contact with the skin and the sites examined at regular intervals (see Table). Further investigations showed that a longer exposure time was necessary to produce a reaction when lower concentrations of the dye were used. It would thus appear that, within certain limits, there is an inverse relationship between the critical levels of exposure time and concentration.

Summary and Conclusions

Three female cases of contact dermatitis due to the aminoazotoluene component in green and red semi-solid inks are described. In each case the distribution of the rash and history of the case suggested an exogenous dermatitis, and this was proved by subsequent patch testing.

The time taken to produce epidermal sensitivity was closely comparable in the first two cases—six to eight weeks: in the third case the interval may have been longer.

A high degree of epidermal sensitivity to the dye has been shown in each case. An attempt was made to demonstrate critical levels of concentration and exposure times in Case 1.

The dye seems, however, to have a low sensitivity index, as only these three cases have so far been published, and yet about two million red and green ball-pointed pens are sold annually in Great Britain. Furthermore, in the manufacture of the ink there have been no cases of dermatitis among the 70 workers who are exposed each day.

We are indebted to Dr. W. N. Goldsmith for permission to publish Case 1, and to Dr. P. J. Hare for drawing our attention to Case 3. Messrs. Biro Swan Ltd., and their chemists, Dr. Rosin Industrial Research Co. Ltd., have been most helpful throughout the investigations, and to them we proffer our grateful thanks.

APLASTIC ANAEMIA OCCURRING EIGHT YEARS AFTER T.N.T. POISONING

BY

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Among the commoner clinical manifestations of trinitrotoluene intoxication are dermatitis, cyanosis, and gas-tritis. Toxic jaundice is less common and the incidence of aplastic anaemia is very small (Hunter, 1943). Despite the rarity of anaemia in T.N.T. workers a good many cases were reported in this country and in America during the two world wars. While most of these cases have had their onset during or immediately after a fairly long period of exposure, anaemia occasionally develops after a latent period free from exposure. Pantón (1917) described the clinical onset of aplastic anaemia in a patient whose exposure to T.N.T. had ceased nine months previously. Both toxic jaundice and aplastic anaemia may develop in the same patient, and Evans (1941) reported the occurrence of aplastic anaemia nine weeks after recovery from an attack of toxic jaundice.

The present communication concerns a patient who suffered from toxic jaundice after two months' exposure to T.N.T. in 1943, and developed a fatal aplastic anaemia early in 1951.

Case Report

The patient, a man aged 45, was employed as a maintenance engineer in a large motor works. Until 1943 he had worked as a builder and his health had always been good. In that year he started work in a filling factory, taking the usual precautions in handling T.N.T. and wearing a respirator. After two months' exposure he suddenly became ill with nausea, vomiting, and constipation which lasted for three weeks. He became jaundiced and the icterus persisted for two weeks. After full recovery he was employed in other departments of the same factory for a further two and a half years. During this period he worked with ammonium nitrate for six months, with aluminium dust for six months, on machine cleaning and maintenance for four months, and with ammonium nitrate again for six months.

After the war he worked for short periods in a brewery and an ice-cream factory before joining the motor works where he had been employed for the five years preceding his admission to hospital. His duties here involved much contact with machine-lubricating oils, and early in 1951 he suffered from an occupational dermatitis of his hands which lasted for two months. At this time he began to feel tired and lifeless, and anaemic symptoms of dyspnoea on exertion, lassitude, headaches, and muscular pains became increasingly severe during the next six months.

In July, 1951, a blood count was carried out with the following result: Hb, 7.3 g. per 100 ml.; red cells, 2,200,000; white cells, 5,200 (13% neutrophils, 84% lymphocytes, 3% monocytes). The smear showed considerable anisocytosis. The patient was admitted to Bedford General Hospital under the care of Dr. J. L. H. Easton. At this time there were no physical signs other than pallor, a few petechiae on the thighs, and hepatic enlargement to about 1 in. (2.5 cm.) below the costal margin. Investigations showed a normal bleeding-time but the platelets were scanty. The stools did not contain occult blood. There was a histamine-fast achlorhydria. The plasma protein levels and hepatic-function tests were within the normal range. A sternal marrow examination revealed aplasia of red cells and granulocytes, with some 60% lymphocytes. Treatment with iron, vitamin B₁₂, and "plexan" did not produce any reticulocytosis or haematological improvement, and transfusions of 5 pints (2.8 litres) of blood were given.

On August 17 the patient was transferred to Addenbrooke's Hospital under the care of Sir Lionel Whitby. He was very pale but not jaundiced or cyanosed. There was some sacral oedema but no oedema of the ankles. Lymph nodes could not be felt. There was a diffuse purpuric rash on both legs, with occasional purpuric spots on the trunk. The sternum was not tender on pressure. There was no koilonychia or clubbing. Cheilosis, sore tongue, and mouth ulceration were absent. Hess's capillary resistance test was positive. No other positive findings were encountered; the liver and spleen could not be felt. A blood count now showed: Hb, 7.4 g. per 100 ml.; red cells, 2,400,000 per c.mm.; P.C.V., 20.4%; M.C.H., 31 $\gamma\gamma$; M.C.V., 85 μ^3 , M.C.H.C., 36.4%; M.C.D., 7.1 μ ; reticulocytes, 0.1%; leucocytes, 1,700 per c.mm.; differential count, neutrophils 67 (stab cells 50, segmented 17), lymphocytes 1,600, monocytes 34 per c.mm.; platelets, 1,000 per c.mm.; E.S.R., 68 mm. in 1 hour, corrected to 18 mm. in 1 hour. Bleeding time was seven minutes and clotting-time 12–20 minutes on several occasions. Clot retraction was poor. The prothrombin content was 62% of average normal (Quick's one-stage method).

A sternal marrow examination on August 20 showed that the marrow was hypoplastic, with many lymphocytes and plasma cells, occasional tissue mast cells, and large numbers of degenerate cells. The differential count figures were: neutrophil polymorphs 2.4%, eosinophils 0.6%, metamyelocytes 3.6%, myelocytes 4.2%, promyelocytes 1.4%, lymphocytes 66.8%, plasma cells 7.4%. Normoblasts 12.2% (early 1.2%, intermediate 4%, late 7%), proerythroblasts

0.4%, tissue mast cells 1.2%. The degenerate cells were not included in the differential count, but they often contained phagocytosed pigment and may have been chiefly reticulum cells.

In view of the suggested relationship between tissue mast cells and marrow aplasia (reviewed by Fadern, 1951), the possibility that the prolonged clotting-time might be due to hyperheparinaemia was considered, and it was found that the clotting-time could be returned to normal by the addition *in vitro* of a suitable quantity of protamine. Protamine sulphate was given intramuscularly to the patient in doses of 40 mg. four times daily for three days, but had no effect on the clotting-time, and was discontinued.

The haemoglobin level fell steadily at the rate of 1 g.% every five to seven days, and there were several severe epistaxes during the first two weeks after admission. A small abscess under the chin developed, and the cervical glands enlarged, but this was controlled by systemic penicillin. Small transfusions were given at frequent intervals, but no evidence of marrow activity was evinced. The leucocyte count fluctuated between 750 and 3,000 cells per c.mm., with neutrophils from 10 to 150 per c.mm. The platelets varied between 1,000 and 20,000 per c.mm.

On September 8 a course of A.C.T.H. was started, 100 mg. daily in divided doses being given for 10 days. No effect was produced on either the clinical condition or the haematological state.

On September 22 severe frontal headache developed, accompanied by nausea and vomiting. Slight neck rigidity and a small retinal haemorrhage in the right fundus occurred, but no other abnormalities were found in the central nervous system. Within 12 hours the breathing suddenly became stertorous and unconsciousness followed. Both pupils were contracted to pin-points and did not react to light. The arms were flaccid, but with tendon reflexes still present and equal. After a short period of coma the patient's respiration failed completely and he died.

Post-mortem Examination.—A large spreading haemorrhage was found extending throughout the left cerebellar hemisphere and breaking through on to the surface. The meninges appeared normal. There was evidence of sub-mucosal haemorrhage throughout the small intestine and in the renal pelvis and ureter on the right side. The haemopoietic marrow of the femur was completely replaced by yellowish fat, and the marrow of the sternum and vertebrae was also very pale and suggestive of hypoplasia. The spleen and liver were congested and gave a positive Prussian blue reaction. Histologically the bone marrow contained very few cellular elements, and these were mostly lymphocytes and normoblasts. The liver showed a few scattered areas of large droplet fatty change, but there was no sign of fibrosis. Apart from congestion and scattered haemorrhages there were no other striking abnormalities in any organs.

Discussion

This case history presents an unusual combination of facts. There is no doubt that the patient was exposed to T.N.T. and developed a toxic jaundice in 1943, that he was later subject to an occupational dermatitis of the hands after working with machine oils in 1950, and that he died in 1951 from an aplastic anaemia. The relationship between these episodes is largely a matter for conjecture. There seems to be no known association between exposure to oil and the development of haematological disorders, and it is difficult to believe that T.N.T. could still exert a delayed effect after eight years. The most likely explanation of the circumstances in the light of present knowledge is that the anaemia was a coincidental primary marrow aplasia, unconnected in any causal way with the toxic agent to which the patient had previously been subjected. It is not impossible, however, that other cases of long-delayed anaemia may have occurred after T.N.T. poisoning and been dismissed as coincidental primary disorders, and it is hoped that this report may stimulate publication of such case histories if they exist.

Summary

The case is reported of a patient who suffered from toxic jaundice after exposure to T.N.T. in 1943, who developed an oil dermatitis in 1950, and who died from aplastic anaemia in 1951.

The possible relationship between these episodes is discussed.

I am grateful to Sir Lionel Whitby, regius professor of physic in the University of Cambridge, for permission to report this case.

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HAEMOPHILIA WITH RESPIRATORY OBSTRUCTION

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Among the more serious hazards of the haemophilic patient's life is haemorrhage into the tissues of the mouth, pharynx, and larynx. Fortunately, this seems to be an uncommon site for bleeding to occur; indeed, we have been able to trace only 14 cases in the literature since 1910. Of these, 11 suffered from respiratory obstruction of varying degree. A survey of the records of the Western Infirmary, Glasgow, makes us wonder, however, if this is not a more common complication of haemophilia than that number of published cases leads one to believe. During the period 1936–51 34 haemophiliacs were treated: as so often happens, many had to be admitted more than once with haemorrhages at different sites, the total number of episodes being 112. Three instances of oral bleeding each associated with respiratory obstruction were found, and it was noted that blood transfusion and other medical measures were enough to bring the condition under control.

The following report concerns another case which came under our care at the same hospital. The problem that confronted us was to decide how best to combat the threat of suffocation. It was the feeling of all who saw the patient that surgical intervention was imperative, and a relief incision was made under the chin. As we hope to show, however, the maintenance of a clear airway by means of an indwelling endotracheal tube was probably the measure that really saved the patient's life.

Case Report

A youth aged 16, a known haemophiliac, was admitted to hospital on September 11, 1951. On the previous day he had complained of pain and a swelling under his tongue, and the swelling had gradually increased in extent. No injury or sepsis had been present to account for the lesion, though one molar tooth was carious and roughened.