Other Substances.—None of the 431 urines contained blood, sugar, bile pigments, or urobilin; 4 contained urobilinogen and considerable porphyrins. A large amount of albumin was present in 1 and a faint trace in 107. Porphyrins were found in 10% more of the albumin-free specimens than of those containing albumin, suggesting that albuminuria is not a factor in the production of porphyrinuria.

Comments

Routine examination for crude porphyrinuria should provide a guide to the progress and cure of actual cases of T.N.T. poisoning, and its detection might assist in confirming the diagnosis in suspected cases. The incidence of porphyrinuria found in the series of 431 workers in contact with T.N.T. suggests that it is probably present during the development of symptoms—and possibly for some time—while the worker's health is subnormal and before disablement compels him to cease work. Routine testing of T.N.T. workers for porphyrinuria might reveal those being affected deleteriously by the T.N.T. in the pre-disablement stage—i.e., before symptoms compel them to report unfit. By this means workers specially susceptible or hypersensitive to T.N.T. would be known. The rapid simple method of liberating the crude porphyrin mixture detailed above would suffice for this purpose. By classifying the results as ++, +, ±, or 0, as explained above, we obtain a rough measure of the degree of porphyrinuria. Removing positive workers from contact should improve health and efficiency; but until a further survey, to include the clinical examination of positive workers, has been undertaken we would suggest that ++ and + workers might be removed and ± workers watched and tested again.

We consider this rapid test for crude porphyrinuria in T.N.T. workers yields information unobtainable from the Webster test and might usefully replace it.

In acute porphyria following sulphonal, trional, veronal, etc., abdominal pain, vomiting, constipation, and jaundice occur, and the severe toxic manifestations after use of the benzene-sulphonamide drugs include headaches, giddiness, drowsiness, sickness, vomiting, cyanosis, colic, anaemia, and jaundice; even a dermatitis sometimes occurs. Long and Bliss (1938) discussed these toxic manifestations in 335 patients, and Rimington (1939) noted that the sulphonamide drugs which caused increased porphyrin excretion could also form methaemoglobin *in vivo*. Though congenital porphyrinurias are light-sensitive, photosensitivity is absent in idiopathic porphyria developing about the thirtieth year. The close resemblance of all the above symptoms to those met with in T.N.T. poisoning is noteworthy, as is the chalky or greyish pallor of countenance, accompanied by lilac-grey cyanosis of lips and margins and lobes of ears, which constitutes the T.N.T. facies.

While T.N.T. workers may suffer in health, only a small proportion become disabled and cease work. Many factors may contribute to this immunity—e.g., selection of workers, working conditions, medical supervision, acuteness of symptoms, and diet. Some may have a constitutional idiosyncrasy to T.N.T., just as some people are intolerant of certain drugs—e.g., the benzene-sulphonamide group, in which toxic symptoms are accompanied by porphyrinuria also. No conclusive explanation, however, has yet been given why some get poisoned and others do not. Moore and others (1917, 1921) showed that some animals varied in their tolerance for T.N.T. and that absorbed T.N.T. in man was finally excreted as an ester of glycuronic acid; hence the suggestion that all workers in toxic nitro-compounds of benzene, phenol, or toluene should take a diet yielding a good supply of glycuronates—fresh vegetables and fruit as in antiscorbutic diet.

The fact that porphyrinuria is an accompaniment of the T.N.T. toxic state suggests the possibility of another food deficiency playing a part. As Spies *et al.* (1938) point out, nicotinic acid appears to have a fundamental role in porphyrin metabolism, the porphyrinuria of pellagra and of other diseases being decreased after its administration. The general toxic state, with porphyrinuria, from the sulphonamides is benefited by it. Its exact role in body nutrition is not clear, but a well-balanced diet should contain an adequate supply to maintain health. As milk, cheese, eggs, and meat contain nicotinic acid, and yeast, wheat germ, and liver are especially rich in it, their

inclusion in T.N.T. workers' diet might be beneficial. Their diet before taking up T.N.T. work may not have been very well balanced and rich in this substance, or may have just sufficed for the requirements of ordinary life and work; but with exposure to T.N.T. the demand for the protective factor may be too great for the limited supply in the customary diet, and so the greater susceptibility of new T.N.T. workers to become toxic might be explained. Workers with longer service are probably better off economically, and so may have taken more suitable food over a longer period.

While the administration of vitamin C (ascorbic acid) may be desirable on general grounds, there seems reason for thinking that the vitamin B complex, and particularly nicotinic acid, might be a better protective factor. The effect of administering nicotinic acid to toxic T.N.T. workers, with porphyrinuria, in the pre-disablement stage awaits opportunities for trial. Incidentally, the anorexia, etc., and abdominal symptoms from which toxic T.N.T. workers suffer in the pre-disablement stage, and which are met with in other toxic conditions with porphyrinuria, may explain an occasional complaint against factory canteen food.

Acknowledgments are due to the Welsh Board of Health, Sir David Munro (C.M.O., Ministry of Supply), and Dr. J. H. Watson.

REFERENCES

- Brownlee, G. (1939). *Proc. roy. Soc. Med.*, **32**, 1276.
 Dobriner, K., Rhoads, C. P., and Hummel, L. E. (1938). *J. clin. Invest.*, **17**, 125.
 Ingham, J. (1941). *Lancet*, **2**, 554.
 Long, P. H., and Bliss, E. A. (1938). *Ann. Surg.*, **108**, 808.
 Moore, B. (1917). *Med. Res. Cttee. Sp. Rep. Ser.*, No. 11, London.
 — and others (1921). *Ibid.*, No. 58, London.
 Rhoads, C. P., and Barker, W. H. (1938). *J. Amer. med. Ass.*, **110**, 794.
 Rimington, C. (1939). *Proc. roy. Soc. Med.*, **32**, 351.
 — and Hemmings, A. W. (1938). *Lancet*, **1**, 770.
 Spies, T. D., Bean, W. B., and Stone, R. E. (1938). *J. Amer. med. Ass.*, **111**, 584.

INCOMPATIBILITY IN HOMOLOGOUS TRANSFUSION

BY

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AND

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Severe reactions seldom occur after a first transfusion. A case recently observed by us may therefore justify the following report, especially as the examination of the patient's serum threw light on the particular features apparently responsible for the reactions.

Case Report

A woman aged 36 was admitted to the Rotunda Hospital on Aug. 19, 1941, and was discharged on Sept. 8. She had been married 15 years and had had 4 children, the last pregnancy being in 1937: She came complaining of uterine haemorrhage for the past 5 weeks. Previous to that she had had no menstrual troubles. Examination of her chest revealed no abnormalities. Her blood pressure was 125/80. Bimanual examination showed that the uterus was large and retroverted and there was bleeding. She was anaemic, her haemoglobin being 40% and the red cells 2,120,000 per c.mm. Her blood group was O. A diagnostic curettage produced thick polypoid specimens, and histological examination showed glandular hyperplasia, a few of the glands being cystic. An enlarged left ovary was felt, and her condition was diagnosed as "metropathia haemorrhagica" and hysterectomy advised.

As she was so anaemic a transfusion of a pint of blood from a Group O donor was administered at drip rate on Aug. 22. She had never had a previous blood transfusion. On the 23rd a severe haemolytic reaction developed, her temperature rose to 102.4° F., and her pulse rate increased from 90 to 120. She was slightly jaundiced, and on that day passed only 1 oz. of urine. Intravenous injections of glucose-saline at drip rate

were given, and next day 8 oz. of urine was passed; after that she soon became normal again. Her jaundice was very definite, and her serum was icteric in appearance, with an indirect positive van den Bergh reaction. Her urine was rather dark, but was not examined spectroscopically for methaemoglobin. For about 48 hours her condition gave rise to anxiety.

Serological Investigation

According to the information available, cross-matching before transfusion had shown no incompatibility. The result was, however, different when we had the opportunity of repeating the examination eight days after transfusion. It was beyond doubt that both the patient's and the donor's blood belonged to Group O. The only uncommon phenomenon on this re-examination was the agglutination of the donor's corpuscles by the patient's serum. The agglutinating action of the patient's serum on the donor's corpuscles was titrated by mixing equal amounts of serum dilutions and of an approximately 1% suspension of the donor's corpuscles; the result was noteworthy in two respects: (1) the titre of the irregular iso-agglutinin was rather high—1:64 at room temperature; and (2) the titre was increased to 1:128 when the tubes were kept in the incubator at 37° C.

Examination of other blood samples belonging to Group O showed that many corpuscles were agglutinated by the patient's serum, though in different degree. The serum yielded marked agglutination with corpuscles of 87 (75%) out of 116 Group O persons. On the other hand, 44 other sera did not agglutinate the donor's corpuscles or such O corpuscles as were agglutinated by the patient's serum. The conclusion must be drawn, therefore, that the uncommon behaviour is due to a peculiar property of the patient's serum. In these circumstances the possibility had to be considered whether the patient and the donor belonged to different types within the M-N system, although anti-M and anti-N antibodies are hardly ever present in human serum and are usually not produced by iso-immunization in man. Actually the patient's and the donor's bloods belonged to different types, the patient's corpuscles containing the factor M, the donor's corpuscles the factor N. The use of anti-M and anti-N sera as well as tests with the patient's serum showed, however, that there was no agreement either between the action of the patient's and anti-M serum or between that of the patient's serum and anti-N serum. The possibility that the accident following transfusion and the presence of irregular iso-agglutinins in the patient's serum was caused by the interference of anti-N agglutinins may therefore be excluded.

Discussion

The iso-agglutinin observed is different from many irregular iso-agglutinins in the fact that it acts in the warmth at least as strongly as in the cold. While other agglutinogens, apart from those characterizing the A-B and the M-N system, share the widespread distribution in human blood with the agglutinin observed by us, they have hardly ever caused a severe reaction after transfusion. In the older literature, however, observations are recorded which indicate that irregular agglutinogens may play an important part in this respect. References to these are given by Wiener (1939). A case reported by Zacho (1936) may be mentioned because of the impressive similarity to our observations. It concerned a pregnant woman who received some transfusions of homologous blood (Group A) and died after a severe haemolytic reaction following on transfusion. Cross-matching tests, made after the accident, showed that the patient's serum agglutinated the corpuscles of two of the three donors. This irregular agglutinin acted most strongly at 37° C., its activity declining with a decrease in temperature. 60% of the blood samples examined (Groups O and A) were agglutinated by the patient's serum. Zacho speaks, therefore, of an irregular agglutinin acting on a hitherto unknown agglutinin.

In this connexion, however, the question must be considered whether the iso-agglutinin playing an important part in our case and in others might not be the same as that discovered by Landsteiner and Wiener (1940) and designated the "Rh factor." This Rh factor is specific for monkey (rhesus) blood and is present in about 85% of human blood samples. On immunizing rabbits or, better still, guinea-pigs with rhesus corpuscles, as was recommended later by Landsteiner and

Wiener (1941), antisera are obtained which after absorption with selected human bloods or even after simple dilution act only on human blood corpuscles which contain the Rh factor. The difference between the percentage of Rh-positive samples and the agglutination of blood samples by the patient's serum in our case or in that reported by Zacho need not be of much significance, for it is understandable that the immune serum used by Landsteiner and Wiener has a greater activity than human sera. Moreover, the patient's serum was withdrawn in our case at different times up to six weeks after transfusion, and the agglutinating power decreased by degrees rather quickly. The calculated percentage in our examinations (75%) refers, however, to the total of all tests, so that it may be considered as an average.

According to the papers recently published by Wiener and Peters (1940), Wiener and Schaefer (1940), Levine and Katzin (1940), Levine, Katzin, and Burnham (1940, 1941), and Wiener (1941), the Rh factor is hereditary. When, therefore, the foetus has inherited the Rh factor from the father, and the mother has not this factor, iso-immunization of the mother may occur from the foetus *in utero*, so that anti-Rh antibodies are produced in the mother. They may, on the one hand, penetrate the placental barrier and in such a way induce erythroblastosis foetalis, as Levine, Katzin, and Burnham (1941) have assumed. On the other hand, their presence in the mother may be the reason that at the first transfusion accidents occurred which have been described especially in intra-partum or post-partum cases. In the same way it is understandable that reactions following repeated transfusion of homologous blood may happen when the patient is Rh-negative and the donor Rh-positive.

As in our case the severe reaction followed the first transfusion, it must be assumed that, if the irregular iso-agglutinins correspond to the Rh antibodies, the patient was immunized during pregnancy. Because of the heredity of the Rh factor the conclusion was reached that the patient's husband must be Rh-positive. Unfortunately the husband's blood was available only about six weeks after transfusion, at a time when the irregular iso-agglutinins of the patient's serum were already very much weaker. Nevertheless it was possible, by freezing the serum and using the layers at the bottom of the frozen serum—a method successfully utilized by O'Meara (1933) for concentrating iso-agglutinins—to obtain a concentrated fluid from the patient's serum which agglutinated the husband's blood corpuscles, also belonging to Group O, distinctly. In this way it could be shown that the iso-agglutinogens, the antibodies of which were in the patient's serum, were present in the husband's corpuscles. Thus it seems justifiable to assume that the irregular iso-agglutinins in the patient's serum may have been the consequence of an iso-immunization of the patient during pregnancy. The children's corpuscles, however, were not available for testing against the mother's serum.

Conclusion

It must be emphasized that the identity of the irregular iso-agglutinin observed in our case with the anti-Rh agglutinin has not been proved, because a known anti-Rh serum was not available for our examinations. Nevertheless, the activity of the agglutinin in the warmth, the frequency of the corresponding agglutinin among the population, and the fact that the irregular iso-agglutinin was detectable only after transfusion for a relatively short period and not on cross-matching beforehand, may favour assumption of interference by anti-Rh antibodies and Rh antigens. The peculiarities correspond to those referred to by the American authors, particularly by Wiener. On the other hand, the fact must be stressed that reactions caused by the interaction of Rh-positive blood and its antibodies are described only on repeated transfusion or in women who had recently given birth or had had a miscarriage or a stillbirth. Our patient had had children. It must be borne in mind, however, that the last birth occurred four years before transfusion. This interval is too long for this case to be identical with the reported cases in which the Rh antigen was responsible for severe reactions after the very first transfusion in intra-partum or post-partum patients. Nevertheless, it is questionable whether this is an essential difference. If it be assumed that the readiness to produce antibodies may

remain after pregnancy of an Rh-negative mother bearing an Rh-positive child, this state of allergic reactivity may exist for very different periods of time, dependent on individual peculiarities and perhaps also on non-specific stimulations which the organism received in the meantime. From these considerations we do not believe that we are entitled to exclude the possibility that in our case the irregular iso-agglutinin which was responsible for the reaction following a first transfusion was an anti-Rh agglutinin.

Summary

A severe haemolytic reaction was observed following a first transfusion of homologous blood (Group O). Although no incompatibility was noted on cross-matching before transfusion, the patient's serum strongly agglutinated the donor's corpuscles on re-examination eight days after transfusion.

While the irregular iso-agglutinin present in the donor's corpuscles was found in 75% of O corpuscles examined and also in the blood of the patient's husband, the irregular iso-agglutinin was apparently a peculiar feature of the patient's serum.

The irregular iso-agglutinin was not identical either with anti-M or anti-N antibodies. It acted more strongly in the incubator than at lower temperatures. It had at first a relatively high titre, but weakened quickly within six weeks.

The question is discussed whether the irregular iso-agglutinin observed is the same as the anti-Rh antibody.

One of us (H. S.) wishes to acknowledge his gratitude to the Medical Research Council of Ireland for the grant which he is holding, and to Prof. O'Meara for all facilities in the Department of Bacteriology at Trinity College.

REFERENCES

- Landsteiner, K., and Wiener, A. S. (1940). *Proc. Soc. exp. Biol.*, N.Y., **43**, 223.
 — (1941). *J. exp. Med.*, **74**, 309.
 Levine, P., and Katzin, E. M. (1940). *Proc. Soc. exp. Biol.*, N.Y., **45**, 343.
 — and Burnham, L. (1940). *Ibid.*, **45**, 346.
 — (1941). *J. Amer. med. Ass.*, **116**, 825.
 O'Meara, R. A. Q. (1933). *J. Path. Bact.*, **37**, 166.
 Wiener, A. S. (1939). *Blood Groups and Blood Transfusion*, Baillière, London.
 — (1941). *Arch. Pathol.*, **32**, 227.
 — and Peters, H. R. (1940). *Ann. intern. Med.*, **13**, 2306.
 — and Schaefer, G. (1940). *Med. Clin. N. Amer.*, **24**, 705.
 Zacho, A. (1936). *Z. Rassenphysiol.*, **8**, 1.

MULTIPLE SMALL- AND LARGE-GUT INJURIES: RECOVERY

BY

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Reliable statistics regarding mortality are available for patients suffering from small-gut injuries who have been submitted to laparotomy. In Sir Cuthbert Wallace's *War Surgery of the Abdomen* a series of 255 cases of injury to the small intestine and its mesentery are recorded, the death rate being 65.9%. Where small-gut injuries were complicated by concomitant wounds of the colon the death rate rose to 74%. It is stated on page 225 of *Surgery of Modern Warfare*, edited by Hamilton Bailey, that "recent experiences in 1940 in no way refute the grave view of wounds of the large bowel that was entertained twenty years ago." In view of the high mortality (74%) of injuries to the small gut combined with colonic wounds, the record of the following case may hold some interest.

Case History

The patient was a schoolboy aged 10. At 5.45 p.m. on April 23, 1941, he was accidentally shot at two yards' range from a 0.22-bore Winchester rifle which was resting horizontally on his father's knee, the right side of the boy's body being towards the rifle. The boy received a wound in the right buttock. He was admitted to hospital at 6.30 p.m., profoundly shocked and apparently moribund. His temperature was 97° F. and his pulse uncountable and very thready; his B.P. was 80/60. The child lay on his left side with his knees and thighs flexed on the abdomen. No further examination was undertaken at this juncture.

Immediate resuscitatory measures were instituted. Morphine sulphate 1/6 grain was given hypodermically and a continuous plasma infusion begun. Two hours later his condition was much improved; the temperature was 97° F., pulse 150, and B.P. 100/80. Examination, with minimal disturbance, revealed an entrance wound in the right buttock, 1½ in. above and 1 in. posterior to the right greater trochanter. There was no exit wound. Abdominal examination left no doubt as to the presence of peritoneal irritation. He had an immobile guarded lower abdominal wall, with generalized tenderness and "release" pain. He passed 4 fl. oz. of urine. This was clear and contained no abnormality, and microscopy revealed no red blood cells. There was no evidence of injury to either the vessels or nerve trunks of the lower limbs. Examination of the whole abdomen, pelvis, and upper half of both thighs, including lateral views of the limbs, by portable x-ray apparatus, showed the presence of the bullet posterior to the left femur on a level with the lesser trochanter. No fracture of the bony pelvis was demonstrable.

At 9.45 p.m. his temperature was 98.6° F., pulse 140, and B.P. 100/70. A transfusion of 450 c.cm. of plasma had now been administered, being followed by whole-blood transfusion preparatory to and during laparotomy.

Operation

At 10 p.m. open ether anaesthesia was induced, with atropine sulphate 1/100 grain as premedication. As the entrance wound was readily accessible without turning the patient it was decided to proceed with the laparotomy. The abdomen was opened through a right subumbilical paramedian incision. The peritoneal cavity contained free blood, and several clots which were removed. Systematic examination of the small gut from above downwards revealed the following:

(1) Three perforations of the ileum within the terminal 3 ft. The two proximal of these were on the antimesenteric border, but the lowermost was at the junction of the bowel and the mesentery. Fortunately the latter was not damaged here or at any other point. These perforations were closed with purse-string sutures, using atraumatic intestinal catgut, the pouting mucosa being invaginated. Escape of intestinal contents here was minimal. (2) Perforation of the appendix. This structure was almost completely divided at its centre, a remnant of the mucosa adjacent to its mesenteric attachment serving to maintain continuity. Appendicectomy with invagination of the stump was performed. Proceeding with inspection of the colon, there were found: (3) two perforations of the antimesenteric border of the pelvic colon with semi-solid faeces oozing from both. There was, in addition, a longitudinal tear about 3 in. in length, involving only the serous coat of the lower pelvic colon. Again, fortunately, there was no injury to the pelvic mesocolon. These perforations were given treatment similar to that of the small-gut wounds, with an appendix epiploica oversewn as a further precautionary measure. The linear tear in the serous coat was repaired with a continuous suture.

The pelvis was cleared of clots and faeces, and a rapid examination was made, which showed no haemorrhage and no injury to the bladder. Powdered sulphanilamide, 3 gm., was dusted into the pelvis, which was drained. The abdominal incision was closed in three layers, with drainage to the rectus sheath.

The edges of the entrance wound made by the bullet were excised and a fragment of trouser material was removed. Devitalized muscle was then excised and the track was syringed with 1/1,000 euflavine solution and insufflated so far as practicable with sulphanilamide powder; the skin was closed with silkworm-gut sutures.

Antitetanus serum, 3,000 units, and anti-gas-gangrene serum, 8,000 units, were given intramuscularly. The blood transfusion was followed by two pints of 5% glucose-saline given by the drip method during the next twelve hours.

Progress

The next day the patient's temperature was 101° F. and his pulse 128. At 10.30 a.m. his bowel opened spontaneously; a soft partially formed stool showing no macroscopic blood was passed. As there was no vomiting, fluids were freely given by mouth. For the next three days 1 gm. of sulphapyridine was given three times daily. The pelvic drain was removed on April 25 and the one to the rectus sheath on the following day. There was only a slight superficial purulent discharge from the lower end of the abdominal incision; this lasted a few days. The entrance wound healed by first intention.

On April 27 a glycerin suppository resulted in the passage of a soft stool. Flatus was freely passed during the whole of the immediate post-operative period. On April 30 the patient's temperature was normal, and remained so for the next two