Increasing disability of a rising diastolic blood-pressure and blurring of the vision due to severe retinopathy were the salient features requiring urgent relief.

This was accomplished successfully by resection and an aortic homograft replacement.

On the basis of the operative findings and of histological examination of the thrombotic aortic sections the aetiology of the lesion was considered to be consistent with vasculitis.

I wish to acknowledge the help of my colleagues, Dr. Edward Halliday and Dr. Anthony Jose, of the Cardiac Investigation

Department; the angiographic studies by Dr. David Stephens; the plates from the Department of Illustration, University of Sydney; and the pathological investigation by Dr. Vincent McGovern, of the Fairfax Institute of Pathology.

REFERENCES

- Bahnon, H. T., Cooley, R. N., and Sloan, R. D. (1949). *Amer. Heart J.*, **38**, 905.
 Beattie, E. J., Cooke, F. N., Paul, J. S., and Orbison, J. A. (1951). *J. thorac. Surg.*, **21**, 506.
 Leriche, R., and Morel, A. (1948). *Ann. Surg.*, **127**, 193.
 Ross, R. S., and McKusick, V. A. (1953). *Arch. intern. Med.*, **92**, 701.

Phenylbutazone-induced Pericarditis

J. SHAFAR,* M.D., M.R.C.P., D.P.H.

Brit. med. J., 1965, **2**, 795–797

The subject of iatrogenic pericarditis was reviewed by Sparer and Davis (1963), and that which follows cardiac surgery has been amply documented. While pneumonectomy is rarely succeeded by pericarditis the post-pericardiotomy syndrome occurs in some 30% of patients in whom a wide pericardial incision has been made (Engle and Ito, 1961). Similarly, pericarditis may ensue subsequent to diagnostic procedures which involve penetration of the pericardium, particularly if blood is effused into the pericardial sac. Therapeutic irradiation of the chest area may result in acute or chronic constrictive pericarditis (Connolly and Burchell, 1961). Only recently has it been realized that pericarditis can be attributable to an untoward reaction of drug medication. The example recorded here is attributed to the administration of phenylbutazone.

Case Report

The patient, a widow aged 64, was known to have osteoarthritis of the cervical spine and of the metacarpal-carpal joints of both thumbs. Because of an exacerbation of the pain phenylbutazone 100 mg. t.d.s. had been prescribed. A week later she developed soreness of the mouth and general malaise and accordingly stopped the treatment. Next day marked and diffuse swelling of the neck and hands appeared and she had a temperature of 100° (37.8° C.). That evening epigastric discomfort, nausea and anorexia, and widespread joint pains were further features. On the following day the joints were swollen and their mobility was considerably restricted, and the urine was noted to be of very dark colour.

On admission to hospital, 15 days from the commencement of phenylbutazone therapy, she was obviously critically ill. Orthopnoea, oedema of the legs, and jaundice were evident. The pulse was rapid and irregular owing to auricular fibrillation, the temperature was 101° F. (38.3° C.), and the respiration rate 30 per minute. The oedema of the neck and hands had to a considerable extent subsided. The apex beat could not be located. Gross pericardial friction was audible over an extensive area of the praecordium. The average B.P. was 120/80. A generalized stomatitis with no ulceration was present, and the liver was enlarged to three fingerbreadths below the costal margin and was tender on palpation.

The results of the special investigations were: Urine, a trace of albumin and heavy concentration of bile. Hb 76% (11 g.). Total W.B.C., 21,300/c.mm. (polymorphonuclears 90%, lymphocytes 9%, mononuclears 1%). Blood urea, 25 mg./100 ml. Paul-Bunnell, no agglutination. Antistreptolysin O titre, 65 units/ml. Serum protein, 5.7 g./100 ml. (albumin 2.6 g., globulin 3.1 g.). Electrophoresis, increase of α 2. Serum G.O.T., 74 S.F. units. Serum G.P.T., 62

S.F. units. Serum lactic dehydrogenase, 580 B.B. units; serum bilirubin, 2.8 mg./100 ml. Thymol turbidity 1 unit. Zinc sulphate turbidity, 3 units. Alkaline phosphatase, 35.3 units. Antinuclear factor absent. Latex fixation test negative. L.E. cells not detected. Serum amylase, 75 Somogyi units. Blood W.R. negative. Virological studies and toxoplasma serology negative. Throat swab culture showed *staphylococcus aureus*. Examination of chest with a portable x-ray apparatus revealed a generalized increase in the cardiac area and venous congestion in the lung fields. The E.C.G. tracing is shown in Fig. 1.

For several days the condition of the patient continued to deteriorate and she was often confused. Digoxin and mersalyl produced no significant change. On her fourth day in hospital prednisone 10 mg. t.d.s. was prescribed. Response to this treatment soon became evident, and six days later normal rhythm was established and the pulse rate fell to 70. Her temperature had by then settled, pericardial friction was no longer detectable, and the dyspnoea and oedema had cleared. The progressive decrease of jaundice was also reflected in the disappearance of bile from the urine and in the pattern of the liver-function tests, the findings of which three weeks from the date of admission were: serum bilirubin, 0.5 mg./100 ml.; thymol turbidity, 1 unit; zinc sulphate turbidity, 4 units; and alkaline phosphatase, 13.1 units. At this time the Hb was 100% (14.6 g.), the W.B.C. 12,900/c.mm., and the E.C.G. tracing showed no significant abnormality (Fig. 2). The patient was fully ambulant, and, apart from persistence of the oral discomfort, symptom-free six weeks from the time when phenylbutazone had originally been prescribed. She has remained well, and when seen three months later the oral symptoms had cleared, physical examination was negative, her E.C.G. had remained normal, and the chest x-ray picture was within normal limits. A cholecystogram revealed a normal appearance and function of the gall-bladder. Prednisone had been tailed off, and she had been without this medication for six weeks with no recrudescence of any of the clinical features.

Discussion

The capacity of a drug to induce pericarditis has been convincingly demonstrated by the observations of Costa, Holland, and Pickren (1961). In a study designed to assess the human pharmacology and antineoplastic value of the purine riboside analogue psicofuranine (6-amino-9-D-psicofuranosyl), three out of four patients treated with this compound developed pericarditis. Necropsy confirmed its presence in the three patients, all of whom were in the stage of advanced neoplastic disease. One patient also manifested pleural inflammatory changes, and it was concluded that psicofuranine had a singular tendency to precipitate inflammatory reactions of serous surfaces. The pericarditis associated with other drugs is, in

* Consultant Physician, Burnley Group of Hospitals.

contradistinction to that of psicofuranine, part of a more generalized disorder.

Excluding haemorrhagic forms of pericarditis which complicate anticoagulant therapy (Goldstein and Wolff, 1951), there is a remarkable paucity of reports of drug-induced pericarditis. Streptomycin, inadvertently injected into a patient whose antituberculous therapy had been stopped on the appearance of features of drug toxicity, resulted in a fatal issue (Chatterjee and Thakre, 1958). Post-mortem examination revealed an acute and severe myocarditis, the histological features of which were compatible with an acute hypersensitivity reaction; the pericardial sac contained about 100 ml. of slightly turbid fluid, and a fine fibrinous deposit was present on the visceral surface of the pericardium. Hydrallazine, continued over long periods, may produce a syndrome simulating a collagen disorder. In a series of 13 patients, three manifested pericarditis (Dustan, Taylor, Corcoran, and Page, 1954), but its incidence in this lupus-like syndrome varies considerably, since pericarditis was not observed in another group of 17 (Perry and Schroeder, 1954). Tetracycline can produce clinical deterioration when administered to subjects affected with disseminated lupus erythematosus; in such circumstances pericarditis may appear as distinct from that form which is a feature of the disease itself (Domz, McNamara, and Holzapfel, 1959).

Only one other report of cardiac complications attending phenylbutazone therapy has been found in the literature. Hodge and Lawrence (1957) recorded two fatal cases. The first of these patients, a housewife aged 38, was being treated for rheumatoid arthritis. The initial moderate dosage was soon reduced, and, as the patient felt unwell, was discontinued after 17 days. Diffuse erythema, oedema of the face and extremities, and jaundice appeared, and enlargement of the liver, spleen, and lymph nodes was noted. Some 10 weeks from starting treatment tachycardia and profound hypotension occurred, with a subsequent fatal outcome. Necropsy revealed an excess of straw-coloured pericardial fluid, and the surface of the heart was found to be studded with discrete and confluent white, smooth, round elevations. The histological appearances were those of a diffuse interstitial myocarditis with very extensive destruction of muscle. The second patient, a widow aged 70, had received phenylbutazone in moderate dosage for three weeks for osteoarthritis. Pyrexia and erythema of the skin became evident two weeks after the start of treatment; this was followed by bronchitis, and she then developed "status asthmaticus," which proved fatal. The heart appeared normal on macroscopic examination, but microscopy showed multiple focal perivascular granulomata, comprising macrophages, acute inflammatory cells, eosinophils, and occasional giant cells. The authors invoked a hypersensitivity state in view of the short duration of treatment, the restricted dosage of the drug, and the presence of focal granulomata discovered in the myocardium of those who had died of granulocytosis or peptic ulcer attributable to phenylbutazone.

The case history recorded above approximates closely to these fatal examples. The generalized reaction and short period of drug consumption are in accord. The patient was in cardiac failure, and her critical state was further contributed to by the severity of the systemic disturbance. Clinical impressions suggest that but for corticosteroid therapy she would have succumbed. Corticosteroids have also proved effective in acute pericarditis associated with serum sickness. Two cases developing subsequent to administration of prophylactic antitetanus serum

are described by Goldman and Lau (1954). One case was of mild degree, and recovery was spontaneous; the condition of the other was grave but responded to cortisone.

Cardiac decompensation and acute pulmonary oedema are among the recognized ill-effects of phenylbutazone therapy, but these arise by virtue of fluid-retention, since the blood-volume may increase even by as much as 50%. As phenylbutazone is a drug often used in rheumatoid arthritis, phenylbutazone-induced pericarditis must be distinguished from the pericarditis which appears in the course of the disease itself. The association of these two states will suggest a diagnosis of disseminated lupus erythematosus, but Wilkinson (1962) described four cases in which he excluded the latter. He raises the possibility of a greater incidence of rheumatoid pericarditis than is usually appreciated, since the condition tends to pass unrecognized in the course of a disorder characterized by widespread pain. The clinical and electrocardiographic abnormalities in Wilkinson's series were of short duration, but chronic constrictive pericarditis has been reported in rheumatoid disease (Gimlette, 1959; Glyn and Pratt-Johnson, 1963; Litchfield, 1963). Pericarditis in juvenile rheumatoid arthritis has been reviewed by

FIG. 1.—E.C.G. tracing, 10 October.

FIG. 2.—E.C.G. tracing, 25 October.

Lietman and Bywaters (1963). Clinical diagnosis was established in 20 (7%) of a series of 285 cases. Common concomitant features were a skin rash, lymphadenopathy, splenomegaly, pulmonary disease, and amyloid disease. The clinical course of this form of pericarditis is usually short and of a benign nature.

A further form which merits mention in the present context is allergic pericarditis. Clarkson, McCredie, and Fleischl (1964) describe an example in which extensive urticaria was associated with clinical evidence of pericarditis and with characteristic E.C.G. changes; signs of a pericardial effusion were also evident in the x-ray picture. Treatment consisted in antihistamine and symptomatic drugs, and recovery was complete. The pericardium must be considered as a structure in which allergic phenomena may occur (Wolff and Grunfeld, 1963). Recognition of the concept of drug-induced and hypersensitivity reactions in the aetiology of pericarditis may help to identify some of the 50% or so of those cases of pericarditis that are labelled "idiopathic."

Summary

In the elucidation of pericarditis of undetermined origin the possibility of a drug-induced state merits consideration. This and other forms of iatrogenic pericarditis are reviewed. The

report of an example attributed to phenylbutazone administration is presented; corticosteroid therapy appeared to be life-saving. Differentiation from the pericarditis of rheumatoid disease is emphasized. Allergic pericarditis is a distinct entity.

REFERENCES

- Chatterjee, S. S., and Thakre, M. W. (1958). *Tubercle (Lond.)*, **39**, 240.
 Clarkson, P. M., McCredie, K. B., and Fleischl, P. (1964). *Brit. med. J.*, **1**, 481.
 Connolly, D. C., and Burchell, H. B. (1961). *Amer. J. Cardiol.*, **7**, 7.
 Costa, G., Holland, J. F., and Pickren, J. W. (1961). *New Engl. J. Med.*, **265**, 1143.
 Domz, C. A., McNamara, D. H., and Holzapfel, H. F. (1959). *Ann. intern. Med.*, **50**, 1217.
 Dustan, H. P., Taylor, R. D., Corcoran, A. C., and Page, I. H. (1954). *J. Amer. med. Ass.*, **154**, 23.
 Engle, M. A., and Ito, T. (1961). *Amer. J. Cardiol.*, **7**, 73.
 Gimlette, T. M. D. (1959). *Brit. Heart J.*, **21**, 9.
 Glyn, J. H., and Pratt-Johnson, J. H. (1963). *Brit. med. J.*, **1**, 262.
 Goldman, M. J., and Lau, F. Y. K. (1954). *New Engl. J. Med.*, **250**, 278.
 Goldstein, R., and Wolff, L. (1951). *J. Amer. med. Ass.*, **146**, 616.
 Hodge, P. R., and Lawrence, J. R. (1957). *Med. J. Aust.*, **1**, 640.
 Lietman, P. S., and Bywaters, E. G. L. (1963). *Pediatrics*, **32**, 855.
 Litchfield, J. W. (1963). *Brit. med. J.*, **1**, 682.
 Perry, H. M., jun., and Schroeder, H. A. (1954). *J. Amer. med. Ass.*, **154**, 670.
 Sparer, P. J., and Davis, H. L. (1963). In *Dyspnoea Diagnosis and Treatment*, edited by A. L. Banyai and E. R. Levine, p. 331. Blackwell, Oxford.
 Wilkinson, M. (1962). *Brit. med. J.*, **2**, 1723.
 Wolff, L., and Grunfeld, O. (1963). *New Engl. J. Med.*, **268**, 419.

Preliminary Communications

Increased Platelet Adhesiveness in Recurrent Venous Thrombosis and Pulmonary Embolism

Brit. med. J., 1965, **2**, 797-799

The relation between platelet adhesiveness and thrombosis has been the subject of considerable investigation (see review by O'Brien, 1964). Studies directed towards venous thrombosis have been few and have been limited to the acute phase of the disease. The present investigation has revealed a significant and apparently persistent increase in platelet adhesiveness in patients with recurrent venous thrombosis and in patients with recurrent pulmonary embolism.

PATIENTS STUDIED

Platelet adhesiveness was measured in nine patients and 20 control subjects. The patient's ages ranged from 26 to 65, with a mean of 45.3 years, and the ages of the control subjects ranged from 23 to 78, with a mean age of 41.3 years. A diagnosis of idiopathic recurrent venous thrombosis, recurrent pulmonary embolism, or thromboembolic pulmonary hypertension had been made in the patients (see Table II). Repeated estimations of platelet adhesiveness were performed during the quiescent stage of the disease when there were no clinical signs of active thrombophlebitis.

The control subjects were 12 healthy members of the laboratory staff and eight hospital in-patients who showed no clinical evidence of vascular disease. Screening tests for fibrinolytic inhibitors were performed on five patients and five healthy control subjects.

MATERIALS

Glass beads (Reflex Perlen), 0.5 mm. in diameter, were prepared as described by Hellem (1960). Portex tubing (Portland Plastics Ltd., Kent) N.T.13, internal diameter 0.217 in. (0.55 cm.), was used in the preparation of the glass bead columns. Bovine thrombin (S. Maw and Sons Ltd., England) was dissolved in equal parts of glycerol and saline to a concentration of 100 units/ml. and stored at -20°C . Human urokinase (Leo Laboratories Ltd., London) was dissolved in 0.5% gelatin in phosphate buffer 0.1 M pH 7.6, stored at -20°C , and thawed immediately before use. Human plasmin was obtained from spontaneously activated plasminogen in 50% glycerin (Kabi Pharmaceutical Ltd., London) and stored at 4°C . Fibrin plates were prepared from bovine fibrinogen (Armour Pharmaceutical Company Ltd., England) by the method of Müllertz (1952) as modified by Alkjaersig *et al.* (1959).

METHODS

Blood for the study of platelet adhesiveness was collected into disposable plastic syringes and mixed in plastic tubes with 3.1% sodium citrate (one part citrate to nine parts of blood). The packed cell volume was measured and an adjustment was made to the patient's blood to bring this value to 40%, either by the addition of high-spun plasma (if the reading was $>45\%$) or packed red cells (if the reading was $<35\%$). The blood was allowed to stand at room temperature ($19-21^{\circ}\text{C}$) and was tested 30 to 60 minutes after collection.

Platelet adhesiveness was measured at room temperature by a modification of the method originally described by Hellem (1960). Two millilitres of citrated blood was passed at a constant rate through a column (6 cm. in length, containing 2.5 g. of glass beads) by means of a motor-driven 2-ml. disposable plastic syringe. The initial studies were performed with 5-g.