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THE ANTI-COAGULATING PROPERTIES OF THE ARSENOBENZOLS.

THEIR CLINICAL APPLICATIONS: "EXO-HÆMOPHYLAXIS"
—BLOOD TRANSFUSION.

BY CH. FLANDIN AND A. TZANCK.

We were the first to make known the anti-coagulating action upon the blood of the arsenobenzols. This action shows itself *in vitro* and *in vivo*. *In vitro*, if the blood is collected in a glass recipient that is perfectly clean and sterile, the sides of which have been moistened with a weak arsenobenzol solution (arsenobenzol, novarsenobenzol, sulfarsenol, &c.) it will remain uncoagulable indefinitely. *In vivo*: When the blood is taken from an individual who has received an intravenous injection of an arsenobenzol, it will be observed that the coagulation of the blood is delayed, and that this delay will last from 30 minutes to 24 hours or longer. If the taking of samples of the blood is repeated, we may then perceive that the incoagulability continues for a period varying from several hours to several days. The phenomenon gradually passes off.

The action in checking coagulation, which the intravenous injection of an arsenobenzol produces, does not seem to depend upon the quantity injected, nor, in a certain measure, on the number of injections given to the patient. We say "in a certain measure," for it has seemed to us that with the patients who have received, in a series, a great number of intravenous arsenobenzol injections, the coagulation of the blood was specially delayed and this continued for a long time, for eight or more days.

The anti-coagulating effect is due absolutely to the arsenobenzol and has nothing to do with the syphilis. In fact, the same phenomenon occurs with those who are not suffering from syphilis. Also it exists, in a very high degree, with animals such as the dog, the guinea-pig, the rabbit—a fact confirmed by M. Launoy. The mechanism of the anti-coagulation has not yet been determined. All that we can say is that the arsenobenzols do not seem to act on the corpuscles or platelets of blood, which are not modified in form or number and which also are not agglutinated.

Without laying undue stress on the question, it is easy to understand the practical utility, for laboratory work, of a means of preventing the coagulation of blood. The adding of a very small quantity of an arsenobenzol does not modify the volume or the quality of the constituent elements of the blood. We have here an advantage over the usual citrated solutions. To obtain and to preserve the cells and the plasma, the use of arsenobenzol now seems to be the most simple and efficacious of means.

From the clinical point of view the innovation which we have introduced seems destined to bear fruitful results. Henceforth, when studying the time which the blood of a patient takes to coagulate, we shall have to consider whether he is under the influence of an arsenobenzol treatment before we conclude he is hypocoagulant. The surgeon or the accoucheur must be warned of the fact that arsenobenzol checks the coagulation of blood so that they may prevent its injection several days before operations or accouchements.

On the other hand, an arsenobenzol injection might have a good effect by permitting bleeding in certain conditions such as occur notably in cases of asphyxia, when the blood coagulates in the lumen even of a cut vein and prevents the flow. It may therefore be justifiable to resort to an intravenous injection of arsenobenzol to reduce or prevent the evolution of

certain thrombotic processes. The two practical applications of our research, which we particularly desire to bring to light are, on the one hand, in connexion with what we term the "exo-hæmophylaxis," and on the other hand their relation to the transfusion of blood.

"Exo-hæmophylaxis" is the name we have given to a method for avoiding, in many cases, the sudden accidents that occur after an intravenous injection of arsenobenzol. We were inspired by facts brought forward by MM. Sicard and Paraf. These observers found that when a patient cannot tolerate arsenobenzol injections, the intravenous injection may be given before removing the bandage placed on the arm to cause the vein to swell, the contact of the injection with the blood in the isolated section of the vein often obviating accidents which might occur when, on removing the bandage, the mixture is propelled into the general current of the circulation. We conceived the idea that by bringing about the contact of the blood and the arsenobenzol outside the subject, that is, during a relatively long time, we would obtain a better display of the phenomenon observed by Sicard and Paraf. Being able to rely on the anti-coagulative action of the arsenobenzol we proceeded to test our theory. The method consists of diluting in 1 to 2 c.cm. of distilled water the quantity of novarsenobenzol or of sulfarsenol in a syringe holding 10 to 20 c.cm.; with this syringe 10 to 20 c.cm. of blood is taken. After waiting 5 to 15 minutes this mixture is reinjected either through a needle that has remained *in situ* or through a new puncture of the vein. In this way we reduced the sensitiveness of the blood outside the organism—exo-hæmophylaxis, and in 60 to 70 per cent. of the cases the accidents that might immediately result from intolerance were avoided, especially during a nitritoid crisis. Our method, in principle and in practice, is entirely different from the proceeding empirically followed during many years by all those who have made intravenous injections and which consisted of drawing a little blood into the syringe before injecting, and of repeating this manœuvre several times, thus mixing the matter injected with the blood during the course of the injection. Our object was merely to provide a mixture and intimate contact during a period of time sufficient to ensure physico-chemical action leading to neutralisation of the toxicity of the arsenobenzol.

Seen under another aspect the exo-hæmophylaxis is a real auto-transfusion of blood. It is easy and convenient to use small quantities of the solution of the arsenobenzol to moisten the needle and the piston of the syringe employed for auto-hæmotherapy. There is no risk that the operation will be impeded by rapid coagulation of the blood.

The anti-coagulating action of the arsenobenzols enables us to realise two new methods of desensitisation to be placed by the side of autohæmo- and autoserotherapy—we allude to autoplasmotherapy and delayed autohæmotherapy. The names alone of these methods explain them. The terms are applied to subcutaneous, intramuscular, and intravenous injections.

When we had in this manner accomplished auto-transfusion of blood, we thought we might have recourse to the arsenobenzols for the transfusion of blood from man to man. To collect the blood of a healthy subject in a glass receptacle containing a small quantity of an arsenobenzol solution, to draw this from the receptacle with a glass syringe and re-inject it into the vein of the patient seemed extremely simple. It appeared to us that the addition of a little arsenobenzol to the blood of a donor was

a less inconvenient proceeding than that which required a large quantity of citrate of soda to prevent coagulation. This method is actually known in France as the Flandin-Tzanck method, and has been sufficiently employed to have established its reputation. It is now known as the most simple and the least dangerous method of transfusion of blood. Naturally it does not avoid the hæmolytic action or agglutination which often takes place between two subjects. It is therefore always necessary to study *in vitro* the reciprocal action of the blood of the person who gives and of the person about to receive, before the operation of transfusion is attempted. We would also call attention to the necessity of only employing glass or metal apparatus. India-rubber sometimes prevents the anti-coagulation effect of arsenobenzols manifesting itself to full advantage.

In a word, the biological action of arsenobenzols in preventing the coagulation of blood, to which we have drawn special attention, has already enabled interesting practical applications to be made. It appeared to us that it would be useful to call the attention of our colleagues in England, who are interested in the French Supplement of THE LANCET, to these new facts.

PHYSIOLOGICAL STUDY OF THE PHENOMENA OF SHOCK:

(NITRITOÏD CRISIS) PRODUCED BY INTRA-
VENOUS INJECTIONS OF ARSENOBENZOLS.

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IN this study I propose to summarise the general results of the investigations on which I ground a purely physical conception of the initial mechanism of the "nitritoid crisis" produced by intravenous injections of the different arsenobenzol compounds generally used in the therapeutics of syphilis. I will not discuss the well-known symptomatological character of this crisis, and propose to deal with the experimental phase of the subject. Therefore I will sum up the results of experiments made on dogs, as far as they enabled me to arrive at the mechanism of the crisis and to produce it experimentally.

As the result of a long series of experiments published elsewhere, and in relation to which I now only mention the principal conclusions, I have shown that arsenobenzol (606), when in aqueous non-alkalised, i.e., in acid solution, precipitates albumins in consequence of the presence of phenolic groups in its molecule. This precipitating power only disappears completely after hyperalkalinisation to a point nearly 60 per cent. above that calculated to produce neutrality, and at such a degree of alkalinity the solution cannot be practically employed. On the other hand, such compounds as type 914 (novarsenobenzol), while giving a neutral solution which still precipitates albumin, but much more feebly, can have the precipitating action intensified if the preparation containing the albumin is rendered acid by carbonic acid.

From the physico-chemical point of view the precipitates observed consist of a protein-arseno-phenolic adsorption complex¹ soluble in alkaline fluids. Its formation in a weak acid medium such as the carbonic acidity of blood depends on the phenolic group (OH) of the arseno- or novarseno-benzols by a mechanical action similar to the precipitation of albumin produced by the Esbach reagent or trinitrophenol.

These facts made manifest, my object was to establish the relation of cause to effect between the formation in blood, when an intravenous injection is

practised, of the complex precipitate described and the appearance of the "nitritoid crisis." In this latter, as in all vasculo-sanguine crises, there is but one major symptom which can be noted with precision by the physiologist, that is the decrease in blood pressure, an important and constant phenomenon which dominates all others (Lumière).

For these reasons and in the course of intravenous injections of the compounds here described, I have systematically recorded, during my experiments with dogs, the variations in the pressure of blood in the carotid, employing a graphic recording instrument for this purpose.

The nitritoid crises produced by arsenobenzols I consider are the result of a phenolic shock; they are analogous to the fall of pressure registered after the intravenous injection of simple phenolic compounds such as trinitrophenol and ordinary phenol which precipitate the albumins like the arsenobenzols. Under the conditions in which I have always operated the question of chemical toxicity has never arisen, for I have never used toxic doses. The intensity of the shock and the decrease in blood pressure I was able to observe was more considerable in proportion as the solutions of phenolic compounds were more acid, and therefore had a greater precipitating effect on the albumins. The process *in vivo* of the nitritoid crisis experimentally produced was therefore connected with a precipitation, or to speak more exactly, with the intravascular flocculation consequent on the formation of the adsorption complex described. The mere presence of this in the circulation is accompanied by the phenomena of anaphylactic shock, peptone shock, or the baryta shock described by A. Lumière. Its origin is purely physical (flocculation of the colloidal particles of serum) and does not originate with any chemical poison.

But the objection may be raised by this question: How does it happen that in man intravenous injections of arsenobenzols are rarely followed by a nitritoid crisis? It is easy to answer this objection. As stated above, the precipitates (arseno-phenolic adsorption flocculi) are soluble in an alkaline medium; the blood is both basic by its bicarbonates and acid by its free acids, and therefore it acts, as we have said, by stimulating, on the one hand, the precipitating power of the phenolic groups of the arsenes and novarsenobenzols, thus bringing about intravascular precipitation, and, on the other hand, it renders soluble, with its alkali reserve (bicarbonate, &c.), the complex precipitate formed early in the *in vitro* process, and found to be soluble in a slightly alkali medium. Thus, if the blood has a normal alkaline reserve, the disturbance caused by the initial proteinic effect of the injection (the *colloidoclasia*, in a word, associated with flocculation) will be at once compensated by the solubility of the precipitate formed and the injection will not produce any appreciable physiological manifestation. On the other hand, if the proportion of the free acid in the blood is large, and if, in consequence of this fact, the alkali reserve is reduced, the intravascular precipitation, accompanying the injection, of the proteino-arseno-phenolic complex will be more considerable and more stable, for what at first was not soluble will, for a certain time, act as an insoluble foreign body, producing the phenomena of shock.

It will be seen, therefore, that this is an important accidental cause of the nitritoid crisis. G. Milian and I have shown that, with patients habitually subject to this crisis, the diminution of the alkali reserve of the blood is considerable. Acting on this discovery, and so as to realise similar conditions in researches upon dogs and produce the hypotension crisis, I utilised acid solutions, either 606 or 914 (or Esbach's reagent). We ascertained also with a dog fed for a long time on a strictly flesh diet that after an acid injection of β -oxybutyric the intravenous injection of neutral novarsenobenzol produced a hypotension crisis of short duration.

By researches of a somewhat different nature I was able to demonstrate that subjects who could

¹ I have qualified these complex adsorption arseno-phenolic precipitates so as carefully to specify their mode of formation and their constitution. I would add that the solutions of phenolic compounds, or arsenobenzols, which I have injected in dogs, precipitated albumins *in vitro*, and *a priori in vivo*, and provoked no coagulation or embolism in the vessels, the flocculi formed being extremely finely divided.