CONTACT DERMATITIS DUE TO AMINOAZOTOLUENE

BY

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Recently we have encountered, quite independently, three cases of contact dermatitis due to the yellow aniline dye aminoazotoluene. This dye, which is readily soluble in fats and waxes, is a constituent in the red and green semi-solid inks used in a popular ball-pointed pen. It is also used in certain popular shoe polishes. We have been unable to trace any previous reference to cases of dermatitis caused by exposure to aminoazotoluene.

Case 1

A hospital nurse aged 21 suffered from an irritant rash on the ulnar aspect of both forearms, but worse on the right, for three weeks. It consisted of an irregular area of erythema with papules and papulo-vesicles. The appearances suggested a dermatitis due to something contacted during her work. When she stopped work for a week the rash improved considerably, but recurred during a period of study when she was not doing any ward work. This second attack showed similar features, except that there was a raised erythematous linear lesion on the left forearm. The patient readily remembered that this was where she had scratched herself with the point of her red-ink pen. She had been using this ball-pointed pen for about six weeks before the eruption started.

In view of these findings patch tests were done using various colours of semi-solid ink of the same make. It was found that, while the red and green inks gave a positive result in 24 hours, there was no reaction to the blue and black inks. The manufacturers of this pen kindly supplied the information that the only substance common to the red and green inks, and not used in any other of their inks, was the yellow dye—aminoazotoluene. A further controlled patch test, using 0.01% aminoazotoluene in yellow soft paraffin, gave a positive reaction after 24 hours' contact.

From these results it appeared that the patient's eruption was due to skin sensitization to aminoazotoluene. The dermatitis healed within four weeks of ceasing to use the red-ink pen, and has not reappeared.

Case 2

A clerk aged 24 stated that she had suffered from a rash on her hands for five weeks, and was advised by her doctor to stay off work. Under his care the rash disappeared in two weeks, but returned on the evening of her first day back at work. She attended hospital four days later.

On examination she was found to have a dry papulo-vesicular eruption along the ulnar border of the right hand and little finger, and on the medial aspect of the tips of her third and fourth fingers. The skin around the left eye showed slight oedema and fine superficial scaling. The clinical picture suggested a contact dermatitis of occupational origin.

It was learnt that she was in contact with green semi-solid ink and carbon paper during her work, and before the second attack had accidentally smudged some green ink on her right upper eyelid. Whilst convalescing from the first attack at home she had used without mishap a similar ball-

pointed pen containing blue ink. She had used a green-ink pen for six weeks before the initial skin eruption developed.

Patch tests to blue semi-solid ink and carbon paper were negative after 48 hours, but there was a brisk response to the green ink.

The manufacturers kindly sent a sample of the yellow dye present in green and red semi-solid inks but absent in the blue ink. The illustration shows the results of different strengths of this dye (aminoazotoluene) diluted in arachis oil and left on the skin for 48 hours. After these results a patch test of aminoazotoluene 0.01% produced a distinct erythema

Dermatitis caused by aminoazotoluene. Percentages indicate strength of dye used.

after only 24 hours' contact. The patch tests, which were all controlled, did not cause any exacerbation of the original dermatitis.

Case 3

A lady clerk aged 52 had suffered from an itching eruption of the anterior aspect of the right wrist for over a year. A few weeks before attending hospital it had spread up the forearm and also appeared on the eyelids. She had used a red-and-blue ball-pointed pen for about two years, and her work involved contact with accounts written in these same inks.

Patch tests read after 24 hours showed she, too, was sensitive to the red and green but not to the blue semi-solid ink. Subsequently a positive reaction was obtained after 24 hours' contact with 0.01% aminoazotoluene in yellow soft paraffin. This eruption cleared up 10 days after she stopped using the red ink, and had not recurred eight months later.

Special Investigations on Case 1

As this patient appeared to be extremely sensitive to this azo dye, further investigations were carried out to determine the critical levels of concentration and exposure time for the skin reaction to occur.

Determination of Threshold Concentration.—The following patch tests were done with decimal dilutions of aminoazotoluene in yellow soft paraffin. The patches were removed after 24 hours, and the sites of contact subsequently examined at regular intervals.

0.1%	..	..	..	Positive at 24 hours
0.01%	..	..	..	" " 28 "
0.001%	..	..	..	" " 72 "
0.0001%	..	..	..	No reaction noted

Determination of the Threshold Period of Contact.—Aminoazotoluene (0.1%) in yellow soft paraffin was used in each case. Patches were removed after differing periods of

Test No.	Patch Contact Time	Reactions Observed After Certain Intervals of Time Recorded in Hours					
		9	12	21	37	45	72
1	5 minutes	—	—	—	—	—	—
2	10 "	—	—	—	—	—	—
3	30 "	—	—	—	—	—	—
4	1 hour	—	—	—	—	—	—
5	3 hours	—	—	+	+	++	+++
6	6 "	—	+	+	++	+++	+++
7	9 "	—	+	+	+++	+++	+++
8	12 "	—	+	++	+++	+++	+++

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