TWENTY YEARS' EXPERIENCE WITH THE CITRATE METHOD OF BLOOD TRANSFUSION*

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THE majority of physicians and surgeons in active practice today do not appreciate the remarkable simplification that blood transfusion has undergone in the past 20 years. The older members of the profession still remember the cumbersome technic which a direct blood transfusion by vessel anastomosis entailed. Direct transfusion represented a major surgical procedure, often lasting over two hours. In addition to the technical difficulties there always existed the uncertainty as to how much blood had been actually transferred from donor to recipient.

However, "necessity is the mother of invention." With advancement in surgical technic and methods, broadening both the indications and the scope for major surgical procedures, it became evident that a simpler method of blood transfusion than the direct method was imperative in order to prepare patients more adequately before operation and to support them in their postoperative course. Furthermore, it was evident that the only way to replace a large loss of blood due to hemorrhage in the shortest possible time was to introduce a simple method for the transfer of blood from donor to recipient.

Thus the different indirect methods were born in rapid succession. Lindeman's syringe-cannula method[1] was followed shortly by the Kimpton-Brown tubes,[2] by the Unger apparatus,[3] and by the citrate method.[4]

In the short space of two years, transfusion had been transformed from a most difficult surgical procedure, requiring expert surgical skill, to a very simple one. In addition, all the indirect methods allowed exact calculation of the amount of transfused blood and thus replaced the inaccuracies incidental to direct transfusion.

In spite of the simplification of the technic, blood transfusion failed to gain general popularity, because of the comparatively great number of post-transfusion chills. The profession felt that in very sick patients—and after all the vast majority of the patients who required blood transfusions were seriously ill—a chill might be of serious consequence to the patient who was hovering between life and death.

Many different theories were brought forward to explain the chills. Some thought that chills could be prevented if specially prepared glassware were used. Others blamed the ordinary rubber tubing and introduced specially manufactured tubing in order to prevent chills. Another suggestion was that the donor should be starved before the transfusion. Others went so far as to apply this principle not only to the donor, but to the recipient.

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Many authors felt that chills could be prevented, if proper safeguards were taken to insure against cooling of the blood during the introduction into the recipient. Even in recent years complicated and expensive electrical apparatus was put on the market to keep the blood at a uniform temperature during the infusion.

I have never used any of these devices or suggestions, as I always felt that none of them was the real cause of posttransfusion chills. I used to surround the glass cylinder containing the citrated blood with hot water bottles. I discarded them a few years ago, as the slight degree of cooling of the blood occurring during a transfusion had no harmful effect on the recipient and did not cause chills. Furthermore, it is unnecessary to put the glass jar with the citrated blood into hot water during the short period required to introduce the cannula into the recipient's vein and to prepare the apparatus necessary for the transfer of the blood.

After all these different theories had been discussed for years, without solving the problem of posttransfusion chills, it was established a few years ago by Rosenthal[5] that chills were due, firstly, to foreign protein reactions, and, secondly, to defects in the distillation of the water.

Careful cleansing of instruments, tubing and glassware immediately after the transfusion is essential. A detailed technic for the safe and thorough removal of old blood which causes these pyrogenic reactions was reported in a previous paper.[5] The great importance of the use of triple distilled water for the prevention of chills was stressed. The importance of triple distillation of the water was doubted by Elser and Stillman.[6] However, its great value in the prevention of chills has been confirmed recently by studies emanating from the Institute for Blood Transfusion in Leningrad.[7]

Following the introduction of this simple technic for the preparation of instruments and solutions, posttransfusion chills on the wards of Mount Sinai Hospital were reduced from 12 per cent (1930) to 1.2 per cent (October, 1931–October, 1932). An even more marked reduction in the number of chills was observed by Satunov[7] (Novøgorod), namely, a drop from 53 per cent to 2.7 per cent chills after adoption of this technic of carefully cleansing the instruments immediately after the transfusion and of using triple distilled water.

Since the introduction of these new methods, which proved that posttransfusion chills are preventable, the citrate method is now used practically exclusively in our hospital. Up to 1932, the medical services and one of the surgical services had favored the Unger method, because it was assumed that sodium citrate, though the technical simplicity of the citrate method was conceded, was the cause of the frequent chills (Table I).

In other words, in 1932, when the new technic for the preparation of instruments was introduced the proportion between citrate and Unger transfusions was about two to one; in 1935, the proportion rose to about eighty to one.

Most hospitals have selected one method for blood transfusion, using

either citrated or noncitrated blood. In our hospital both the Unger and the citrate method were used extensively for about 17 years. Both methods had their staunch supporters. However, since the reduction of chills to a minimum, the Unger method is hardly used at all any more, even on the medical services where many transfusions are given for a great variety of blood diseases.

TABLE I

STATISTICAL RÉSUMÉ SHOWING THE RELATIVE USE OF THE CITRATE AND UNGER METHODS

	Number of Transfusions	Citrate Method	Unger Method
1923	143	83	60
October, 1931—October, 1932	477	331	146
1935	794	784	10

The present investigation (frequency of posttransfusion chills in 1935) was undertaken to find out whether the chills had been kept at the low level reported in 1932. It is easy to get good results immediately after a new technic has been introduced and every member of the organization tries hard to establish a good record. However, a certain laxity may creep in later and spoil the results. It is gratifying to note that the incidence of chills after citrate transfusions by the gravity method has been kept on the same low level, 1.2 per cent (Table II).

TABLE II

INCIDENCE OF CHILLS AFTER CITRATE TRANSFUSIONS IN 1935

723	Citrate transfusions with 11 chills..... (including pediatric service: 70 transfusions—Hirsch apparatus—with 3 chills, 4%)	1.5%
653	Citrate transfusions with 8 chills..... (exclusive of pediatric service)	1.2%
	Not included in statistics:	
	Aplastic anemia, 61 transfusions with 12 chills	
	Total number of citrate transfusions.....	784

Of further interest is the fact that with the change in the original method on the pediatric service the percentage of chills rose to 4 per cent in 1935, whereas in 1934, before the technic had been changed, it had been 1 per cent. During the last year this service replaced the gravity method by the Hirsch apparatus.[8] The collection of the blood is the same as with the original citrate procedure. However, the apparatus is used to inject the citrated blood into the vein of the infant.

This apparatus consists of a metal case with two narrow channels, through which the blood is aspirated and injected. The proper cleansing of the channels through which the blood flows is very difficult. Thus old blood is apt to collect and stay in them. The increase in chills observed during the

last year on the pediatric service is due to a foreign protein reaction. The quadruplication of the incidence of chills seems to prove the advisability of adhering strictly to the original technic (gravity method).

I have not included in the statistics three cases of aplastic anemia observed at the hospital during 1935. The extremely high incidence of posttransfusion chills in this disease is so utterly at variance with the low record of chills in all other diseases that it would be unfair to include them in our statistics. They must be due to the underlying disease and cannot be ascribed to a faulty technic of blood transfusion. The first case had 31 transfusions with four chills, the second case had 18 transfusions with eight chills, and the third case had 12 transfusions without a chill. In other words, 61 transfusions for aplastic anemia were followed by 12 chills (20 per cent).

However, I have included in these statistics three cases of posttransfusion chills in ulcerative colitis, though two of these patients had been treated with dysentery serum. One patient had one chill among three transfusions, the other patient one chill among five transfusions, and the last patient had one transfusion followed by a chill. While two of these chills may have been due to a serum reaction, they were included in the statistics.

The results obtained since the establishment of the special department for the proper preparation of instruments and solutions used for intravenous therapy (saline solutions, glucose solutions, blood transfusions) prove conclusively that chills after citrate transfusions can be held permanently at a very low level (about 1 per cent), if the proper technic in the preparation of the instruments and solutions is used. The only change in the administration of a citrate transfusion since its original introduction 20 years ago is the change from a rapid infusion of the blood to the slow-drop method. The slow-drop infusion of saline and glucose solutions was first suggested by Friedemann[9] in 1913. He has used this method continuously for over 20 years and has published a number of papers on this subject. The slow-drop infusion was popularized in this country by Hyman and his coworkers.[10] I consider the slow-drop infusion, which safeguards against a sudden overloading of the circulatory system, one of the most important additions to the technic of blood transfusions. This principle can be utilized only when citrated blood is used. Citrated blood through the mixture with an anticoagulant may be introduced very slowly by the drop method without the risk of coagulation of the blood.

On the surgical services the majority of transfusions are given during the postoperative course in connection with the intravenous administration of glucose solution. The picture as it presents itself is usually the following: The patient has been returned to the ward and glucose solution is administered intravenously by the drop method. In fact, the intravenous glucose infusion usually has been started in the operating room. I use this method in practically every major abdominal operation, as soon as the patient reaches the operating room. The patient is then returned to the ward with the infusion apparatus in place. Whenever blood transfusion is indicated,

the glucose solution in the glass container is replaced by citrated blood. After the desired quantity of blood has been given, the intravenous administration of glucose solution is continued. Sometimes this procedure is repeated, blood being given again six or 12 hours later (and if necessary even at shorter intervals). In many instances the patient is not aware of the seriousness of his condition and does not know that a blood transfusion is being given. The citrate technic is the only procedure which allows us to change from one method (blood) to the other (glucose) with the greatest ease, as the exigencies of the case demand.

The sudden increase in the number of transfusions, since a safe method for the prevention of chills was introduced, is possibly partly due to lax indications. As blood transfusion may be given now without any discomfort to the patient, it is tempting to order transfusions without definite indications. I would like to sound a note of warning against indiscriminate use of blood transfusion which may not only be harmful to the patient, but would bring discredit to the method.

It is gratifying to see how the citrate method of blood transfusion has gradually overcome all the strenuous opposition which it encountered in its earlier years. It has traveled across the ocean and is now used even in small communities as far removed from us as Siberia. It has long been proved that citrated blood is absolutely harmless and may be used in any disease in which transfusion is indicated. With the present technic of the preparation of instruments and solutions the chills have been practically eliminated.

Bull[11] stated recently: "In a review of methods the place of honor unquestionably belongs to the citrate method of Lewisohn which has the longest record of accomplishment. This it owes to widespread use and to its technical simplicity which adds it to the armamentarium of any doctor who can introduce a needle into a vein accurately and carry out a few simple directions."

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DISCUSSION.—DR. WILLIAM DEW. ANDRUS (New York) reported some of the statistics of transfusion from New York Hospital. In one section of 65 beds, in a period from September, 1934, to 1936, 634 transfusions were given with 13 reactions. There was at least one case of aplastic anemia. The method used was that described by Doctor Lewisohn, and the citrate solution was prepared in Doctor Elser's laboratory. In addition, Doctor Andrus spoke of two individual cases who had received a long series of transfusions. One was a case of Streptococcus septicemia in which 37 small repeated transfusions were employed, with two reactions. The other case was a boy with hemalytic Staphylococcus osteomyelitis and septicemia. In a period of several months he received 86 blood transfusions with two reactions.

DR. FRANK B. BERRY (New York) said that although nearly everyone was familiar with the work that Doctor Lewisohn had done and the very brilliant results that could unquestionably be obtained with the citrate method, nevertheless there are certain instances in which it is not possible to have control of the preparation of the solution so that the more direct methods were indicated.

DR. R. S. MUELLER (Bellevue Hospital, New York) expressed his preference for the direct method of blood transfusion for the following reasons: First, the blood in the direct method is out of the body for only ten or 15 minutes, during which time it comes in contact only with the glass and metal syringe which are invariably washed out after each use. With the indirect method, the blood is out of the body a considerably longer time, temperature changes can take place, a chemical mixing occurs with the blood, there is a rubber tube, and the blood has to be sterile. A second reason for favoring the direct method is that in cardiac cases on the medical and surgical services, and in transfusions during operation, it is possible to feel one's way along; that is, with the direct method one can give as little or as much as desired. Moreover, by using the Lindeman needle, part may be given before operation and, by leaving the needle in during the operation, an additional amount, if required, may be given after the operation.

DR. CONDICT W. CUTLER, JR. (New York) said that although his immediate association with the method and results of transfusion has been only that of the general surgeon, nevertheless he had been very much interested in the preparation of intravenous solutions, having taken up this problem three years ago at a time when, in Roosevelt Hospital, a great many chills were occurring not only from intravenous blood transfusions but from the intravenous injection of other solutions. Following the brilliant work of Doctor Lewisohn, he undertook to find some solution of this problem at Roosevelt Hospital, and a method was instituted which involved careful distillation of the water, accepting the dictum that undistilled water was most likely the source of the reactions. Furthermore, a careful, uniform technic of preparation of the tubing and glass was adopted, as was the use of an infusion set. These methods were followed by a reduction of infusion reactions from 18 or 20 per cent to less than 0.3 per cent. It has not been possible even yet to get the result desired. Infusion reactions should be entirely eliminated. One

hampering feature was being unable to obtain a triple still so that it was necessary to resort to the use of baffle plates installed in the old still, which is not ideal even though a real improvement.

The chill reactions as applied both to transfusion and infusion may occur from other factors than simply undistilled water. Two rather interesting instances illustrate this. It was felt that very satisfactory results were being obtained when, all at once, there developed 11 infusion chills. A check up investigation revealed the fact that the granular salt was coming from the drug room. The method of handling it there was investigated and it was discovered that a metal cup was being used for measuring both salt and boric acid crystals. As soon as that was stopped and the measuring of salt was transferred to the department's preparation room, reactions ceased.

Lately, however, several reactions occurred for which it was impossible, for a time, to ascribe a reason. On thorough investigation, it was learned that someone had succeeded in selling to the hospital the idea that there is a certain type of rubber tubing which does not need preparation. This had been employed without Doctor Cutler's knowledge. As soon as the use of this tubing, that had not been prepared with sodium hydroxide, as was previously the custom, was discontinued and new tubing was subjected to sodium hydroxide, the difficulties were momentarily at an end.

Doctor Cutler stressed the importance, also, of using thoroughly distilled rather than imperfectly distilled water. Within the past five or six days, he said, in the midst of a very satisfactory record and a continuation of the process that had been developed, transfusion chill reactions again occurred which were traced down only with considerable difficulty. Every part of the technic was checked over and over without revealing the flaw. Then a specific investigation was undertaken of the still and the baffle plates, and, finally, inquiry was made into the condenser. Thereupon it was discovered that in the reorganization of the system the condenser had not been taken down. This was immediately done and the coil removed. It was found that there was a leak permitting undistilled water from the jacket to penetrate the tube that carried the distillate. Certainly an experience of this kind points out the necessity of keeping the distillate free of undistilled water.

Dr. Howard Lilienthal (New York) referred to the important matter of rapid or slow introduction of blood or fluid, particularly of blood. This depends, he said, entirely upon the nature of the conditions that call for transfusion. When a disease is accompanied by anemia, slow transfusion is best. But in the case of a healthy person who has been operated upon with the loss of a large quantity of blood, this should be replaced as rapidly as possible. Tremendous credit for the kind of work that has been done at Mt. Sinai Hospital belongs to Doctor Rosenthal. Whereas, formerly there was a certain percentage of reactions, since the establishment by Doctor Rosenthal of a central department for making and preparing solutions, the absence of reactions has become pronounced. This department takes care of the preparation of apparatus as well as of solutions.

Dr. Paul C. Morton (New York) reported that, in 1930, similar difficulties had occurred at St. Luke's as occurred two years later at Roosevelt Hospital. At that time the general principles given by Doctor Lewisohn were followed. After two years' investigation and experimentation, in 1932 a special room was equipped for the preparation of intravenous solutions and equipment. A few minor modifications were made in the Mt. Sinai technic, such as an increase in the size of the metal box, an increase in the size of the gravity flask, and separation of the clysis sets from the infusion sets. The

general technic of rubber, and solution preparation, remained the same. During the four year period, from 1932 to 1936, 11,173 infusions have been given, with nine reactions, eight of which occurred in a period of four months, the source of contamination having been in a gelatin seal which covered the glucose ampule cap. Whenever any of this gelatin seal fell into the gravity flask a reaction occurred, and as soon as the technic of adding glucose to the solution was changed, and double-tipped glass ampules used, reactions ceased.

Four months ago, however, one other chill was encountered, following an intravenous treatment. It has seemed impossible to determine the cause of this reaction. It has been the experience at St. Luke's that whenever a reaction occurs, it can be traced back to some break in technic, the chills and reactions being due to a foreign protein entering the system through a direct contamination, as noted above: through improperly distilled water, or through improperly prepared rubber tubing. Experiments in Doctor Morton's hands have shown that improperly prepared rubber tubing will produce chills. It is felt now that triple distilled water is not essential, but that great care should be used in keeping the still clean and in having a high boiling chamber and adequate baffle plates. When this is done consistently good results following Doctor Lewisohn's technic, either in blood transfusions or in the introduction of fluids intravenously, can be expected.

In Doctor Morton's experience, hydrogen ion concentration has played no part in the production of chills. Neither has temperature of the solution. Speed shock has not been encountered, intravenous solutions having been given as rapidly as 1,000 cc. in ten minutes, and as slowly as the drip method can supply the liquid without having the blood clot. No chill has been dependent upon this factor. Neither has concentration of the solution produced chills. As much as 200 cc. of 20 per cent salt solution, 50 per cent glucose solution in plain distilled water, has been given without untowards effect.

In reference to the sale of commercially prepared solutions for intravenous use, Doctor Morton said that at various times members of the staff at St. Luke's Hospital have been interviewed by all the companies making commercial solutions. In spite of the greatest confidence in the chemical purity of the product, experiences at St. Luke's do not concur with the statements of those who claim that they have not encountered chills and reactions with such solutions. The uncontrollable factor in these preparations lies in the rubber tubing through which the solution is given. The original tubing as distributed with the sets is adequately prepared, but, following its initial use, it is used over and over again with other flasks, and is, in the greatest majority of cases, inadequately prepared, so that it proves to be a source of contamination and constitutes the great danger that lies in the use of commercial transfusion preparations.

Doctor Lewisohn (closing) stated that he was surprised to hear that a number of hospitals in this city still use the syringe method, in spite of the fact that the citrate method is simpler and safer. It might be of interest to point out that the Lahey and Mayo Clinics use the citrate method, with the same good clinical results and the same low incidence of chills as reported at Mt. Sinai and other hospitals using the citrate method.