HEPATIC NECROSIS AND OTHER VISCERAL LESIONS ASSOCIATED WITH PHENYLBUTAZONE THERAPY

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Toxic manifestations during phenylbutazone ("butazolidin") therapy for rheumatic disease have been recorded by many observers, and in some series of cases the incidence is over 40% (Freeland *et al.*, 1953; Cudkowicz and Jacobs, 1953; Bruck *et al.*, 1954). Fatalities have also been observed and necropsy findings reported. It is the purpose of this paper to place on record the necropsy findings in another fatal case.

Case Report

A married woman aged 73 was first seen on April 30, 1954, when she gave a history of mild rheumatic pains of many years' duration. On the previous day she awoke with severe pain and swelling of small joints of her right hand. This spread during the day to her right wrist and elbow, and on the morning of the 30th had started in the left metacarpo-phalangeal joints.

On examination her temperature was 100.2° F. (37.9° C.), pulse 90 and regular, and respirations 20. The affected joints were red, tender, and swollen. Movement was very limited and painful. The small joints of both hands, both wrists, right elbow, and right shoulder were affected. Her weight was 8 st. 8 lb. (54.4 kg.). Urine: S.G. 1014; no albumin or sugar present. B.P. 130/60. E.S.R. 40 mm. in first hour. Serum sodium, 290 mg. per 100 ml.; serum potassium, 24 mg. per 100 ml.

As the arthritis was very acute and spreading rapidly she was given cortisone acetate by mouth, starting with a dose of 100 mg. a day; this was rapidly increased to 200 mg. with satisfactory results, her joints showing improvement, with disappearance of the redness and swelling and a return of the lost movements.

Some difficulty was experienced in reducing the dosage, as each reduction was followed by a return of the arthritic symptoms. From June 12 to 16 she was given three 200-mg. phenylbutazone tablets a day, a total of 20 tablets being given. This was done to tide her over the symptoms due to the withdrawal of cortisone. She left hospital on July 2 on a maintenance daily dose of 50 mg. of cortisone. Her weight was 8 st. 7 lb. (54 kg.)

When readmitted on July 24 she stated that she had taken no cortisone since July 17, as she had noticed that her ankles and feet were swollen. Her B.P. was now 150/60. She was breathless at rest, with signs of congestive heart failure. Her joints were again painful and swollen. Her E.S.R. was 110 mm. in one hour; serum sodium, 314 mg. per 100 ml.; and serum potassium, 32 mg. per 100 ml. She was given phenylbutazone from August 5 to 15, three 200-mg. tablets a day; total tablets, 33. On August 15 the phenylbutazone was stopped, as examination revealed impaired resonance with weak breath sounds and numerous rales over the upper zone of the right lung and signs of an effusion at the left base.

X-ray examination confirmed the presence of a pleural effusion on the left side and revealed dense mottling in the right upper and middle lobes and to a less extent in the right lower lobe. There also appeared to be a dense area near the left hilum. Some enlargement of the cardiovascular shadow was present with some slight calcification of the aortic arch.

*Since deceased.

Her blood picture on August 20 showed: Hb, 11.5 g. (72%); red cells, 3,500,000; white cells, 7,500 (lymphocytes 17%, monocytes 2%, polymorphs 75%, eosinophils 4%, basophils 2%). She also complained of nausea and a dry mouth. There was never any sign of jaundice or ascites. She now developed a moderate albuminuria.

On August 22 the serum sodium was 314 mg. per 100 ml. and serum potassium 20 mg. per 100 ml. She died on August 23. From June 12 to 18 4 g. of phenylbutazone was given, and from August 5 to 15 6.6 g.—a total of 10.6 g.

Summary of Post-mortem Findings

External Appearance.—Characteristic changes of rheumatoid arthritis; generalized oedema; no jaundice.

Body Cavities.—About three pints (1.7 litres) of clear amber-coloured fluid in each pleural cavity.

Circulatory System.—Heart: weight, 627 g.; mitral valve cusps slightly thickened; hypertrophy of left ventricle and papillary muscles; fibrosis and calcification of aortic valve; epicardium and pericardium covered by dense shaggy exudate, beneath which were scattered tubercle-like nodules. Blood vessels: slight atheroma of coronary arteries and aorta, with focal calcification in the aortic arch.

Respiratory System.—Lungs: weight—right 913 g., left 513 g.; upper lobar oedema and congestion most marked on right side; moderate bronchiectasis; small area of pleural thickening right apex. Trachea: frothy mucus present.

Spleen.—Weight, 199 g.; pattern retained.

Gastro-intestinal Tract.—Stomach: numerous fundal mucosal erosions.

Liver.—Weight, 1,482 g.; diffuse mottling and congestion.

Pancreas.—Nothing of note.

Genito-urinary System.—Kidneys: weight—right 151 g., left 143 g.; scattered white cortical streaks and prominent vascular markings. Bladder: haemorrhagic cystitis. Uterus: calcified interstitial leiomyomata.

Central Nervous System.—Permission for examination of brain refused.

Endocrine Glands.—Thyroid adenomatous; small accessory thyroid present on left side.

Adrenals.—Nothing of note.

Histology

Heart.—There was interstitial oedema of the myocardium with focal collections of polymorphonuclear cells, often numerous, with histiocytes, plasma cells, lymphocytes, and pigment-laden macrophages. Only an occasional eosinophil could be found. None of these cellular aggregations showed any definite relationship to blood vessels. The latter showed fibrillar scarring of the rheumatic type. The muscle fibres showed considerable variation in their nuclei as well as degenerative changes. The endocardium was normal, except in the left auricle, where it was thickened. No cellular infiltrations were found in or beneath it. The epicardium was greatly thickened and nodular. Its surface showed patchy areas of caseous necrosis with polymorphonuclear infiltration beneath which there were epithelioid cells arranged in a radial fashion with giant-cell formation. The innermost layer consisted of a diffuse collection of lymphocytes, plasma cells, polymorphonuclear cells, with some fibroblasts. The blood vessels were dilated. A section taken from the left auriculo-ventricular groove showed a collection of cells between the coronary artery and the auricular myocardium (Fig. 1). Epithelioid cells were arranged in a palisade around a central area of necrosis with peripheral lymphocytes and plasma cells. The necrosis was of the complete or caseous type.

Lungs.—These showed a moderate amount of oedema with scattered polymorphonuclear cells in the fluid. Strands of fibrin lay free in many of the alveoli, and some of them showed early organization while others were arranged in strip-like fashion against the alveolar walls. A striking feature was the presence of large atypical mononuclear

cells in all parts of the lungs. Their nuclei were basophilic, and occasional giant-cell formation occurred. No typical Aschoff cells were found. Plasma cells could be seen in moderate numbers. There was thickening of the alveolar walls and focal emphysema. A large bronchus showed bronchiectasis. There were perivascular collections of mixed cells, but the vessel walls showed no change. At the site of the pleural scar the pleura was thickened by fibrosis, anthracosis, and lymphocytic infiltration. Part of it was necrotic, and the histological picture was the same as that described for the epicardial lesion in Fig. 1. A tracheo-bronchial lymph node showed sinus catarrh and anthracosis.

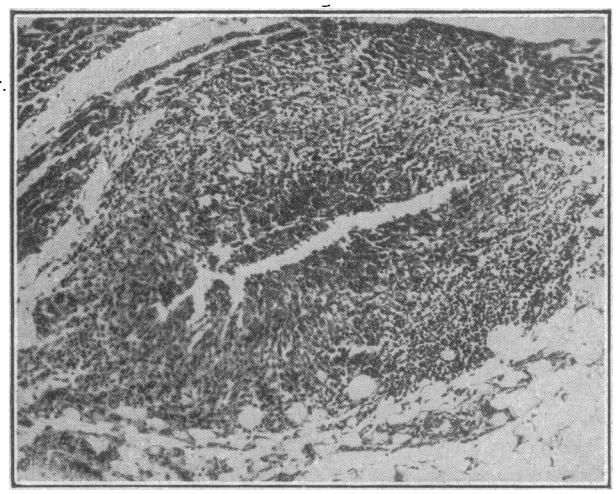

FIG. 1.—Granulomatous lesion in the auriculo-ventricular groove.

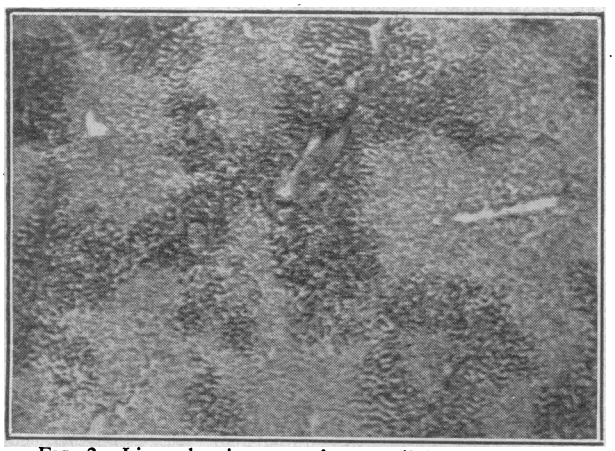

FIG. 2.—Liver showing extensive centrilobular necrosis.

Liver.—There was extensive necrosis of parenchymatous cells of centrilobular distribution (Fig. 2). The outlines of the liver cell cords were preserved, but the areas involved were infiltrated by polymorphonuclear cells. The Kupffer cells remained intact. There was slight congestion of the central venous part of the lobules. The remaining liver cells showed toxic nuclear changes, with cytoplasmic fat present in moderate amounts. There was minimal parenchymatous regeneration. Lymphocytes in insignificant numbers were present in the portal areas.

The *spleen* showed congestion of the pulp, which was infiltrated by polymorphonuclear and plasma cells.

The *adrenals* showed some abnormal vacuolization in the cells of the zona fasciculata.

Kidneys.—The glomeruli were within normal limits. There were widespread degenerative changes in the tubules, particularly in the convoluted tubes. Some of these were necrotic, but there was no cellular infiltration. Hyaline casts were also present.

The *bone marrow* was moderately hyperplastic, of normoblastic type.

Special stains failed to reveal the presence of tubercle bacilli or other organisms in the granulomatous lesions. The caseous necrosis in these areas did not stain for fibrin.

Discussion

The dosage in this case, 600 mg. a day, is that most often used, but it is noticeable that there was an interval between the two courses of treatment of nearly two months. The total number of days—18—on which phenylbutazone was given was not large, nor was the total dosage of 10.6 g.

The histological findings fall into three main categories: (1) necrotic parenchymatous lesions in the liver and kidneys; (2) granulomata in the epicardium, pericardium, and lungs; and (3) interstitial myocardial lesions.

The hepatic and renal lesions are similar to those found in chemical poisoning, and in this instance they were almost certainly due to phenylbutazone administration. Necrosis of this degree in both organs, and with this distribution in the liver, has not previously been described as caused by phenylbutazone. There have been reports of milder hepatic damage in other cases of rheumatoid arthritis receiving phenylbutazone. In Nassim and Pilkington's (1954) patient who recovered, a liver biopsy revealed "foci of focal necrosis into which infiltration with mononuclear cells has occurred, and there is also some accumulation of mononuclear cells in the portal tracts." Engleman *et al.* (1954), in the U.S.A., described six cases of jaundice due to this drug, with two deaths. The first case coming to necropsy showed "infiltration of portal spaces with polymorphonuclear and mononuclear cells. Projecting from the portal spaces were septal strands of fibrous tissue which were also infiltrated with inflammatory cells. Adjoining liver cells showed degenerative changes, and a smaller number were necrotic. The pathological changes are those of acute toxic hepatitis." The second case received phenylbutazone for 10 days, after which it was stopped because of vomiting; death occurred 40 weeks later, and the liver showed toxic cirrhosis. Other causes for this liver change were ruled out.

The renal tubular damage in the present case was of the isolated nephrotic type. Degeneration of the convoluted tubules was described by Bruck *et al.* (1954) in a patient who died of oliguria and renal failure while receiving phenylbutazone for rheumatoid arthritis, but the kidney showed old pyelonephritic and hypertensive changes. In Johnson and Larkin's (1954) case, death occurred in a patient with contracted kidneys who was on the same treatment.

There are at least three possible explanations for the granulomatous lesions: (1) That they are rheumatic manifestations, either unmodified or modified by drug therapy; (2) that they are of infective (tuberculous, viral, or fungal) origin; (3) that they are a direct hypersensitivity reaction to phenylbutazone.

The histological changes in the epicardial and pleural lesions are those of the rheumatoid nodule that have been previously described in these sites (for review see Ellman *et al.*, 1954). A striking feature in the case now presented is that the necrosis in those lesions was not fibrinoid but was caseous in character. Ellman *et al.* (1954) found a similar change in their case of rheumatoid arthritis with widespread serous membrane involvement by rheumatoid nodules. Their patient received no phenylbutazone, but had cortisone for 71 days. This may be of some significance, since our patient received the hormone for 77 days. Is it possible that this form of treatment could account for the atypical necrosis in an otherwise typical rheumatoid nodule?

An alternative explanation to a rheumatic origin is the breakdown of a latent infective granulomatous focus by cortisone and/or phenylbutazone, a tuberculous focus being most probable. However, as was previously mentioned, no organisms were found and the lesions are not histologically typically tuberculous. The possibility of an aggravation of this type has to be considered in view of the work of D'Arcy

Hart and Rees (1950) on the influence of cortisone on the tuberculous lesion.

Granulomata of somewhat similar though not identical character to those under review have been found in other cases of phenylbutazone toxicity (Steinberg *et al.*, 1953; O'Brien and Storey, 1954). Associated vascular lesions of the hypersensitive type were present in both these cases, and when necrosis was found it was fibrinoid in type. Widespread microgranulomata were present. The changes in these patients are probably a direct hypersensitivity reaction to phenylbutazone, and they parallel those described by More *et al.* (1946) in persons dying from sulphonamide hypersensitivity. No vascular lesions were found in the patient in the present report, and the granulomata do not appear to originate from phenylbutazone hypersensitivity.

The interstitial myocarditis is non-specific and probably anaphylactoid. Apart from old paravascular fibrillar scarring, no rheumatic lesion was found. Similar myocardial lesions were also described by More *et al.*

The pulmonary histological changes, apart from the granuloma, have many of the characteristics of those described by Gouley and Eiman (1932) for "rheumatic" pneumonia of a proliferative type. These lesions are of a type which may occur in the lungs, independent of any form of therapy, during the course of an acute rheumatic attack. They draw attention to the importance of relating the findings in cases of drug toxicity to the known pathological findings in the diseased state for which the drug has been administered, as well as to the normal. Otherwise, toxic effects may be ascribed to the drug which it does not possess. The coincidence of acute rheumatic lesions and those of rheumatoid arthritis in the present instance also raises the question whether phenylbutazone may not be more toxic in such cases than in cases of simple rheumatoid arthritis.

It is reasonable to suggest that in this case the myocarditis, and the necrosis in the liver and possibly also in the kidney, were related to one another in so far as, with the development of the myocarditis, passive congestion supervened and the anoxia thus induced in the parenchymatous cells of the liver and kidney aided the development of necrosis by the toxic action of phenylbutazone.

Summary

A fatal case of rheumatoid arthritis in a woman of 73 who received phenylbutazone and cortisone is reported. Necropsy revealed multiple pathological lesions, among which hepatic and renal necrosis were prominent; these lesions are ascribed to toxic action by phenylbutazone. An interstitial myocarditis was probably due to hypersensitivity to phenylbutazone. Pleural and epicardial granulomata were most probably modified rheumatoid nodules. Other pulmonary changes conformed to those found in acute rheumatic disease. The importance of relating the pathological changes found in cases of drug toxicity to the known changes found in untreated cases of the disease for which the drug is administered, as well as to the normal, is indicated.

We wish to thank Professor R. A. Q. O'Meara for much help and criticism and Mr. F. A. Murray for the photographs.

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MEGALOBLASTIC ANAEMIA DUE TO PHENYTOIN SODIUM

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The possibility that phenytoin sodium might produce a megaloblastic anaemia was first suggested by Badenoch (1954), who described two patients on phenytoin sodium therapy with a megaloblastic anaemia and with normal vitamin B_{12} absorption. A total of five further cases have been reported by Hawkins and Meynell (1954), Chalmers and Boheimer (1954), Rhind and Varadi (1954), and Webster (1954), although one of the two cases reported by Chalmers and Boheimer probably had pernicious anaemia. Hawkins and Meynell mention one further example brought to their notice by Dr. J. F. Wilkinson.

Recently we have had under observation two patients with a megaloblastic anaemia and normal gastric acidity who were on phenytoin sodium therapy. In order to determine the frequency of the condition, the records of 56 patients with megaloblastic anaemia who were admitted to Whiston Hospital during the last four years were studied, but no further cases were revealed. In addition, blood examinations were made on 102 epileptic patients in Rainhill Mental Hospital, all of whom had been taking phenytoin sodium for several years, and the laboratory records of 140 patients with a haemoglobin value below 70% in Rainhill Hospital during the last four years were surveyed. None of the 102 epileptic patients had a megaloblastic anaemia, but one possible case was discovered from the survey of the records (Case 3).

Case 1

A man aged 32 was admitted to Whiston Hospital in February, 1953; he had had dyspnoea on exertion and lassitude for three months. His diet had been adequate, and there was no history of haemorrhage. He had previously been healthy except for attacks of grand mal, which started in 1939. During the last five years he had been taking 1 gr. (65 mg.) of phenobarbitone and 300 mg. of phenytoin sodium daily, which completely controlled the epilepsy. On examination he was thin (weight 8 st. 1 lb.—51.3 kg.), there was pallor of the skin and mucous membranes, ulcers were seen on both legs, and his temperature was 102° F. (38.9° C.). The tongue and gums were normal, the spleen was not palpable, and there were no abnormal neurological signs. The chest *x*-ray examination showed consolidation in the left mid-zone.

Laboratory Investigations.—R.B.C., 770,000 per c.mm.; Hb, 36% (5.2 g.%); W.B.C., 8,500 per c.mm. (normal differential count); P.C.V., 9%; M.C.V., 128 cubic μ; reticulocytes 2%. Blood films showed macrocytosis, and the sternal marrow contained megaloblasts. Serum bilirubin, 0.7 mg. per 100 ml. Occult blood tests on three specimens of faeces were negative. No excess of faecal fat. A fractional test meal showed the normal amount of free hydrochloric acid.

Treatment.—Vitamin B_{12}, 100 μg., was given daily by the intramuscular route for the first week, and then twice weekly for six weeks. There was a small reticulocyte response of