SEVERE SHOCK SYNDROME DUE TO CONTAMINATED INFUSIONS

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The use of infusions and transfusions has become a daily routine in medical practice, and there is a tendency to forget that they are not devoid of danger. There have been several reports in the literature concerning the inherent dangers of transfusions, and the number of fatalities they exact has been estimated to be at least as high as that of appendectomies (*New Engl. J. Med.*, 1951). There have been fewer reports concerning the dangers of infusions. Having observed a severe incident of this sort, we are reporting it because we feel that it can occur at any time, and, unless recognized early and treated vigorously, can be rapidly fatal.

On July 31, 1957, six patients in our ward were receiving infusions of corticotrophin and chlorpromazine in Darrow's solution. Five of them developed reactions ranging from a mild disturbance to very severe shock, while no reaction was noted in the sixth patient.

Case 1

A woman aged 45 had a herniated lumbar disk, which did not respond to the usual conservative treatment. Previous to the present incident she had received 70 units of corticotrophin in all and was in excellent general condition. At 11.30 a.m. on July 31, 1957, an intravenous infusion of 10 units of corticotrophin and 50 mg. of chlorpromazine in 300 ml. of Darrow's solution was started. At 1.30 p.m., after having received about 100 ml. of the solution, she was seized by a violent chill, and her temperature rose to over 39° C. (102.2° F.). She complained of headache and abdominal pains, her face was very flushed, and she started to vomit. The infusion was immediately stopped, and, in the belief that it was an ordinary pyrogenic reaction, an injection of 0.01 g. of morphine was given. However, her condition did not improve; the flushing was very marked, the pulse was around 140 a minute, and the blood pressure, to our surprise, was 60/30, her normal pressure being 110/80. The low pressure persisted despite 50 mg. of ephedrine, and within 45 minutes from the beginning of the reaction an infusion of noradrenaline, 10 mg. in 500 ml. of saline, had to be started. With a small quantity of noradrenaline the systolic blood pressure could be kept at 100–110, but at every attempt to stop the noradrenaline the pressure immediately fell to below 60–70 systolic. During the first two hours the appearance of the patient changed considerably, the temperature came back to normal or below, and the abdominal pains and vomiting stopped. The flush persisted, sweating was very profuse, and the picture was one of severe vascular collapse. During the next 12 hours the shock persisted.

Since the clinical picture did not suggest bacterial infection, and because of a preliminary laboratory report hinting at a possible fungal contamination, no antibiotics were given. After 12 hours an intravenous infusion of cortisone was added. The systolic blood pressure rose immediately to 190–200, and it was possible to reduce the quantity of noradrenaline, but not to withdraw it. On the following day the patient's general condition improved gradually, but the

shock persisted, necessitating continuous noradrenaline for 30 hours. Thereafter noradrenaline was stopped and the blood pressure remained around 90/70 for a further 12 hours and then returned to normal. Recovery was uneventful and without sequelae.

During the shock she received in all 30 mg. of noradrenaline and 105 mg. of cortisone (75 mg. of this intramuscularly). The day after the onset of the reaction the infusion solution was found to be contaminated with a viable coliform bacterium sensitive to several antibiotics. Streptomycin, 2 g., was given the same day and 1 g. on each of the next four days.

Laboratory data during the reaction:—There was no evidence of intravascular haemolysis; blood bilirubin, 0.4 mg./100 ml.; urinary urobilinogen, normal; urine examination, normal. Blood electrolytes: NaCl, 550 mg./100 ml.; K, 15.4 mg./100 ml.; CO₂, 48 vols. %.

Case 2

A woman aged 47 with Guillain-Barré syndrome had received 100 units of corticotrophin during the seven days previous to July 31, 1957. At noon on that day an infusion of 10 units of corticotrophin and 50 mg. of chlorpromazine in 300 ml. of Darrow's solution was started. About two hours later, after receiving about 120 ml. of the solution, she had a violent reaction, with chills, fever up to 39° C. (102.2° F.), headache, abdominal pains, nausea, flushed face, and rapid pulse. The blood pressure was 60/40 (her normal pressure was 165/90). There was no response to ephedrine, and within half an hour from the onset an infusion of noradrenaline was started. During the next few hours all the previously mentioned symptoms disappeared, with the exception of very profuse sweating and profound shock. Any attempt to discontinue the noradrenaline resulted in blood pressure around 30/20. After 12 hours, intravenous and intramuscular cortisone was added with good results. The blood pressure rose to 190–200 systolic, and it was possible to slow the noradrenaline drip but not to stop it. After 24 hours 2 g. of streptomycin was given, and was continued on the following days. The patient's condition improved gradually, and the noradrenaline was discontinued 24 hours after it was started, the blood pressure remaining around 95/60 for another 10 hours and then returning to normal. The patient made an uneventful recovery. She received in all 20 mg. of noradrenaline, 30 mg. of cortisone intravenously and 25 mg. intramuscularly.

Laboratory data during the reaction:—Urine examination, normal; blood bilirubin 0.4 mg./100 ml.; blood electrolytes on the second day of the reaction: NaCl, 594 mg./100 ml.; K, 12.4 mg./100 ml.; CO₂, 49 vols. %; blood electrolytes on the third day of the reaction: NaCl, 598 mg./100 ml.; K, 10 mg./100 ml.; CO₂, 36 vols. %; no evidence of haemolysis.

Case 3

A woman aged 34 had myasthenia gravis and thymoma which reacted poorly to irradiation and neostigmine. Two days previously corticotrophin infusions were started and she had received 30 units. On July 31, 1957, an infusion of 15 units of corticotrophin and 50 mg. of chlorpromazine in 300 ml. of Darrow's solution was started. This infusion, in common with all the other infusions, was discontinued because of the reactions in the first two patients. She had received about 100 ml. of the solution. The reaction began an hour later with fever, chills, flushing, etc., and continued, as in the other patients, with profuse sweating and shock. The noradrenaline drip was started within 30 minutes of the beginning of the reaction and continued for three hours, when it was discontinued and the blood pressure kept at about 80–90 systolic for eight hours with intramuscular injections of ephedrine 50 mg. (three injections). Later the noradrenaline drip had to be reinstalled for another 37 hours. This was the most difficult case of the five, as the

shock lasted for almost 48 hours and was complicated by an exacerbation of the myasthenia gravis, necessitating hourly injections of 1 mg. of neostigmine, while previously she had been stable with 5 tablets of neostigmine (15 mg. each) a day. She received in all 40 mg. of noradrenaline, 100 mg. of cortisone, and, starting the day after the beginning of the reaction, tetracycline, 1 g. a day for four days. She made a complete recovery without sequelae.

Laboratory data:—Urine, normal; no haemolysis; blood bilirubin, 0.5 mg./100 ml. Blood electrolytes: NaCl, 520 mg./100 ml.; K, 12.2 mg./100 ml.; CO₂, 59 vols. %.

Case 4

A girl aged 19 with ulcerative colitis had received 110 units of corticotrophin previous to July 31, 1957. On that day an infusion of 10 units of corticotrophin and 50 mg. of chlorpromazine in 300 ml. of Darrow's solution was begun. After one and a half hours and after about 100 ml. of the solution had been given the reaction started with chills, fever, vomiting, and rapid thready pulse, as in the other patients. The blood pressure was 60/40. A noradrenaline drip was started, and after she had received 5 mg. of noradrenaline in eight hours it could be discontinued. The pressure stayed low for some hours, then went up to normal. No cortisone was given. She continued to receive corticotrophin for a few days and made a good recovery.

Laboratory data:—No signs of haemolysis; blood bilirubin, 0.4 mg./100 ml.; urine, normal.

Case 5

A woman aged 42 with macroglobulinaemia (Waldenström disease), thrombocytosis, and nephrotic syndrome had not received corticotrophin for the previous 10 days to July 31, 1957.

On that day she received an infusion of 25 units of corticotrophin and 50 mg. of chlorpromazine in 300 ml. of Darrow's solution. After more than two hours and after about 100 ml. of the solution had been given the infusion was stopped. Her reaction started a quarter of an hour later. This was the mildest case of all the five. She had the prodromal signs with chills, fever, abdominal pains, vomiting, headache, flushed face, and rapid pulse, but her systolic pressure never fell below 80. Neither noradrenaline nor cortisone was given. She received 50 mg. of ephedrine intramuscularly and in four to five hours the blood pressure returned to normal, and the nausea and vomiting stopped. The next day no signs of the reaction remained.

Bacteriological Findings

The five suspected bottles of Darrow's solution were marked with the same sterilization date, nine days before. The bottle of the sixth patient, who did not show any reaction, was of another date. Within five hours of the reaction they were sent for bacteriological examination. At first sight nothing unusual could be detected; but with the help of a strong light a slight turbidity could be seen. Cultures were prepared from three of the suspected solutions and from all of them a coliform bacterium was grown. The solution received by the sixth patient was sterile. Unopened transfusion sets bearing the same sterilization date as those used with the contaminated bottles were examined and found sterile. In order to exclude exogenous contamination of the solution by the corticotrophin and chlorpromazine introduced, an unopened bottle of Darrow's solution bearing the same date as the contaminated ones was cultured and the same coliform bacterium was again isolated. This undoubtedly incriminated the Darrow's solution autoclaved nine days previously as the source of contamination.

All infusion solutions used in this hospital are prepared in the central supply department and sterilized in a big autoclave heated by steam under pressure. During the eight years that this department has been functioning there have occurred occasional pyrogenic infusion reactions, but this

was the first time that solutions were found non-sterile. Investigation revealed that the sterilization by autoclave nine days previously was defective owing to a temporary arrest of steam supply which passed unnoticed. The following day some bottles aroused the suspicion of the autoclave attendant. They were cultured and found contaminated, partly with fungi. All bottles of this batch were immediately discarded. Five bottles unfortunately did escape detection, with the results described above.

The coliform bacterium was a motile, non-spore-bearing, Gram-negative rod. The following biochemical reactions were noted: Indole +; M.R. +; V.P. -; Simmons's citrate +; urea -; H₂S not produced on T.S.I. agar; lactose was fermented after one day to acid and gas. Not haemolytic. No growth at 4° C. Good growth at 25° C. and 37° C. This bacterium shows all the characteristics of *Escherichia coli*, except the ability to grow on ammonium citrate. Since the question of nomenclature is yet under discussion it will be referred to as coliform bacterium. It was sensitive *in vitro* to streptomycin, chloramphenicol, and tetracycline.

Darrow's solution contains 260 mg. of KCl, 400 mg. of NaCl, and 500 mg. of sodium lactate per 100 ml. The latter may serve as an adequate source of carbon for bacteria with simple nutritional requirements, but the solution is deficient in nitrogen. Nevertheless growth was obtained when Darrow's solution was experimentally inoculated with small numbers (10–20) of the same coliform bacterium. After 48 hours at room temperature (26–28° C.) countings resulted in 6 to 8 million viable organisms per ml., remained on this level for a week, and later on declined. All experimentally infected solutions remained clear. Although reagents of B.P. grade were used for the preparation of the Darrow's solution, apparently enough nitrogen-containing impurities were present to make bacterial growth possible. These findings are in accordance with those of Garvie (1955), who found that *E. coli* was able to multiply in phosphate buffer containing citrate or lactic acid, or even in phosphate buffer only.

Discussion

Reactions following the introduction of contaminated fluids into the blood stream vary considerably, according to quantity and type of the micro-organisms involved. One possible result is that of infection, as illustrated by Rabinowitz and Shiffrin (1953), who report a series of ward infections ranging from local suppurations to fatal meningitis arising from a contaminated infusion solution. Michaels and Ruebner (1953) report two cases of pyrexia associated with a prolonged intravenous infusion which was contaminated.

Another possibility is that of a short-lived "pyrogenic" reaction. Doubtless many slightly contaminated infusions pass unrecognized this way. A reaction less intense than that of Case 5 might fall in this category.

The complication to which we want to draw attention here is that of mild or severe shock of rapid onset, due to the endotoxins contained in the solution or liberated by the rapid dissolution of the bacteria in the blood stream.

All our patients presented a uniform type of reaction. It started with chills, high fever, restlessness, flushing, abdominal pains, and vomiting, with a rapid pulse. This violent reaction lasted for about two hours, but concomitant with it and masked by it there was a rapid development of severe shock. Less than half an hour after the onset of the symptoms the systolic blood pressure measured between 30 and 60 mm. Hg. After two to three hours the violent reaction abated, the temperature returning to normal or below, but there persisted severe shock with profuse sweating. We would emphasize that the shock is not clinically apparent in the first two or three hours, and, unless looked for, precious time may be wasted and life-saving treatment delayed.

This syndrome is essentially the same as that described by Whitby (1949), Borden and Hall (1951), Stevens *et al.*

(1953), Braude *et al.* (1953), McEntegart (1956), and others after the transfusion of contaminated blood. The blood in those cases was contaminated by cold-growing micro-organisms, most of them Gram-negative. The effects of endotoxins of Gram-negative bacteria have been extensively studied in animals. The main manifestations were fever, diarrhoea and vomiting, hypoglycaemia, changes in leucocyte distribution, and shock, resulting in death. Ebert *et al.* (1955) injected meningococcus toxins intravenously into dogs, producing a precipitous fall in blood pressure. They concluded that this was due to venous pooling of the blood in the viscera. The shock was treated successfully with noradrenaline. Augmentation of the blood volume was less effective, and cortisone was of no help. Weil *et al.* (1956) produced shock in dogs with coli endotoxin. They also explained this phenomenon by venous pooling and were able to correct it by metaraminol.

The role of adrenal damage or insufficiency in the production of shock in those cases of acute septicaemia seems to be of less importance than previously thought. Of the various necropsy reports of fatal contaminated transfusion reactions only one case showed unilateral adrenal damage (McEntegart, 1956). None of the dogs in the experiments of Ebert *et al.* (1955) showed gross adrenal lesions. Although no extensive studies in this direction were done in our patients, results of serum sodium and potassium estimations did not point to adrenal insufficiency.

The severity of the shock seems to be in direct proportion to the quantity of endotoxins introduced into the blood stream. The effect is the same whether the bacteria are dead or alive. The endotoxins of most of the Gram-negative bacilli have the same action—for example, the meningococcus and *E. coli*.

The fatality rate in reported transfusion accidents due to contaminated blood is quite high, especially when Gram-negative bacilli are concerned. Stevens *et al.* (1953) report 32 cases assembled from the literature, including their own, of which 65% ended fatally. Two fatal cases are described by McEntegart (1956).

All our patients recovered. As the reactions began in the early hours of the afternoon, at a time when all the doctors were in the ward, and occurred almost simultaneously, immediate attention was directed to them and treatment was started early. Within 30 to 45 minutes of the beginning of the reaction all the patients in shock were being given noradrenaline drips.

In our opinion this early treatment is one of the main factors that contributed to the recovery, the importance of the time factor in shock being well known. Another factor, not given to comparison or measurement, is the quantity of endotoxins introduced.

The amount of noradrenaline given was not great, an average of 20 mg. per 24 hours being sufficient. Cortisone was found to be of definite value, probably owing to its potentiating effect on noradrenaline, as experimentally demonstrated by Kurland and Freedberg (1951), although, as mentioned above, it has no direct effect on the shock.

Antibiotics were started only the day after the beginning of the reaction and did not seem to play an important part in the treatment.

Because of the severity and potential dangers of this condition no effort should be spared in its prevention. Since no macroscopic abnormalities can be seen in the contaminated solutions, the strictest control of sterilization procedures is essential, with sterility checks of every batch of fluids before distribution.

Summary

Five cases of mild to severe shock due to the intravenous infusion of Darrow's solution contaminated with coliform bacteria are reported. Attention is called to the rapid though masked onset of circulatory collapse, and its mechanism discussed. All patients were successfully

treated with noradrenaline and cortisone. The importance of early recognition and treatment of the shock is emphasized.

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REFERENCES

- Borden, C. W., and Hall, W. H. (1951). *New Engl. J. Med.*, **245**, 760.
 Braude, A. I., Williams, D., Siemieniuk, J., and Murphy, R. (1953). *A.M.A. Arch. intern. med.*, **92**, 75.
 Ebert, R. V., Borden, C. W., Hall, W. H., and Gold, D. (1955). *Circulat. Res.*, **3**, 378.
 Garvie, E. I. (1955). *J. Bact.*, **69**, 393.
 Kurland, G. S., and Freedberg, A. S. (1951). *Proc. Soc. exp. Biol. (N.Y.)*, **78**, 28.
 McEntegart, M. G. (1956). *Lancet*, **2**, 909.
 Michaels, L., and Ruebner, B. (1953). *Ibid.*, **1**, 772.
New Engl. J. Med., 1951, **245**, 745.
 Rabinowitz, K., and Schiffrin, R. (1952). *Acta med. orient. (Tel-Aviv)*, **11**, 181.
 Stevens, A. R., jun., Legg, J. S., Henry, B. S., Dille, J. M., Kirby, W. M. M., and Pinch, C. A. (1953). *Ann. intern. Med.*, **39**, 1228.
 Weil, M. H., Hinshaw, L. B., Viascher, M. B., Spink, W. W., and MacLean, L. D. (1956). *Proc. Soc. exp. Biol. (N.Y.)*, **92**, 610.
 Whitby, L. (1949). In *Blood Transfusion*, edited by G. Keynes, p. 467. Williams and Wilkins, Baltimore.

Medical Memorandum

Incontinentia Pigmenti (Bloch-Sulzberger)

Incontinentia pigmenti is a rare developmental anomaly involving the skin and other ectodermal tissues. The first case under this name was described by Bloch (1926) and again by Sulzberger (1928), though in 1925 Bardach had reported two cases of an identical condition under the diagnosis of systematized naevus formation. In view of the apparent rarity of the condition the following three cases are described.

CASE 1

A female infant, the fifth child of healthy parents, was born after a short labour. During pregnancy the mother had suffered from hyperemesis and mild toxæmia. The birth weight was 7½ lb. (3.4 kg.). Soon after birth a slight discharge was noticed from both eyes; otherwise the child appeared normal. On the second day she developed a generalized rash, and the following day there was twitching of the right arm and right side of the face; as a result of this she was admitted to hospital.

On examination a rash was seen over her trunk and limbs: this consisted of raised erythematous areas, some surmounted with papules and some with pustules. Certain of these erythematous areas showed desquamation and yellow-brown pigmentation (Fig. 1). In addition there was twitch-

FIG. 1.—Case 1, showing the appearance of the skin lesions.

ing of the right arm and right side of the face; the cry was cerebral in type. No other abnormality was found.

A diagnosis was made of cerebral birth trauma with an associated infective erythema, and treatment was begun with phenobarbitone and chlortetracycline. The twitching soon ceased but the rash persisted. Because of this failure