PHENINDIONE HEPATITIS COMPLICATING ANTICOAGULANT THERAPY

BY

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Many toxic effects of phenindione have been reported since it was introduced as an anticoagulant by Soulier and Gueguen (1947). These were reviewed by Burns and Desmond (1958) and more briefly by Bingle and Shine (1959). Fever, dermatitis, pharyngitis, and leucopenia are common reactions to phenindione therapy, but hepatitis is rare, and only six cases have been reported, none of which occurred in this country. The following three cases are therefore recorded, although their investigation was incomplete.

Case Reports

Case 1.—A man aged 58 started treatment with phenindione on November 14, 1959, after a myocardial infarction. Thirty-eight days later (December 22) he became febrile (up to 103° F.; 39.4° C.), with sore throat

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and diffuse maculopapular rash, and four days after this he was jaundiced. The fauces and pharynx were inflamed and there were enlarged painless lymph nodes in the neck, axillae, and groins. The liver was just palpable, but the spleen was not felt. Liver-function tests (see Table, No. 7) suggested cholestatic jaundice with slight cellular damage. There was a neutropenia with a white cell count of 4,000/c.mm. (neutrophils 6%, lymphocytes 84%, eosinophils 4%, monocytes 3%, plasma cells 2%, histiocytes 1%). Phenindione was stopped on admission to hospital (January 1, 1960) and intramuscular penicillin given. The rash faded within 10 days, and profuse generalized exfoliation followed; the enlarged glands regressed and the jaundice diminished. Fifteen days after the onset of icterus the serum bilirubin had fallen to 1.25 mg. and two days later to 0.6 mg./100 ml.

His recovery was complicated by pneumonia and anaemia; the pneumonia probably prolonged his fever, which lasted for 26 days.

Case 2.—A married woman aged 64 developed a venous thrombosis of the leg after a mitral valvotomy. Phenindione was started on August 26, 1960, and 18 days later she developed fever with a diffuse macular erythematous rash involving arms, knees, and the anterior part of the upper chest. Five days later nicoumalone ("sinthrome") was substituted for phenindione, but the fever (up to 103° F.;

Details of Cases

No.	Reference	Dose of Phenindione	Interval Between Start of Treatment and Onset of Jaundice	Duration of Jaundice	Drugs Given	Liver-function Tests	Other Features
1	Makous and Veer (1954)	266 mg. (average) for 14 days, then 2nd course (total 2.75 g.) starting with 1.150 mg. in 24 hours	About 30 days (course interrupted)	About 24 days	A.C.T.H.	Serum bilirubin 14 mg. Alkaline phosphatase 28.3 units (modified Bodansky). Thymol turbidity 15.5 units. Cephalin flocculation +++. Serum protein: total 5.4 g., albumin 3.1 g.	Fever, morbilliform rash, adenopathy. Liver firm, tender, enlarged 4 cm.
2	Kirkeby (1954)	112.5 mg./day	About 35 days	Not given	Cortisone	Serum colour index 37 (Meulengracht). Thymol turbidity 0.05 unit. Takata negative. Serum protein: total 5.6 g., albumin 3.3 g.	Fever, morbilliform rash, urticarial swelling, mouth ulcers, granulopenia, eosinophilia. Died uraemic
3	East and Beamish (1957)	223 mg. (average) for first 14 days	30 "	9 days	Prednisone	Icteric index 15 units. Alkaline phosphatase 19.2 K.-A. units. Thymol turbidity ++. Cephalin flocculation +++. Thymol flocculation 4 units	Fever, rash. Liver not tender, enlarged 4 cm.
4	Burns and Desmond (1958)	125 mg./day	30 "	A few days	A.C.T.H. and prednisone	Serum bilirubin 4 mg. Alkaline phosphatase 29 K.-A. units. Thymol turbidity 3 units (MacLagan)	Fever, desquamating rash, stomatitis, pharyngitis, urticarial swelling, leucopenia, eosinophilia
5	Brooks and Calleja (1960)	90 "	30 "	No jaundice after 33 days (inexact)	A.C.T.H.	Icteric index 44 units	Fever, exfoliating rash, nephritis. Tender liver, enlarged 2 fingerbreadths
6	Jones (1960)	Maintenance dose 200–300 mg./day	25 "	Bilirubin absent from urine on 32nd day; serum bilirubin 0.6 mg. on 41st day	—	Serum bilirubin 1.2 mg. Alkaline phosphatase 8 K.-A. units. Zinc sulphate 2 units. Serum protein 7.5 g.	Fever, eosinophilia; liver enlarged 3 in. (7.5 cm.) on 28th day; rash appeared 5 days after jaundice
7	Case 1 (see text)	100–150 mg./day	42 "	15 days	—	Serum bilirubin 5.3 mg. Alkaline phosphatase 32 K.-A. units. S.G.O.T. 45 units; S.G.P.T. 144 units (Mohun and Cook). Thymol turbidity 1.5 units. Thymol flocculation 0 Serum protein: total 4.7 g., albumin 3.3 g.	Fever, exfoliating rash, adenopathy, neutropenia
8	Case 2	75 mg./day	35 "	A few days	—	Serum bilirubin 2.3 mg. Alkaline phosphatase 46 K.-A. units. S.G.O.T. 35 units; S.G.P.T. 14 units (Mohun and Cook). Thymol turbidity 1 unit. Zinc sulphate 5.5 units. Serum proteins: total 6.1 g., albumin 2.9 g.	Fever, macular rash
9	Case 3	100 "	46 "	2–3 months	—	Serum bilirubin 5.1 mg. Alkaline phosphatase 24 K.-A. units. Thymol turbidity 3 units. Zinc sulphate 4.5 units. Serum protein: total 7.8 g., albumin 3.9 g.	Rash. Liver just palpable and tender

Note.—Where tests were carried out more than once during the reaction only those showing the greatest abnormality are given.

39.4° C.) and rash continued for 22 days. Jaundice appeared 35 days (September 30) after starting phenindione treatment. During the next week the jaundice, fever, and rash subsided rapidly. Liver-function tests (see Table, No. 8) suggested cholestatic jaundice. The blood count was normal. Three months later the blood count, serum proteins, and liver-function tests were repeated and found normal.

Case 3.—A man aged 62 started treatment with phenindione on January 10, 1957, after his second myocardial infarction. Three weeks later he developed a rash on the arms and legs, and nicoumalone was substituted. On February 15 he felt unwell and had developed anorexia. A week later he had epigastric pain and two days after this became jaundiced, 46 days after treatment with phenindione was started. Throughout his illness he remained apyrexial with a bradycardia of 55–60 a minute. Initially the liver was just palpable and slightly tender. Liver-function tests (see Table, No. 9) suggested cholestatic jaundice. The blood count was normal. He improved slowly, but was still jaundiced two months later (on April 25 the serum bilirubin was 1.2 mg./100 ml.), and it was not until towards the end of the third month that he was well and his serum bilirubin returned to normal (0.6 mg. on May 23). Anticoagulants were stopped when the jaundice developed, and were not used again. He was symptom-free when last seen (January, 1961).

Discussion

Selected details from the previously recorded cases and of the three described here are given in the Table, and the Diagram shows the chronology of phenindione hepatitis.

The dose of phenindione associated with hepatitis was within the usual therapeutic range except in one case (Makous and Veer, 1954). Jaundice never appeared within 25 days of the beginning of phenindione therapy, and never lasted more than three months. A.C.T.H. or steroids were used in the first five cases reported, but there is no evidence that this treatment influenced the duration of jaundice. In the three cases reported here, as in the six already in the literature, jaundice was not the first symptom but appeared 3 to 25 days after the initial toxic manifestation. Jones (1960), however, found bilirubin in the urine of his patient within 24 hours of the onset of fever, three days before the appearance of jaundice. Routine liver-function tests might therefore reveal subclinical hepatitis in some patients who never become icteric.

The type of jaundice is uncertain from the reported investigations, which do not include liver biopsy. Burns and Desmond (1958) suggested that in their case it was "mildly obstructive" and of "chlorpromazine type," and Jones (1960) pointed out the resemblance of this form of hepatitis to that produced by chlorpromazine and methyltestosterone. On the present evidence and by analogy with chlorpromazine jaundice it is reasonable to regard phenindione hepatitis as a sensitivity reaction and therefore associated with intrahepatic obstructive or cholestatic jaundice. Liver-cell damage also occurs, as indicated by the abnormal flocculation tests (Table, Nos. 1 and 3), and by the raised serum transaminase (No. 7). In chlorpromazine jaundice Zelman (1959) correlated the raised serum transaminase levels with biopsy studies, which showed centrilobular and periportal necrosis.

Summary

Three cases of hepatitis due to phenindione are described and compared with the six previously reported. The evidence suggests that hepatitis is an unusual complication of phenindione therapy, and that the

jaundice produced is mainly cholestatic in type, although liver-cell damage may occur.

Case 1 was under the care of Dr. Richard Asher at the Central Middlesex Hospital, and Cases 2 and 3 were under the care of Dr. Paul Wood, at the Brompton and National Heart Hospitals respectively. We are most grateful to these physicians for their help and permission to publish their cases.

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EPIDEMIC OF TUBERCULOSIS IN A PRIMARY SCHOOL

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It has been demonstrated repeatedly that a pupil can have open pulmonary tuberculosis without causing an outbreak of tuberculous disease among his or her classmates (Ivar Lundius, 1928–9; Anderson and Grenville-Mathers, 1952). Most outbreaks reported in these islands have been traced to a member of the teaching or non-teaching staff. The epidemic here reported is of interest not only because the probable source was a pupil, but because the pupil in question had a routine contact x-ray examination at the time she was probably spreading infection and her film was not thought to show a significant lesion.

On March 5, 1960, a girl aged 13 was admitted to Daisy Hill Hospital, Newry, County Down, with erythema nodosum, which had been present for one week. Her x-ray film showed a primary tuberculous complex in the right lung. She volunteered the information that several other children sharing the same classrooms at school had a similar rash, and on investigation nine further cases were found. These children were all radiographed, disclosing four more cases of primary pulmonary tuberculosis, and making a full investigation of the school necessary. It was a church school, consisting of three classrooms, in a small seaside town. The classroom where the outbreak occurred was 29½ ft. (9 m.) long, by 22½ ft. (6.8 m.) wide, by 15 ft. (4.6 m.) high, well lighted and ventilated, but overcrowded. New classrooms were in process of erection at the time. There were 71 girls, aged 9 to 15 years, in this room, which was separated from a smaller classroom by a glass partition. The total number of pupils attending the school was 153.

Investigations

All the teaching and non-teaching staff, including the man who delivered milk (pasteurized), were radio-