THE USE OF IMMUNIZED BLOOD DONORS IN THE TREATMENT OF PYOGENIC INFECTIONS BY WHOLE BLOOD TRANSFUSION.

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SEVERE septicaemia, generally of streptococcal origin, was a wound complication which was only too frequent and fatal during the war.

The usually desperate condition of such cases and their high mortality made an urgent appeal for attempts at a cure, and almost any method which promised success worthy of trial. The marked benefit attendant upon whole blood transfusions which were being performed in large numbers in No. 8 General Hospital in the summer of 1918, suggested the use of immunized blood donors for transfusion in cases of septicaemia and chronic wound infections.

The large number of transfusions and the wide field for selection of blood donors afforded by numerous light duty patients gave an unusually favourable opportunity for a trial of the method. This so-called "vaccination" transfusion had been tried by Ransom Hooker¹ in five cases of staphylococcal septicaemia, three of which recovered. A successful result had been reported by Heyd² in a case of endocarditis with a positive *Streptococcus viridans* blood culture, and McClure and Dunn³ had experienced satisfactory results with cases of typhoid fever.

The hypothetical advantages envisaged in the present series by the use of this method were:

1. The antibacterial mass action obtained by the use of a large volume of immune serum—for example, 900 c.cm. as against the 20 to 40 c.cm. of antistreptococcal serum usually employed.
2. A "protein shock therapy" on a considerable scale, and the use of a homologous serum.
3. The possible "sensitizing" of the patient towards a vaccine by means of the immune serum, the same vaccine being used for the patient as was employed for the production of immunity in the blood donor.
4. The replacement of red blood cells in the circulation of the patient instead of those broken down by the haemolytic activity of streptococci, thus directly combating the anaemia caused by the infection.

Methods Employed.

1. *Blood donors* were light duty patients. All those selected were volunteers, who fully understood what was necessary and performed their part with enthusiasm. Their age varied from 20 to 36. Their medical history was investigated, and only those free from malaria and trench fever or any recent infectious disease were taken. Wassermann reactions were done in all cases and were negative in all the donors selected.

2. *Blood matching* was performed by the method of Lee.⁴ For donors only men of Class IV (universal donors) were taken. The blood of the recipients was similarly tested before transfusion to determine their class.

3. The vaccine employed for the immunization of the donors was a polyvalent one prepared as follows:

Purity of culture of the various strains having been determined by broth and agar cultures, the strains were inoculated into 5 c.cm. broth containing 1 c.cm. fresh sterile human serum. They were incubated at 37° C. for twenty-four hours, in which time sufficient growth was usually obtained. The tubes were centrifuged at high speed and the supernatant fluid was pipetted off and 5 c.cm. sterile saline added. The emulsion was well shaken and allowed to stand a quarter of an hour to permit large particles to sediment. Upper layers of fluid were taken for the vaccine, which was sterilized by cold in the ice chest, with the addition of 0.1 c.cm. of 1 in 20 carbolic acid for each 1 c.cm. of vaccine. The vaccine was then incubated twenty-four hours, tested for sterility, and diluted to required strength. The vaccine was estimated by Wright's method or in the counting chamber.

Strains of streptococci from the following series were employed for vaccines, together with one strain of staphylococcus:

Series 1:

1. Fatal streptococcal infection in a case of cerebro-spinal fever.
2. Wound of knee-joint. Pure culture from fluid from joint.
3. Wound of knee-joint. Pure culture from pus from joint.
4. Fatal septicaemia following gunshot wounds. Blood culture.
5. *Staphylococcus aureus* from case of furunculosis.

Series 2:

1. Streptococcal septicaemia following gunshot wounds. Blood culture.
2. Gunshot wound of knee. Pure culture from pus from joint.
3. Fatal streptococcal septicaemia. Blood culture.
4. Gunshot wound of chest. Isolated from haemothorax.
5. Gunshot wound of leg and fatal septicaemia. Isolated from thrombus in femoral vein and by blood culture.
6. Gunshot wound of chest. Isolated from haemothorax.

TABLE I.—Bacteriology of Strains Employed.

		Lactose.	Cane Sugar.	Salicin.	Mannite.	Inulin.	Litmus Milk.		Length of Chain.	Haemolysis.
							Acid.	Clot.		
<i>Series 1:</i>										
1	...	+	+	+	+		+	0	Medium	+
2	...	+	+	-	-	-	+	0	Short	-
3	...	+	+	-	+	-	+	+	Short	-
4	...	+	+	-	-	-	+	0	Medium	+
<hr/>										
<i>Series 2:</i>										
1	...	+		-	+		+	0	Short	+
2	...	+		-	+		+	0	Short	-
3	...	+		-	-		+	0	Medium	+
4	...	+		-	+		+	0	Medium	-
5	...	+		-	-		+	0	Medium	+
6	...	+		-	+		+	+	Medium	-

Strength of Vaccine.—Series 1: 60 million streptococci and 105 million *Staphylococcus aureus* per 1 c.cm. Series 2: 120 million streptococci per 1 c.cm.

Dosage.

The total number of injections given to each donor was on the average 6, the greatest number being 9 and the least 3, the injections being given at intervals of five days. The amount of the final dose was on the average 120–150 million streptococci and 400 million staphylococci where a mixed vaccine was used. The period of immunization was about one month or more. None of the donors were the worse for the administration of the vaccines and some appeared to be benefited. The lapse of time between the last dose of vaccine and the giving of blood was on an average five days, but varied from one to thirty-one days, according to the exigency of circumstances.

Determination of Immunity.

The necessity was felt of an accurate method for rapidly determining the changes in the immunity reaction, both in the donors in response to the vaccine, and in the patient before and after the transfusions and during the course of the treatment. Complement fixation tests were not practicable. Various other methods were tried, such as estimates of the haemophagocytic index and increase in the agglutinins in the serum. No sufficiently accurate results were however obtained, and the attempt was abandoned. In this respect the investigation is lacking in accurate data. Ransom Hooker (loc. cit.) states the want of a method for determining the immunity response under these conditions.

Transfusion was in all cases performed by means of the Kimpton paraffined tube with the usual technique. The amount of blood transfused was generally 900 c.cm., but varied from 450 c.cm. upwards.

The total number of cases treated by transfusion with the blood of immunized donors was nine, of which six were acute septicaemia and three severe suppurative wounds of the thigh.

Following is an account of the cases mentioned in Table II.

A. ACUTE INFECTIONS.

CASE 1.—Septicaemia: *Haemolytic Streptococcus*: Complete Recovery.

Lieut. W., aged 22; gunshot wound of chest and right arm, July 23rd, 1918.

Admitted July 25th. Condition: Wounds very foul; temperature high. Wounds opened up and damaged muscle cut away. Fractured right humerus above surgical neck. Large foreign body removed from under right pectoralis major. Axillary and brachial vessels and nerves exposed for about three

TABLE II.—Analysis of Cases.

Class of Case.	Bacteriology (Blood Culture).	Result.
A. Acute Infections.		
1. Septicaemia	Haemolytic streptococcus	Complete recovery.
2. Septicaemia	Ditto	Died.
3. Septicaemia	Ditto	Died.
4. Septicaemia	Ditto	Died.
5. Septicaemia	Ditto	Died.
6. Septicaemia	Staphylococcus	Died.
B. Chronic Infections.		
7. Acute suppurative arthritis of right knee-joint: gunshot wounds of leg	Pus from joint; streptococcus—pure culture	Rapid recovery.
8. Chronic suppurative wounds of left thigh: fractured femur	Pus from wounds; mixed streptococci and staphylococci	Rapid recovery.
9. Wound of right buttock: fractured neck of femur	—	Rapid recovery.

Mortality of streptococcal cases (Cases 1-5) = 80 per cent.; of all cases of septicaemia (Cases 1-6) = 83.5 per cent.

inches. Wounds packed with Dakin's gauze. July 25th to August 8th: Temperature 100° to 102°. Thrombosis left femoral artery. On August 9th there was secondary haemorrhage from third part of right axillary artery; rapidly controlled and vessel tied.

Transfused; ordinary donor, Class IV, amount 600 c.cm. August 11th: Temperature 105° F. and remaining high. August 15th: Conscious but drowsy; pale and anaemic, tremulous and twitching, occasional delirium. Left thigh very swollen. Blood culture positive—haemolytic streptococcus, medium length of chains. Blood group, Class IV.

August 18th: Apparently moribund, delirious, twitching, Hippocratic facies, sordes on lips. The following day transfused, immunized donor, Class IV, 600 c.cm. The donor had received five injections—highest dose 90 million streptococci, 150 million staphylococci; blood donation eleven days after last injection. August 20th: Slept quietly after transfusion, conscious on waking, tremor and twitching absent, colour improved, appetite improved. August 22nd: Condition again becoming unsatisfactory; marked tremor, drowsy, semi-conscious, incontinence of urine and faeces.

August 23rd: Transfused; immunized donor, Class IV, 800 c.cm. The donor received five injections—highest dose 90 million streptococci, 150 million staphylococci; blood donation fifteen days after last injection.

August 24th: Result of transfusion again very good; slept well, delirium and tremor absent, appetite returned. Satisfactory condition maintained on August 26th, but on the following day his condition was again grave; temperature high, unconscious and delirious; marked oedema of left ankle and leg from thrombosis of vessels.

August 28th: Transfused; immunized donor, Class IV, 900 c.cm. The donor had received six injections—highest dose 120 million streptococci; blood donation two days after last injection. Result again excellent; slept well, consciousness recovered, free from twitching, good appetite. His condition still good on August 31st, when an autogenous vaccine was given.

September 3rd: Thrombosis of left femoral vein extending; veins prominent on abdomen, great oedema of left thigh and leg. September 5th: General condition improved; drowsy, but quite conscious; autogenous vaccine. On the 9th he had a rigor, but general condition was satisfactory. On the 13th he was better, temperature remaining on lower level; autogenous vaccine.

September 16th: Autogenous vaccine. Condition improved; thigh softer and less swollen. September 21st: Condition unchanged; autogenous vaccine.

September 27th: Thrombosis of right femoral vein and swelling of right leg and groin; abscess in right arm evacuated and drained. Autogenous vaccine was injected on this date and again on October 3rd. On the 4th a large abscess of the left thigh was evacuated and drained; the right leg and foot were swollen from thrombosis of the right femoral vein.

Autogenous vaccine was injected on October 7th and 12th, when the patient's condition was much improved. A blood culture taken four days later proved sterile. October 17th: Autogenous vaccine; condition still improving. The temperature was normal on the 19th, and on the 22nd the last dose of vaccine was given. On November 1st the drainage tubes were removed from the right arm, and two days later he was evacuated to the United Kingdom, the temperature having been normal since October 19th; pulse about 100.

Subsequent history, 1919: Alive and well and walking with the aid of a stick.

CASE 2.—Streptococcal Septicaemia: Death.

Pte. T.; gunshot wound of thigh, compound fracture of left femur, October 18th, 1918. Injured portion of left femoral artery ligatured and excised at casualty clearing station.

Admitted October 28th with gangrene of left foot, suppurating fracture of left femur, and acute bilateral bronchitis. Amputation; bipp; sutured. The same day secondary haemorrhage occurred, and the left common femoral was tied. Transfusion 900 c.cm. from ordinary donor. A blood culture on November 1st resulted in the growth of a haemolytic streptococcus. Blood group, Class IV.

November 2nd: Temperature 104°-105°, rapid respiration, tremor, muttering delirium. Transfused 900 c.cm. from immunized donor, Class IV. The donor had received eight injections—highest 150 million streptococci, 160 million staphylococci; blood donation three days after last injection. On the following day the patient died in coma.

Autopsy.—Thin blood-stained oedema below subcutaneous tissue near wound of thigh. Left ilio-psoas muscle soft and oedematous. Spleen enlarged (17 oz.) and contained recent infarcts. Parenchyma necrotic. Liver large, with pin-point multiple abscesses. Lungs: Subserous petechiae, nodular abscesses along posterior borders from which *B. welchii* was isolated. The pleural and pericardial cavities contained blood-stained fluid.

CASE 3.—Streptococcal Septicaemia: Death.

Pte. B.; gunshot wound of thigh, October 13th, 1918; fractured left femur.

Admitted October 16th. Temperature 99° to 101°. Wounds apparently clean; bipp and suture above knee. On October 28th the wounds were broken down; temperature 102° to 104°. Three days later metastatic abscess of hand opened; urine contained albumin, blood, and granular casts. A blood culture, on November 2nd, produced a growth of a haemolytic streptococcus. Blood group, Class IV.

November 3rd: Drowsy, semi-delirious, twitching; urine scanty, casts numerous. Transfused (800 c.cm.) from immunized donor, Class IV. The donor had received seven injections—highest 150 million streptococci, 160 million staphylococci; blood donation four days after last injection. The following day the patient's condition very bad—tremulous, respiration rapid.

On November 5th he was again transfused (900 c.cm.); immunized donor, Class IV. The donor had received seven injections—highest 150 million streptococci, 360 million staphylococci; blood donation one day after last dose. The patient died two days later.

Autopsy.—The left pleural cavity contained 20 oz. of turbid fluid. Left lung collapsed; bronchitis both lungs. The heart showed an old fibrous nodular vegetation on the mitral valve. Kidneys showed a chronic mixed nephritis with cysts and a calcareous patch in the left kidney. The spleen showed interstitial haemorrhages.

CASE 4.—Streptococcal Septicaemia: Death.

Pte. P.; gunshot wound of right knee, fractured left femur, September 30th, 1918.

Admitted October 10th with single suppurating anterior wound of left thigh; oblique fracture of middle third of left femur in fair position. Wound of right knee partly sutured, partly packed with flavine gauze; bipp. Left leg, Carrel's tubes and bent Thomas's splint.

On October 26th posterior drainage to left thigh. On the 28th the temperature rose rapidly to 104° and remained high; pulse rate 160. On November 6th blood culture resulted in the growth of a haemolytic streptococcus. Blood group, Class IV. Condition very grave—pallid, semi-conscious, sordes on lips, dry furred tongue; very tremulous and unable to speak; wounds clean. The following day he was bled 500 c.cm. and then transfused (immunized donor, Class IV), receiving 900 c.cm. The donor had received seven injections—highest dose 150 million streptococci, 360 million staphylococci; blood donation three days after last dose. The next day the temperature was a little lower, but his condition still very bad; semi-conscious and unable to speak.

On November 10th the temperature rose to 106°; pulse 160. The patient died on the 11th.

Autopsy.—Turbid fluid in right pleural cavity, blood-stained fluid in left. Lungs showed tuberculous, caseous and cicatricial, foci at apices; recent small infarct at base of left lower lobe. Spleen soft and friable.

CASE 5.—Streptococcal Septicaemia: Death.

Capt. L., aged 22; gunshot wound of right leg, November 1st, 1918. Vessels tied; supracondylar amputation right thigh.

Admitted November 5th; temperature 101°, pulse 86. The next day the stump was cleaned with spirit and flavine; delayed primary suture. On the 7th the temperature rose to 104°, pulse 120; stump clean. Blood culture showed growth of a haemolytic streptococcus. Blood group, Class IV.

On November 13th his condition was fair: conscious, not tremulous, no marked pallor. Temperature 103°, pulse 120; stump clean. The following day he was bled 200 c.cm. and then transfused; immunized donor Class IV. The donor had received eight injections—highest dose 150 million streptococci, 400 million staphylococci; blood donation four days after last injection. Patient slept well after the transfusion, but there was no marked improvement.

November 16th: Pleural effusion at base of right lung; fluid from right pleural cavity gave pure culture of a streptococcus with same fermentation reactions as were given by the organism obtained by blood culture. On the 17th he was given a polyvalent vaccine—the same as was used for immunizing donor. The next day there was a marked fall of temperature, and his condition showed great improvement. On the 19th the tempera-

ture was normal, respiration more rapid but easy; slept well. On the 20th, temperature rising, respiration rapid; left-sided parotitis. Vaccine given. The next day he was delirious and very restless; respiration increased. On the 22nd he was better—conscious, parotitis diminishing, no cough or pain in chest. On the 24th the respiration was rapid and rather laboured; 300 c.cm. purulent fluid removed from right side of chest. The patient died the next day.

Autopsy.—Left pleural cavity contained 60 oz. of purulent fluid; right 30 oz. Lungs collapsed; some small abscesses with bronchopneumonia at base of right lung; three small infarcts at base of left lung. Spleen large, soft and friable.

CASE 6.—*Staphylococcal Septicaemia: Death.*

Lieut.-Cpl. F., aged 21; gunshot penetrating wound of right chest, August 1st, 1918.

Admitted August 5th with basal pleurisy of left side of chest. X rays showed foreign body on left side under left dome of diaphragm; no haemothorax. Entry wound right side of chest. Temperature 102° to 104.2°.

On August 28th abscess of liver drained along track of foreign body; about 4 oz. of purulent fluid in cavity. On September 2nd patient was semi-delirious, emaciated and pale; temperature 102° to 104°, pulse 130. Blood culture gave a growth of *Staphylococcus pyogenes* in pure culture. On September 5th he was transfused (900 c.cm.) from immunized donor, Class IV. The donor had received seven injections—highest dose 155 million staphylococci, 150 million streptococci; blood donation five days after last injection. The next day patient's condition was still bad; semi-conscious. He died on September 7th.

Autopsy.—Fragment of metal (weight 9 grams) lying in gastro-splenic omentum; partly closed suppurating track through liver. Spleen much enlarged through pressure on splenic vessels. Pylephlebitis. Semi-purulent fluid in right ventricle; recent vegetations on auricular surface of cusps of tricuspid valve; *Staphylococcus pyogenes* isolated from heart blood of left ventricle.

B. CHRONIC INFECTIONS.

CASE 7.—*Suppurative Arthritis (Streptococcal): Rapid Recovery.*

Pte. K., aged 20; gunshot wound of right knee and multiple wounds, July 7th, 1918. Foreign body removed from external condyle of right femur; joint not involved; bipp.

Admitted July 7th with suppurative arthritis of right knee-joint. Joint laid open and drained; leg oedematous below right knee. Temperature 104°; drowsy. Pus from joint gave pure culture of streptococcus. Blood group, Class IV.

On July 12th he was transfused (450 c.cm.) from immunized donor, Class IV. The donor had received five injections—highest dose 90 million streptococci, 150 staphylococci; blood donation five days after last injection. Two days later patient's condition satisfactory; autogenous vaccine given. On July 18th the temperature was normal; condition improved; wounds very clean and healthy. On the 19th autogenous vaccine again given. Two days later abscess in calf opened. On July 31st the wounds were healing rapidly; general condition good, temperature normal; vaccine discontinued.

CASE 8.—*Chronic Suppuration (Wound Sinus): Mixed Infection: Rapid Recovery.*

Pte. P., aged 20; gunshot wound of left thigh, August 23rd, 1918. Perforating shell wound above left knee-joint; compound fracture of femur. Wounds freely excised; Carrel's tubes and gauze packs.

Admitted August 25th. Wounds appeared clean; completely closed by delayed primary suture. On September 17th one large loose fragment of bone was removed; backward, displaced lower fragment of femur suspended by silver wire loop.

October 28th: Sutured wounds broken down ten days after suture. Large open sinuses discharging profuse thick greenish pus. Patient very pale, anaemic, and rather emaciated. Blood culture sterile. Pus from wound yielded streptococci, medium length chains, and staphylococci. The following day he was transfused (900 c.cm.) from immunized donor, Class IV. The donor had received nine injections—highest dose 150 million streptococci, 250 million staphylococci; blood donation twenty-six days after last injection. The transfusion was followed by a sharp rise of temperature, which immediately returned to normal. Patient looked and felt better.

On November 2nd a polyvalent mixed vaccine was given, similar to that used for immunizing donors; no marked reaction. On the 5th, sinus in thigh opened up. On the 7th, polyvalent mixed vaccine again given; temperature down to normal. On the 10th the discharge from sinuses was much less. Polyvalent mixed vaccine was again given on the 12th and 17th, when the condition was much improved. The last dose of vaccine was given on the 22nd, when the wounds were very clean and discharge slight; temperature normal.

CASE 9.—*Chronic Suppuration (Wound Sinus): Mixed Infection: Rapid Recovery.*

Lieut. L., aged 29; gunshot wound of right buttock, November 1st, 1918.

Admitted November 7th with penetrating wound of right buttock and right inguinal region; bulging of right buttock.

On the 13th the posterior wound was discharging thick greenish pus. X rays showed fracture of right acetabulum. Posterior wound incised; cavity granulating; fragments of bone removed and bare bone felt. Two days later wound enlarged obliquely down and inwards; fairly large infected cavity; posterior half of wound sewn up; bipp and gauze packs.

On December 14th x rays showed necrosis of head of right femur. Temperature swinging. Head of right femur excised; through drainage established. On December 24th the patient looked anaemic and thin; temperature 102°. Blood culture sterile. Transfused (900 c.cm.) from immunized donor, Class IV. The donor had received five injections—highest dose 120 million streptococci, 480 million staphylococci; blood donation twenty-four days after last injection. The next day the temperature was lower and patient's condition satisfactory. He continued to improve. On December 31st he was again transfused (900 c.cm.) from a donor of the same class as before who had received five injections—highest dose 120 million streptococci, 960 million staphylococci; blood donation thirty-one days after last injection. The patient was evacuated to England on January 8th, 1919; colour good and general condition much improved: temperature 98° to 100° F.

DISCUSSION.

A superficial examination of the above results obtained by the use of immunized donors in septicaemia suggests that the method is not of any value. If, however, the case and *post-mortem* reports are analysed it will be noted that in all except two cases the conditions of the patients were absolutely hopeless before the transfusions, and that they were, indeed, practically moribund. In the first case, which appeared equally desperate, a completely successful result was, however, achieved, a result which alone was worth the trouble of immunization, and justified the trial of the method. Without personal knowledge of the case a just estimate of the result obtained in this instance can hardly be conveyed. In the previous experience of none of the observers of the case has a patient in such a condition recovered.

It is true that cases of septicaemia due to infection by haemolytic streptococci may recover by their own powers, as in one case investigated by the writer which had no special treatment; but the patient in this instance never presented very grave symptoms. In all except two instances the method was adopted as a last resort, too late for any hope of success.

Some details of technique suggest themselves as a result of the trial of this method. The treatment should be commenced as early as possible. Donors of the same group as the patient are probably to be preferred.

The transfusion should be done very slowly to prevent a sudden overfilling of the venous system with a consequent transudation into the serous cavities. Such transudations might be rapidly converted into purulent fluids owing to the presence of circulating pyogenic organisms. For this reason, prior to the transfusion, bleeding the patient is, perhaps, advisable if his condition permits.

Care should be taken to guard against the formation of small clots during the transfusion in order to prevent the formation of septic emboli.

The cases of chronic suppurative infections of wounds which were treated by this method all made a rapid and satisfactory recovery.

Precise evidence as to the value of the treatment in these conditions is lacking, but the fact remains that the patients were in a stationary and chronic condition before the adoption of the method, and that the wound surfaces appeared to become rapidly more healthy, to heal quickly, and the discharge to diminish after the treatment had been instituted.

The use of the method in civil practice may be rather limited by the difficulty in obtaining suitable donors. It seems worthy of further trial and may prove of value in the treatment of malignant endocarditis, acute and chronic suppurative bone or joint infections, or puerperal septicaemia.

I am indebted to Lieut.-Colonel S. G. Butler, D.S.O., R.A.M.C., for permission to use the notes of these cases, and desire to emphasize my acknowledgements to Major Taylor, R.A.M.C., Officer in Charge Surgical Division, and to the surgeons to whose skill and care the success in the treatment of certain of these cases was largely due.

REFERENCES.

- 1 Ransom Hooker, *Ann. of Surg.*, vol. lxvi, 1917, November, p. 513.
- 2 Heyd, quoted by L. B. Robertson, *Lancet*, 1918, i, p. 761.
- 3 McClure and Dunn, *Bull. Johns Hopkins Hosp.*, xxviii, 1917, p. 99.
- 4 Lee, *BRITISH MEDICAL JOURNAL*, 1917, ii, p. 686.