

Medical Memoranda

Sensitivity Reaction to Phenindione with Urticaria, Hepatitis, and Pancytopenia

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Sensitivity reactions to phenindione continue to be the subject of increasing concern (*Medical Letter*, 1962; *B.M.J.*, 1963; *Drug and Therapeutics Bulletin*, 1963, 1964). The fact that, until recently, there was no national registry for recording adverse reactions makes it difficult to assess the true frequency of such reactions, and individual experience has suggested an incidence as widely divergent as 0.1% (Ager and Ingram, 1957) to 10.7% (Stafford, 1961) of the patients treated. Perkins (1962) was able to review 138 cases; the large majority had skin sensitivity, but there were 10 patients with agranulocytosis, five with nephropathy, 10 with hepatitis, and two with thrombocytopenia. Diarrhoea, with or without steatorrhoea, was present in 20 cases, and recently Kerwin (1964) has reported a fatal myocarditis.

Anaemia has been noted on two occasions (Makous and Veer, 1954; Johnman, 1957), but data regarding its nature are scanty, and indeed the latter publication contains contradictory statements regarding even the presence of anaemia. This report describes a patient with sensitivity reactions to phenindione, including hepatitis, thrombocytopenia, agranulocytosis, and probable erythroid aplasia.

CASE REPORT

A 55-year-old man was admitted on 23 February 1963 with atherosclerotic heart disease, congestive cardiac failure, deep-vein thrombosis, and pulmonary embolization. He received digoxin, phenindione, phenobarbitone, mersalyl, and chlorthalidone (Fig. 1). On the fourth day penicillin was added for a purulent sputum. On the eighth day a scanty, discrete, pruritic, erythematous eruption

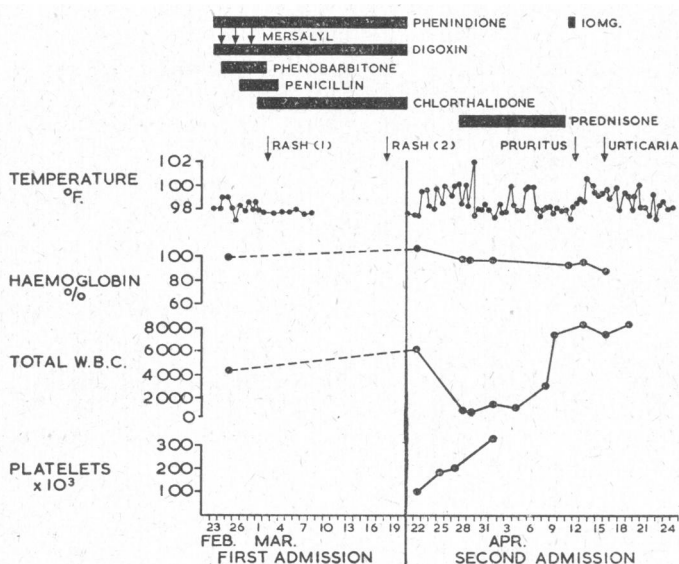


FIG. 1.—Temperature chart, blood values, and details of drugs administered during first and second hospital admissions. Note: (1) onset of "minor" rash (rash 1) on eighth day and "major" rash (rash 2) on twenty-fourth day of phenindione therapy; (2) progressive serial involvement of platelets and white cells with slow gradual fall in haemoglobin; (3) recurrence of pruritus, pyrexia, and urticaria with a "provocative" dose (10 mg.) of phenindione.

appeared over the hands and the face. At first the phenobarbitone and later the penicillin were withdrawn. The rash gradually regressed, and he was discharged on the fourteenth day on digoxin, chlorthalidone, and phenindione.

Ten days later he developed an extensive pruritic erythematous eruption progressing to giant urticaria of the face and neck. There was striking faucial injection with scanty petechiae, marked dysphagia, and profuse watery diarrhoea. The liver was enlarged two fingerbreadths, but there was no lymphadenopathy or splenomegaly.

The results of investigations showed haemoglobin 110% (Sahli); white blood cells 6,300/c.mm. (neutrophils 79%, lymphocytes 21%); platelets 100,000/c.mm. The Hess test was positive; throat swabs, stool cultures, and the Widal test were negative. There was a trace of albumin and a moderate excess of urobilinogen in the urine; blood urea was normal; the prothrombin time was 22 seconds (control 15 seconds). Tests for L.E. cells were negative, and liver-function tests showed moderate impairment (see Table). Within a few days when the platelet count was rising spontaneously the W.B.C. count fell to 800/c.mm., with a virtual absence of neutrophils, 31% eosinophils, 1% basophils, 67% lymphocytes, and 1% monocytes. Two bone-marrow aspirates consisted almost entirely of peripheral blood with 1% myelocytes, 2% plasma cells, and 4% normoblasts.

Abnormality in Liver-function Tests in Present Case (Case 14) Compared with Values in 13 Other Cases Reported in Literature

Case	Bilirubin (mg./100 ml.)	Alkaline Phosphatase (K.A. Units)*	Serum (g./100 ml.)		Thymol Turbidity	S.G.O.T. (Frankel Units)†		Excess Urinary Urobilinogen
			Albumin	Globulin				
1 (Kirkeby, 1954)	3.7		3.3	2.3	—			
2 (Makous and Veer, 1954)	14	28	3.1	2.3	+			
3 (East and Beamish, 1957)	1.5	19			+			
4 (Burns and Desmond, 1958)	4.0	29			—			
5 (Brooks and Calleja, 1960)	4.4							
6 (Jones, 1960)	1.2	8			—	60		+
7 (Wallace, 1960)	11.0	22			—			+
8	5.3	32	3.3	1.4	—	45	144	
9	2.3	46	2.9	3.2	—	35	14	
10 (Portal and Emanuel, 1961)	5.1	24	3.9	3.9	—			
11	4.0	31			—	350	700	+
12 (Perkins, 1962)	3.7	51			—	650	550	+
13 (Baker and Williams, 1963)	5.4	20			—	30	76	
14 (Present case)	0.8	18	2.0	2.7	—	55	115	+

* Case 2, Bodansky units. † Case 6, King units.

Treatment with prednisone 60 mg. daily resulted in a dramatic improvement with gradual resolution of the rash, fever, and the diarrhoea, and the W.B.C. rose to normal (Fig. 1) with a transient eosinophilia of 600/c.mm. The haemoglobin fell to 88%, though at the time the significance of this was not appreciated. The results of the liver-function tests gradually reverted to normal, with the exception of a persistent hypoalbuminaemia of 2 g./100 ml.

The prednisone was gradually withdrawn after five afebrile days. A "provocative" test dose of phenindione, 10 mg., was then administered by mouth. Within 24 hours there was a recurrence of fever and a pruritic erythematous rash with urticaria over the face which, however, settled with promethazine alone.

The patient remained well but the haemoglobin had fallen to 59% Sahli (P.C.V. 26%; M.C.H.C. 30%) a month later (Fig. 2).

Investigations showed W.B.C. 5,700/c.mm.; normal differential; slight hypochromia and polychromasia of the red cells; platelets 235,000/c.mm.; reticulocytes 2-4%; serum iron 106 µg./100 ml.; total iron-binding capacity 210 µg./100 ml.; serum albumin 3.5 g. and globulin 3.99 g./100 ml., and the blood sedimentation 80-100 mm. (Westergren) in the first hour. Radio-chromium red-cell survival was normal (26 days). Bone-marrow aspirates were cellular with normoblastic hyperplasia, there was a slight shift to the left of the myeloid series, a mild eosinophilia, and the plasma cells were at the upper limits of normal. An aspiration liver biopsy was reported as showing "inequality of the liver cell size denoting liver cell regeneration. Slight haemosiderosis; Kupffer cell hyperplasia. A diagnosis is not warranted, but the picture is compatible with the clinical suggestion of a Dindevan sensitization."

Tests for red-cell osmotic fragility and liver function were normal, and negative results were obtained for the Coombs test, faecal occult blood, urinary urobilinogen and haemoglobin, L.E. cells, and the anti-nuclear factor.

The haemoglobin rose spontaneously to 92% over the next six weeks (Fig. 2), and has been well maintained without treatment. The blood sedimentation gradually fell to 28 mm. over the next six months. In April 1964 he received treatment for congestive cardiac failure and primula dermatitis in another ward of this hospital. Results of relevant investigations were haemoglobin 107% Sahli; W.B.C. 4,100/c.mm.; albumin 3.5 g., globulin 3.8 g./100 ml.; alkaline phosphatase 6 King-Armstrong units; seroflocculation tests negative; bromsulphalein retention 11% at 45 minutes (normal 3%).

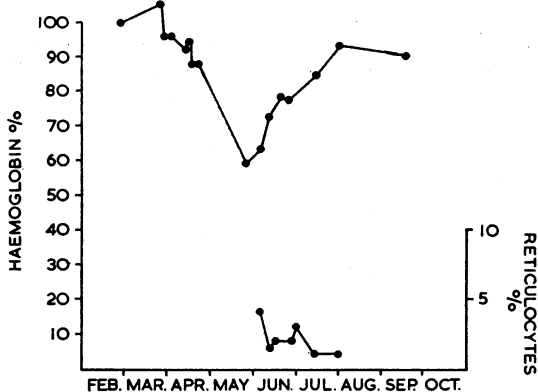


FIG. 2.—Haemoglobin level (% Sahli) and reticulocyte count throughout illness. Note: (1) progressive slow fall in haemoglobin from March till May; (2) spontaneous rise in haemoglobin to normal from June to August with low-grade reticulocytosis.

COMMENT

The striking feature of the sensitivity reaction in this patient was the graded progression of the various sensitivity phenomena. Thus, a transient erythematous rash comparable to the "minor" rash of Stafford (1961) on the eighth day of treatment was followed by a major rash on the twenty-fourth day with stomatitis, pharyngitis, irregular fever, thrombocytopenia, and diarrhoea progressing to agranulocytosis and biochemical evidence of hepatitis. The features of the latter were comparable to those reported in 13 other cases in the literature (see Table). The biochemical picture is variable and non-specific, at times favouring hepatocellular damage and in others a cholestatic process, in keeping with the liver histology recorded in the few cases examined.

Blood loss and haemolysis were excluded as possible causes of the anaemia, but the red-cell survival studies were carried out at a time when the haemoglobin was beginning to show a spontaneous improvement. While a transient haemolytic reaction cannot be excluded, the extent and the rate of fall in the haemoglobin level is considered to be explained more adequately on the basis of an aplastic reaction of the erythroid series. The known rates of turnover of the formed elements of blood and the striking progression of involvement of the thrombocytes, granulocytes, and erythrocytes would seem to suggest an aplastic reaction involving all three elements in the bone-marrow.

Burns and Desmond (1958) suggest that sensitivity reactions from phenindione may be due to the presence of the potentially toxic modified benzene ring in the compound. Söderberg and Wachtmeister (1956) demonstrated an interference with energy transfer mechanisms in experimental animals, and Perkins (1962) has suggested that this may be responsible for the toxic action of phenindione on the liver, kidney, and bone-marrow in man.

In one of the two cases of thrombocytopenia cited in the literature specific platelet agglutinins were demonstrated (Farwell, 1959). A rapid fall in haemoglobin in response to a "provocative" dose of phenindione, noted by Makous and Veer (1954) in their patient, suggested a haemolytic reaction. The haematological features in the present case are, however, best explained on the basis of a transient aplasia of the bone-marrow. The eosinophilia and the possible slight increase of plasma cells in the marrow are of note. An immunological reaction sometimes involving the formed elements directly and sometimes the precursors in the bone-marrow seems to be a reasonable alternative hypothesis for the mechanisms producing the varied haematological changes observed. What determines the site of immunization in the individual patient remains unexplained.

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