late from plasma uric acid readings before and after treatment the total loss of body uric acid and to correlate this calculation with the actual excess observed in the urine. Such a calculation is shown in Table VI. Case 4 is excluded, as measurements of actual body weight were not taken. Where more than one estimation of circulating uric acid was made before treatment the mean has been taken. Such calculations require certain assumptions which need not be discussed here. Nevertheless, if the falls in plasma levels were greater than could be accounted for by the excess excretion, clearly a consistent discrepancy would appear. In Cases 2 and 5 the discrepancy is small, and in Case 3 slightly more uric acid was excreted than can be accounted for by the fall in plasma levels.

Only in Case 1 is there the sort of discrepancy which would be required to claim that the fall in plasma levels is greater than can be accounted for by the excess excretion. It was in this case, however, that an acute attack developed during the control period, with a rapid rise in blood levels. The excess excretion of uric acid during this period is more than enough to account for the change in total blood uric acid. Calculating the plasma volume as 0.051 body weight, and assuming that the fall is due to clearance by the kidneys, it would require an excess excretion of 243 mg. to reduce the level from 9.4 to 3 mg. per 100 ml. In the event 483 mg. was excreted in excess during the relevant period.

Conclusions

There are thus two possible effects exerted by phenylbutazone and influencing uric acid estimations: (1) uricosuric—while this is no more than a mild effect it is nevertheless sufficient to account for the observed fall in circulating urate levels; and (2) water retaining—this was sufficient to precipitate congestive heart failure in the one case in which a uricosuric effect was not observed.

It is suggested that the variable preponderance of uricosuric and water-retaining effects would account for the variable findings. Much further evidence is required to establish still a third effect, on uric acid metabolism itself; and the fact that uric acid excretion may be increased when phenylbutazone is administered is against such a possibility.

Summary

Four cases of gout and one control case were treated with phenylbutazone and the changes in plasma uric acid and urinary uric acid levels were studied.

The findings suggest that phenylbutazone has no more than a slight uricosuric effect. This may be neutralized if considerable water retention occurs at the same time.

No evidence was found that phenylbutazone has any direct effect on uric acid metabolism.

Cases 1 and 2 were under the care of Dr. W. S. C. Copeman, to whom I wish to record my gratitude. I am also grateful to Dr. T. Simpson for allowing me to study Case 3.

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DEATH FROM HYPERSENSITIVITY DUE TO PHENYLBUTAZONE

BY

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Toxic effects of phenylbutazone have been described by a number of authors, and death has been ascribed mainly to agranulocytosis and to intestinal haemorrhage or perforation. A case is recorded in which death is attributed to a hypersensitivity reaction (in the course of phenylbutazone therapy).

Case Report

The patient was a man aged 73. Five years ago he began to have pain and stiffness in his hands and wrists. At first the pain was intermittent, but later it became continuous, until three years ago he had difficulty in moving his shoulders, elbows, wrists, and hands, and a diagnosis of rheumatoid arthritis was made. During the next year his knees and ankles were progressively affected. Two years ago he was unable to walk. He then received a course of gold injections, which produced little improvement, but was followed by a rash.

Nine months ago he was admitted to the London Hospital. Examination at that time showed a wasted, anaemic man, with classical rheumatoid arthritis. Ulnar deviation and spindling of the fingers, and swelling of the metacarpophalangeal joints, were present, with little movement of the wrists. Movement at the elbows and shoulders was painful and limited. His knees were swollen and his ankles painful and limited in movement. Other systems were normal, except that his pulse showed frequent extrasystoles, with a soft systolic murmur at the apex, probably not organic, but related to the anaemia. His blood pressure was 150/60. The erythrocyte sedimentation rate was 104 mm. in one hour; haemoglobin 69%; and leucocytes 8,700 per c.mm., with 74% polymorphonuclears. Rose's test was negative. He was treated by physical methods and with iron by mouth. After discharge, and five weeks before final admission, phenylbutazone was started, 0.2 g. twice daily by mouth. This produced a marked subjective improvement, so that he was able to walk a mile. After five weeks' treatment, however, his face began to swell, his eyes watered, and his mouth became dry and sore. He drank more fluids, but noticed that he passed scanty reddish-brown urine. He was short of breath, felt drowsy, and complained of a tingling sensation all over. Phenylbutazone was stopped, and he was admitted to hospital one week later.

Examination showed that his arthritis had undergone no striking change. He was rather confused and slightly flushed, with puffiness of the face. His tongue was dry and furred, and there were three tender ulcers on the inside of the lower lip, the largest 0.5 cm. in diameter. His pulse was regular, rate 120, and his blood pressure was 120/80. His apex beat was displaced outwards, and a third heart sound was heard at the apex but no murmurs. There were signs of fluid at both lung bases, and the liver was just palpable. The urine, which was orange-coloured, contained a cloud of albumin, and the deposit contained a few red cells and granular casts. An x-ray film of the chest showed cardiac enlargement, with hilar congestion and small bilateral pleural effusions, but the electrocardiogram showed only slight abnormalities—namely, ST depression in CR7. The leucocytes were 6,000 per c.mm. (polymorphonuclears 77%) and the blood urea was 38 mg. per 100 ml.

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He was treated with restricted fluids and a low-salt diet. The day after admission transient auricular fibrillation was diagnosed clinically, and he was digitalized. At first he improved, his mouth became less sore, and his urinary output increased, but he died suddenly during the fourth night after admission.

Summary of Necropsy

Heart failure; hypersensitivity angitis; rheumatoid arthritis. Mottled fawn-brown myocardium (left ventricle 1.5 cm. thick; right ventricle 0.6 cm. thick). Slight dilatation of right and left ventricles. Endocardium normal. Moderate atheroma. Clear yellow left pleural effusions (360 ml.). Obliteration by fibrous adhesions of right pleural cavity. Partial collapse of lower lobe and lingula of left lung. Congestion and slight oedema of lungs. Cortical pattern and cortico-medullary junction blurred in moderately enlarged kidneys. Two small calculi (the larger 0.8 by 0.6 cm.) in moderately dilated pelvis of right kidney. Two shallow ulcers (the larger 1.5 cm. diameter) in mucosa between lower lip and alveolar margin. Seven ulcers (up to 0.5 cm. diameter) in mucosa of lower ileum. Reticular congestion of enlarged liver. Distinct pattern in enlarged

FIG. 1.—Fibrinoid necrosis of muscular artery in pectoralis minor muscle ($\times 360$).

spleen. Firm, grey, slightly swollen pancreas. Red marrow in upper two-thirds of shaft of femur. The joints confirm the clinical description.

Weights.—Heart, 525 g.; liver, 2,520 g.; spleen, 360 g.; kidneys, together, 620 g. Body weight, 55.84 kg.; length, 1.6 metres.

Microscopical Examination

The histological changes were of mixed character. On analysis they were separable into those typical of rheumatoid arthritis and those attributable to drug hypersensitivity. These latter were of three types: polyarteritis nodosa, "hypersensitivity angitis" (Zeek, Smith, and Weeter, 1948), and granulomatous lesions.

(1) *Polyarteritis Nodosa* (Fig. 1).—A short segment of a muscular artery in the left pectoralis minor muscle was characteristically affected. All coats were destroyed and replaced by fibrin, outside which there was infiltration with polymorphonuclear leucocytes and lymphocytes. The lumen was empty. This was the only lesion of this kind found.

(2) *Hypersensitivity Angitis* (Fig. 2).—Occasional arterioles and venules in the epicardium, myocardium, and renal medulla were infiltrated with histiocytes, lymphocytes, and occasional eosinophil and neutrophil leucocytes. This exudate extended radially outward from the lumen to the extravascular tissues, and, although composed of round cells, gave the impression of a palisade. The walls of the vessels were obscured by the cellular infiltration, and no foci of necrosis or fibrinoid impregnation were apparent,

though a perivascular fibrinoid corona surrounded an arteriole in the submucosa of the ileum. No thrombus was present in the lumen of any of these vessels.

(3) *Granulomatous Lesions* (Fig. 3).—There were widespread miliary or submiliary granulomatous foci in the

FIG. 2.—Hypersensitivity angitis of two venules close to branch of left coronary artery ($\times 67$).

epicardium, myocardium, lung, kidney, portal tracts of the liver, thyroid, the anterior and posterior lobes of the pituitary and its capsule, an inguinal lymph node, and the pectoralis minor, psoas, and abductor pollicis longus muscles. There were fewer nodules in the splenic pulp and in the marrow from the femur. The submiliary foci in the heart were composed of round, elongated, and irregular large cells with dark nuclei, the cytoplasm varying from deeply basophil to pale eosinophil. Anitschkow myocytes were not present. About some of the larger lesions were small numbers of lymphocytes and occasional eosinophil leucocytes. One or two multinucleated giant cells were present in some of the lesions in the epicardium. In the hepatic lesions small histiocytes with small round or indented nuclei predominated, but larger and elongated cells also occurred; in some foci eosinophil leucocytes were numerous, and there were fewer lymphocytes and scanty neutrophil leucocytes. Giant cells were not present. The numerous miliary lesions in the inguinal lymph nodes were composed of epithelioid histiocytes, small multinucleated giant cells—some with foamy cytoplasm—and a few

FIG. 3.—Giant-celled granulomatous lesion in abductor pollicis muscle ($\times 205$).

eosinophil leucocytes. In the connective-tissue septa of skeletal muscle the lesions were formed by small multinucleated giant cells, epithelioid histiocytes, lymphocytes, and occasional eosinophils (Fig. 3).

Multinucleated giant cells were present in almost all the lung foci (Fig. 4). These occurred mainly in the alveoli, but they were found also in the bronchial submucosa, in the peribronchial connective tissues, and in the interlobular septa. These foci resembled the granulomatous lesions of tuberculosis or Boeck's sarcoidosis. Stains for tubercle

bacilli were negative. The epicardium also contained the only area of fibrinoid impregnation of collagen fibres seen. This was close to a vascular lesion, but there was no inflammatory cellular reaction about the fibrinoid area. The splenic pulp was infiltrated with many eosinophil leucocytes and plasma cells. The ulcers of the mouth and ileum showed an inflammation in which histiocytes predominated and polymorphonuclear leucocytes were unexpectedly sparse. In addition to the granulomatous foci in the kidney, diffuse interstitial oedema and casts in many tubules were present, but there were no definite glomerular changes. There was a diffuse subacute inflammation of the pancreas, with infiltration of interlobular and intralobular connective tissue with neutrophil and eosinophil leucocytes, lymphocytes, and spindle fibroblasts, but no vascular lesion was present in the parts examined.

In bone marrow from the femur and rib the more mature forms of neutrophil leucocytes were scanty, the picture suggesting a maturation arrest of this series. In seven blocks from the carpal joints the appearances were typical of

FIG. 4.—Granulomatous foci close to branch of pulmonary artery in lingula ($\times 230$).

rheumatoid arthritis. Many lymphorrhages were present in the abductor pollicis longus muscle. These were identical with those described by Cruickshank (1952), and were easily distinguished from the granulomatous foci mentioned above.

Discussion

Clinically our patient with classical rheumatoid arthritis developed toxic symptoms during phenylbutazone therapy. The effects—namely, sore mouth and water retention—have been said to occur often during treatment with this drug (Freeland, Storey, and Thompson, 1953; Green and Williams, 1953).

That the histological changes represent an exacerbation of the rheumatoid disease is unlikely. Neither the hypersensitivity angitis nor the granulomatous foci described above have been identified among the cardiovascular lesions of rheumatoid arthritis (Bywaters, 1950; Sokoloff, 1953). The cardiac lesions do not resemble the rheumatoid lesions, similar to the subcutaneous nodule described by Baggenstoss and Rosenberg (1944), and by Raven, Weber, and Price (1948). The patch of fibrin impregnation of the epicardial collagen does not resemble that seen in rheumatic carditis or disseminated lupus erythematosus. The association of rheumatoid arthritis and polyarteritis nodosa is uncommon, and in the few cases reported is regarded as fortuitous (Lowman, 1952). On the other hand, the association of polyarteritis nodosa with hypersensitivity reactions is well established and has been attributed by Landsteiner (1945) to a reaction against products of the conjugation of non-protein therapeutic agents with body protein.

Polyarteritis nodosa in association with angitis attributed to hypersensitivity has been provoked by sulphonamide

(Hartroft, 1944; More, McMillan, and Duff, 1946), by iodine (Rich, 1942), by "dilantin" (Van Wyk and Hoffmann, 1948), by thiourea (Gibson and Quinlan, 1945; Dalgleish, 1952), and by penicillin (Waugh, 1952). Although these two vascular lesions are often associated, the difference between them is distinct. The classical lesion of polyarteritis nodosa is a perivascular infiltration with neutrophil, eosinophil, and lymphocyte leucocytes about a segment of fibroid necrosis of the wall of a medium-sized artery. Hypersensitivity angitis affects much smaller vessels—namely, arterioles and venules—while fibrinoid change is not a feature. In view of the paucity of the former lesions in the case presented, it is important that the significance of this hypersensitivity angitis lesion should be recognized.

Both types of vascular lesion are described by More *et al.* (1946), in association with more widespread and numerous granulomatous foci. The frequency of granulomatous foci with multinucleated giant cells in the extra-vascular connective tissues, and their association with polyarteritis nodosa and hypersensitivity angitis, were stressed by Churg and Strauss (1951) in a study of 13 cases of asthma. The similarity of the foci in the lung to Boeck's sarcoidosis is interesting in view of the possible background of hypersensitivity in that condition.

Our interpretation is strengthened by the report of a similar occurrence during phenylbutazone, cortisone, and A.C.T.H. therapy for rheumatoid arthritis presented by Steinberg, Bohrod, and Roodenberg (1953).

Summary

The clinical and necropsy findings in a subject dying from a generalized hypersensitivity reaction during phenylbutazone treatment of rheumatoid arthritis are described.

The hypersensitivity reaction was histologically demonstrated by three types of lesion: polyarteritis nodosa, hypersensitivity angitis, and granulomatous lesions, the two latter predominating.

Such a condition should be considered when the appearances at necropsy are indefinite in fatalities during this therapy.

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The annual report for 1953 of the Medical and Dental Defence Union of Scotland records that its membership is now 7,617, an increase of 126. Subscription income was £13,901, and claims paid amounted to £1,122; it is expected that the figure for settlement of claims during the coming year will be much higher, as several outstanding cases may result in the award of large sums of damages. Anxiety is expressed at the increased number of claims being made against hospital staffs; 75% emanate from treatment in hospital in contradistinction to claims against general practitioners or consultants in their private capacity.