by the continuous flow of nitrous wastes from the tissues into the blood as their concentration in the blood decreases. Moreau (1954) said that changes occurring in the blood composition after exchange transfusion are always smaller than the ones expected according to calculations because between the blood and extracellular fluid dialysis takes place continuously. Taking into consideration the unequal effectiveness of different methods of eliminating extrarenally nitrous wastes from the blood, Moreau recommends repeating exchange transfusion every second or third day, intestinal dialysis daily for several hours, peritoneal dialysis every three days and the use of the artificial kidney every four days or more depending on the purifying strength of the apparatus. Derot with coworkers (1951) considers that exchange transfusion increases the patient's tolerance to uremic intoxication to 2 days and peritoneal dialysis to 4 days. Technically simple exchange transfusion can be performed in any medical establishment and can be repeated with varied degrees of intensity. In maintaining the rules of the application technique and in taking the preventive measures required in blood transfusion, exchange transfusion should not cause any severe complications. This has been proved in extensive experimental and clinical practice. The patients usually tolerate it well. Buhot states that when it is necessary exchange transfusion must be performed "anywhere and by anyone without the use of expensive and rare materials and it should not be avoided because of any condition of the patient, such as the state of his veins, his consciousness, etc". The chief negative factors of this operation are, first of all, the necessity of incising a vessel (an artery or a vein) and, secondly, the need of a large quantity of blood from a donor with the same blood group. However, these difficulties are secondary and should not influence us in refusing to perform exchange transfusions in cases where the patient's life is in danger.

In fighting against acute uremia, all the methods of extrarenal elimination described above can be applied. When choosing a method, one should not consider only the one familiar to the doctor or whether the apparatus needed is available, it is also important to evaluate the positive and negative sides of each method and the peculiarities of each case. Thus no dialytic method is effective in removing from the blood hemoglobin diluted in the plasma; therefore if renal failure is caused by posttransfusion complications or if it develops as the result of a septic process with hemolytic symptoms then only an exchange transfusion can produce a suitable effect in removing hemoglobin and nitrous wastes and, at the same time, eliminating anemic symptoms. Derot and coworkers (1951) like to combine exchange transfusion with peritoneal dialysis in acute uremia. It is curious to point out that at the same time that Derot and coworkers (1951) consider that in hyperpotassemia all the methods of extrarenal clearance are effective except exchange transfusion, Goldbloom (1954) thinks that it is important to repeat exchange transfusions in hyperpotassemia, preferring this method to that of the artificial method.

It is necessary to take into account one very important factor common to all the methods of active therapy of toxicoses independently of the principle on which they are based. All the methods must not be "extreme measures" taken to save the patients' life when imminent death hovers about them. It is now necessary to include all these methods in the program of everyday therapy to accelerate the recovery of patients. They should be applied as soon as possible without delaying the question of their timing and selection. All the authors with sufficient experience in the use of the methods described above agree on this matter. Thus, Merrill (1950, 1952) thinks that the artificial kidney cannot be considered as the last "heroic resort" for it is a valuable method supplementary to a careful conservative treatment. V. V. Parin (1955) and Alwall with coworkers (1955) share Merrill's opinion and, speaking against the opponents of hemodialysis, state that up to now they have used dialysis to supplement conservative therapy in critical cases. They consider that the importance of hemodialysis and of ultrafiltration has been fully established in efficiently treating renal failure and, therefore, they intend to use the artificial kidney therapy more extensively. Hewlett (1955) wrote that: "peritoneal dialysis should not be examined as the last heroic resort and, in some cases, it should become a part of an organized plan of the treatment of renal insufficiency". We stated repeatedly in the last few years that the method of exchange transfusion must be used not only as the last resort but as a method of therapy.

An early intervention applied in time and energetically in a pathological process is the condition required for the new methods of active therapy to effectively combat acute toxicoses.

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