CARDIAC LESIONS IN REITER'S DISEASE

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Reiter's disease is a condition of unknown aetiology and in its generally recognized form is a triad consisting of urethritis, arthritis, and conjunctivitis. With increasing knowledge a number of characteristic though less constant features have been added to the clinical picture. However, many patients show only two of the cardinal features (commonly urethritis and arthritis), but the subsequent course is similar to the fully developed condition, and it is generally assumed that these are variants of a single disease entity. The condition may follow bacillary dysenteries, non-specific diarrhoea, or venereally acquired urethritis, and it most commonly affects young men. Its outstanding feature is acute arthritis, which usually involves several joints and may show a rapid evolution ; it has thus some resemblance to rheumatic fever, and this had led investigators to search for cardiac lesions.

Literature

In the older literature endocarditis was freely diagnosed on finding systolic murmurs and sometimes vague precordial discomfort soon after the onset of Reiter's disease (Stettner, 1917 ; Sick, 1918). There was no follow-up of these cases and the clinical evidence does not justify the claims made. Later some clinicians used electrocardiography as a routine investigation in Reiter's disease, and abnormal tracings were reported in a fairly high proportion of cases (Master and Jaffe, 1934 ; Gadrat and Morel, 1935 ; Candel and Wheelock, 1945 ; Feiring, 1946 ; Warthin, 1948 ; Lövgren and Masreliez, 1949 ; Shapiro *et al.*, 1949 ; Trier, 1950 ; Weinberger *et al.*, 1952 ; Mayne, 1955). The most constant finding was a prolonged P–R interval and sometimes there was a flattening of the T wave. No mention of symptoms or signs attributable to the heart was made in these cases. In the majority the changes were noticed in the first weeks after the onset of Reiter's disease ; in some the electrocardiographic abnormalities disappeared after a few weeks, in others they persisted for longer periods, but owing to the relatively brief observation time no definite conclusions could be drawn. Abnormal cardiac signs and symptoms, in addition to electrocardiographic ones, were described by several authors.

Bang (1940) reported six cases of what he called "gonorrhoeal myocarditis" ; however, the primary condition in five of them conforms to the classical picture of Reiter's disease. One of these patients had a pericardial type of pain and another had angina pectoris. The electrocardiograms showed prolonged P–R intervals, incomplete bundle-branch block, and flat or negative T waves. Films of the heart were normal and no significant murmurs were heard. Beiglböck (1943) diagnosed "mild mitral valve involvement" in one patient ; unfortunately, no details were given. Schuermann (1943) described three cases of "endocarditis" developing early in Reiter's disease and based his diagnosis on finding systolic murmurs and electrocardiographic changes which included flat T waves and slightly prolonged P–R intervals. Paronen (1948) studied 344 post-dysenteric cases of Reiter's disease in Finland during the second world war and found that 23 developed cardiac abnormalities: 7 had clinical pericarditis and 16 showed electrocardiographic changes only, which consisted of prolonged P–R interval, widened QRS complex, elevated ST segment, and flattened T waves. Owing to the circumstances of war, facilities for follow-up studies were limited, but it was noted that the pericarditis recurred in one patient some years later after he developed a further attack of Reiter's disease.

Csonka and Oates (1957) described three cases of pericarditis which developed during the course of venereally acquired Reiter's disease and noted electrocardiographic changes similar to those previously described. These patients have been closely observed since. One patient suffered a second attack of Reiter's disease with electrocardiographic evidence of transient myocarditis. The second patient had further episodes of conjunctivitis and experienced a mild attack of pericarditis three years after the first one. The third patient developed aortic incompetence and is fully described below (Case 1). Two additional cases, in which aortic incompetence developed in the course of Reiter's disease, are recorded. A fourth case, that of a woman with valvular lesions who came to necropsy, is also presented as she had several features in common with other patients ; there is, however, not sufficient evidence to diagnose Reiter's disease in this case.

Case 1

A West Indian developed non-gonococcal urethritis in 1955 at the age of 38. He gave a history of gonorrhoea in 1946, but no history of rheumatic fever or syphilis. The urethritis was followed 10 days later by arthritis involving joints of arms and legs, plantar fasciitis, and swelling of the Achilles tendons. The temperature was raised to 100° F. (37.8° C.) during the first week. A month later a mild conjunctivitis developed, and subsided in a few days. At about the same time the patient complained of central chest pain and a pericardial friction rub was heard. There was also a harsh systolic murmur at the apex. The apex beat was displaced to the left (5 in. (12.5 cm.) in the fifth space). The blood-pressure was 150/100. The electrocardiogram showed a prolonged P–R interval of 0.28 second and minor ST elevation in V_1–V_4. A chest *x*-ray film showed an enlargement of the heart due to prominence of the left ventricle (transverse diameter was 153 mm.). The affected joints and the spine were radiologically normal. Erythrocyte sedimentation rate (Westergren) was 80 mm./hour, the haemoglobin and blood count were normal. Wassermann and Kahn reactions were negative, the gonococcal fixation reaction was strongly positive. Treatment with oxytetracycline and salicylates was ineffective ; fever therapy with intravenous *Escherichia coli* vaccine was then tried with symptomatic improvement of the joints.

He was discharged from hospital three months after admission and resumed work as a porter a month later. He kept well until August, 1956, when he contracted gonorrhoea which responded to penicillin but was followed by non-specific urethritis ; two weeks later he complained of pain in both feet and lower back which lasted several months.

He recovered eventually and was back at work until in September, 1957, when there was a recurrence of polyarthritis, which responded to prednisone. He resumed work but has had several mild recurrences in the peripheral joints since. At an assessment in September, 1959, he felt reasonably fit and was able to manage heavy work without dyspnoea. The erythrocyte sedimentation rate was 23 mm./hour, and there was a slight swelling of the left knee, left ankle, and several interphalangeal joints. The blood-pressure was 160/96. The apex beat was displaced to the left (5½ in. (14 cm.) in the fifth space) and of left ventricular type. There was still an apical systolic murmur to be heard and, in addition, a soft blowing early diastolic murmur at the left sternal edge. On screening, a moderate left ventricular enlargement with diffuse dilatation of the aorta was seen. The E.C.G. showed little change from the first one taken four years before (Fig. 1). Serological tests for syphilis, which included the standard Wassermann and the treponemal immobilization test, were all negative. There were no L.E. cells in the peripheral blood; the differential agglutination test and latex fixation test were negative.

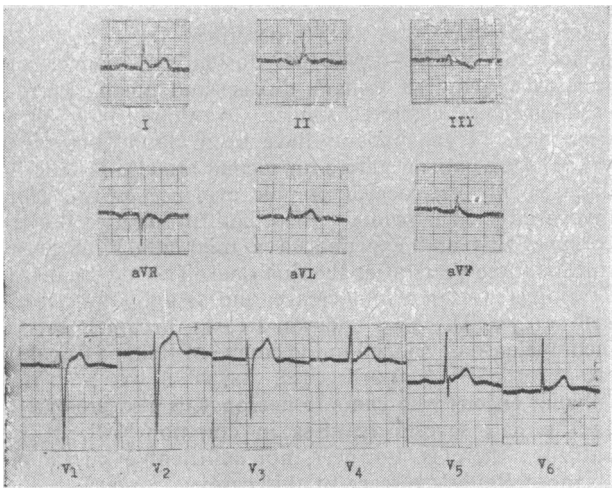

FIG. 1.—Case 1. Electrocardiogram showing P–R interval of 0.24 second and ST elevation in leads I, aVL, V_1, V_2, and V_3.

Case 2

In 1940, at the age of 27, the patient contracted gonorrhoea from his wife, and this was followed by non-gonococcal urethritis. A few days later painful swelling of several toes occurred; this subsided after a few weeks. He joined the Army and remained fit until 1945, when he developed arthritis in both ankles, low backache, plantar fasciitis, Achilles tendinitis, and bilateral iritis. Because of his illness he was invalided out of the Army soon afterwards and no abnormality of the cardiovascular system was recorded. He resumed his old occupation as a baker but found it difficult to keep working because of recurring pains in the joints of the legs, and backache. In 1950 he complained of central chest pain, but this was not investigated. In 1955–6 two iridectomies were performed; these were followed by cataract, which reduced his vision severely and he had to give up work. Since then there have been further attacks of iritis but no joint pain or swelling. For the past year he has noticed shortness of breath and palpitation on exertion.

There was no history of rheumatic fever or syphilis. On examination in July, 1959, he was found to have aortic incompetence. The blood-pressure was 170/50 and capillary pulsation in the fingers was present. The apex beat was displaced to the left (5½ in. (14 cm.) in the fifth space) and of left ventricular type; there was a soft systolic murmur and a loud blowing diastolic murmur maximal at the left sternal edge (Fig. 2). The peripheral joints and the spine were clinically normal. Vision was extremely poor and the patient could count fingers only with difficulty.

Investigations. — E.S.R. (Westergren) 33 mm./hour. Haemoglobin and blood count were normal. No L.E. cells were seen in the peripheral blood. The anti-streptolysin titre was 100 units/ml. Serological tests for syphilis were negative, and included the standard Wassermann and treponemal immobilization test. A chest *x*-ray film showed some left ventricular enlargement with a moderately prominent aortic arch. The transverse diameter in 1951 was 135 mm.; this had increased to 170 mm. in 1959. On screening the appearances were those of aortic regurgitation. In the electrocardiogram the P–R interval was 0.28 second. *X*-ray films of the sacro-iliac joints showed bony subarticular sclerosis and narrowing of joint spaces; no changes were visible in the lumbar or thoracic spine. There was a small calcaneal spur on the left side.

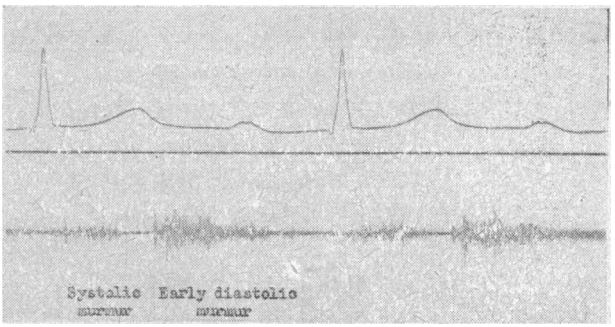

FIG. 2.—Case 2. Phonocardiogram showing systolic ejection murmur and diminuendo diastolic murmur of aortic incompetence.

He was treated with rest in bed and prednisone, starting with 40 mg. daily and reducing to half this dosage after one week. He was discharged on this dose after one month in hospital. During this time the sedimentation rate became normal. An electrocardiogram taken six months later showed a P–R interval of 0.20 second. At the time of writing he was quite well and complained only of occasional tiredness.

Case 3

A man aged 53 was first referred to one of us in February, 1957, while under observation for aortic incompetence, which was suspected of being syphilitic in spite of negative serum tests with lipoidal antigens. He gave a history of having contracted gonorrhoea in 1927 at the age of 30. In 1935 he developed arthritis of the feet and was in hospital for nine months. Later a low-grade non-gonococcal urethritis was found. Wassermann, Kahn, and gonococcal fixation tests were negative. In 1936 chronic prostatitis was diagnosed and he received intermittent treatment for a year. In 1940 he developed bilateral iritis, and there were several recurrences in the following years. In 1941 he attended with cystitis; no gonococci were found. In 1956 he noticed increasing shortness of breath.

A year later there was no history of rheumatic fever or syphilis. On examination (February, 1957) he was found to have aortic incompetence. The blood-pressure was 180/60 and there was a waterhammer pulse. On auscultation a soft diastolic murmur was heard at both sternal margins. *X*-ray examination of the heart showed some left ventricular hypertrophy (transverse diameter 140 mm.) but no calcification of the aorta. The only abnormality of the electrocardiogram was a prolonged P–R interval of 0.24 second. There was no urethral discharge and the urine and prostatic secretions were free from pus. The eyes showed multiple opacities in both anterior chambers. Both feet were deformed, with marked lateral deviation of the toes. *X*-ray examination of the feet showed disorganization of the metatarsophalangeal joints, with subluxation and lateral deviation of the phalanges as well as bilateral calcaneal spurs. *X*-ray examination of the spine showed some sclerosis of both sacro-iliac joints (Figs. 3–5). The Wassermann and treponemal immobilization tests were negative. On

examination of the cerebrospinal fluid the findings were normal (no cells, protein 40 mg./100 ml., Lange 0000000000, Wassermann negative). E.S.R. (Westergren) 36 mm./hour. Haemoglobin and white-cell count were normal.

Between February, 1957, and December, 1959, the patient had two further attacks of iritis, otherwise his general condition remained unchanged. In December, 1959, a further cardiac assessment was made, when it was felt that there were no symptoms referable to the cardiovascular system. E.S.R. was 6 mm./hour. Peripheral signs of aortic incompetence were marked. The blood-pressure was 150/40. The other findings were similar to those of 1957 except for the electrocardiogram, which now showed evidence of left ventricular hypertrophy and a P–R interval of 0.42 second.

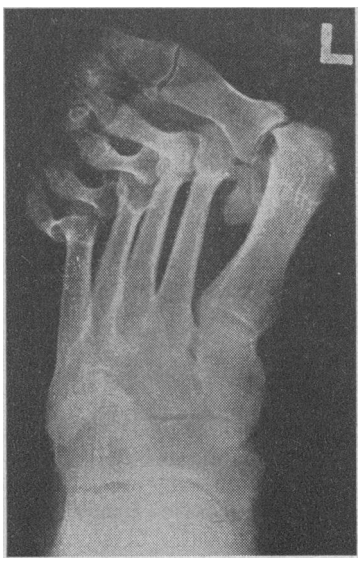

FIG. 3.—Case 3. Disorganization of metatarsophalangeal joints with lateral deviation of the toes.

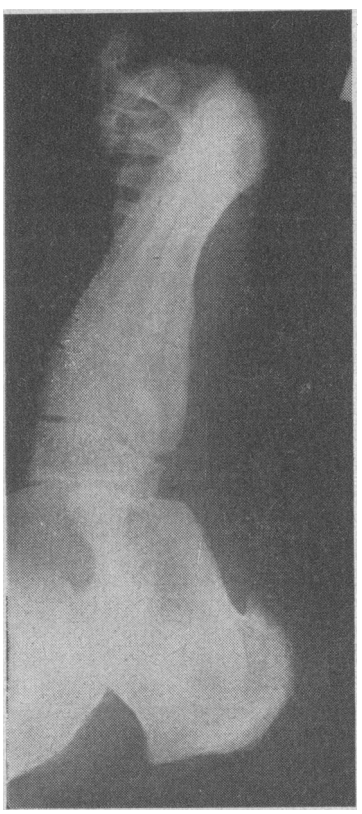

FIG. 4.—Case 3. Calcaneal spurs.

No specific treatment has been given to this patient, and his physical condition has remained virtually unchanged during the three years of observation.

A further case, that of a woman who came to necropsy, is described below, though the diagnosis of Reiter's disease could not be made with certainty. The aetiology of the cardiovascular lesion which led to her death was puzzling, and it was only in retrospect that the possibility of Reiter's disease suggested itself.

Case 4

A married woman developed iritis of the left eye in 1943 at the age of 37. Right iritis followed in 1947; since then she had noticed dyspnoea and palpitation on moderate exertion. In 1951 aortic regurgitation was diagnosed. Earlier in that year painful swelling of both knees and ankles occurred, lasting for a few weeks. She was admitted to St. Mary's Hospital for investigation. The pulse was of waterhammer quality; the blood-pressure 140/40. The cardiac impulse was 5¼ in. (13.3 cm.) out in the left fifth space. A grade 3 systolic murmur was maximal over the aortic area and there was a faint early diastolic murmur down the left side of the sternum. No signs of cardiac failure were found. Clinically, no abnormalities of the peripheral joints or spine were noted. There was a low-grade fever of 99° F. (37.2° C.). No history of rheumatic fever, chorea, or syphilis was obtained.

Investigations.—Haemoglobin 90%; white blood count 12,000, with 8,650 neutrophils; E.S.R. 48 mm./hour. (Westergren); blood Wassermann reaction and Kahn test were negative. The electrocardiogram showed sinus rhythm, a P–R interval of 0.24 second, and a Q–T interval of 0.40 second. There was a slight ST depression in the left

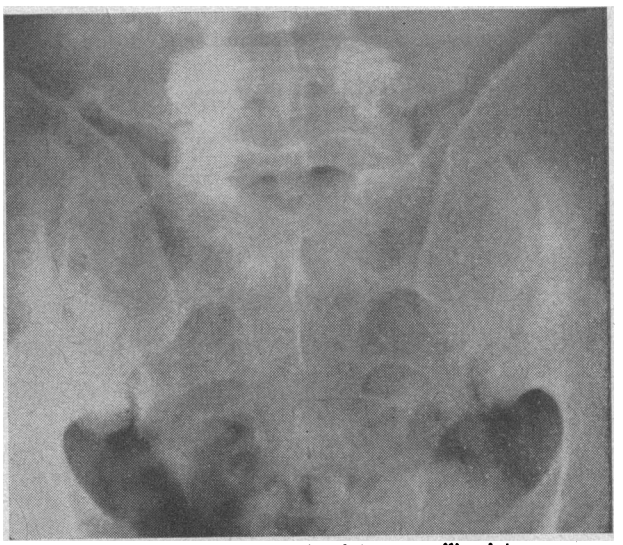

FIG. 5.—Case 3. Sclerosis of the sacro-iliac joints.

ventricular leads, thought to be an effect of digitalis. Chest *x*-ray examination showed some left ventricular enlargement with a transverse diameter of 150 mm. Muscle biopsy gave no evidence of polyarteritis nodosa.

Her dyspnoea improved after rest and the administration of digitalis. Repeated attacks of iritis caused progressive loss of vision, despite a right iridectomy in 1954. The E.S.R. remained slightly raised.

In 1956 attacks of nocturnal dyspnoea necessitated readmission to hospital. Auricular fibrillation was now present and the jugular venous pressure was raised. The cardiac enlargement was more marked and there were numerous crepitations at the left base. A to-and-fro aortic murmur was present. The E.C.G. showed auricular fibrillation. On the *x*-ray film of the chest the transverse diameter of the heart measured 170 mm. and both lung fields showed widespread congestive changes.

Cardiac failure responded slowly and incompletely to rest, digitalis, mersalyl, and salt restriction. She quickly relapsed after discharge from hospital and died on April 19, 1956, in intractable cardiac failure, hastened by the occurrence of pulmonary emboli.

Post-mortem Findings

Post-mortem examination by Dr. E. A. Wright at St. Mary's Hospital showed evidence of long-standing congestive heart failure with terminal pulmonary infarction.

Gross Appearances.. — *Externally* deceased showed moderate pitting oedema of the ankles and lumbar pad. *Internally* there was a recent pericarditis with fibrinous exudate over the epicardium. The heart was greatly enlarged (565 g.), owing mainly to hypertrophy of the left ventricle. The thickening of the tricuspid valve cusps was considered to be within normal limits. The commissures of the pulmonary valve cusps were separated respectively 1, 0.5, and 0.5 mm. The endocardium of the left atrium was opaque and thickened. The mitral valve cusps were slightly thickened and the cordae tendinae were moderately shortened, thickened, and matted together. There was considerable endocardial thickening over the apices of the papillary muscles. The mitral valve was, however, not

stenosed, although it was thought that there was a slight degree of incompetence. The aortic valve was incompetent to a marked degree, its cusps being elongated, and showed thickened, rolled, cord-like edges which prevented their approximation. The commissures were, however, neither separated nor fused. The coronary arteries were free of disease. The thoracic aorta showed five distinct scarred areas up to 1 cm. diameter where the wall was thinned, stretched, and pearly grey in colour. In addition there was extensive superficial irregularity indiscriminately mixed with superficial plaques of fatty atheroma. The pulmonary artery was also superficially scarred but atheroma was not present. The lungs were congested and showed three small branches of the pulmonary arteries occluded with emboli. The embolus in the right lower lobe was associated with a recent infarct, 5 cm. in diameter, estimated to be 2 to 3 days old. The liver and kidneys were congested. The spleen (360 g.) was enlarged and showed a firm pulp. The right femur showed red marrow throughout its length. The uterine cervix was eroded. There were no significant lesions in any of the other organs.

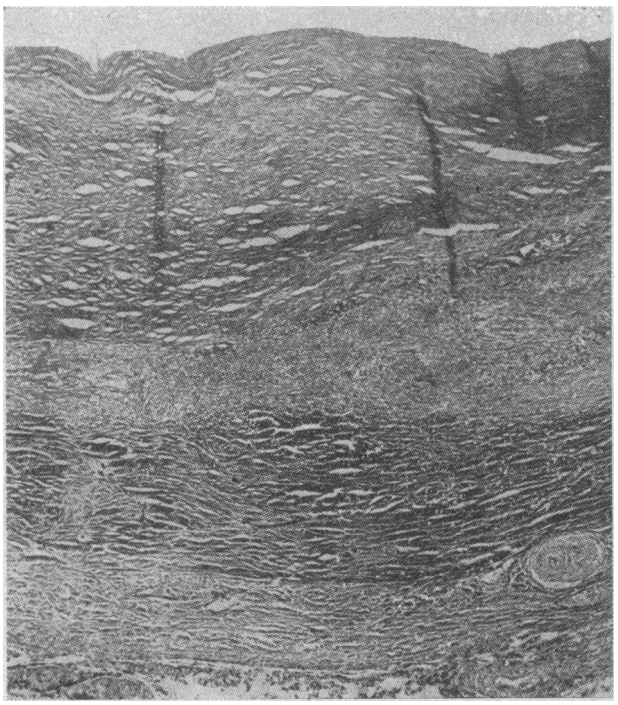

FIG. 6.—Case 4. Low-power view (×50) of thoracic aorta stained with haematoxylin and eosin. The thickening of the intima and adventitia and the irregular thinning of the media are seen.

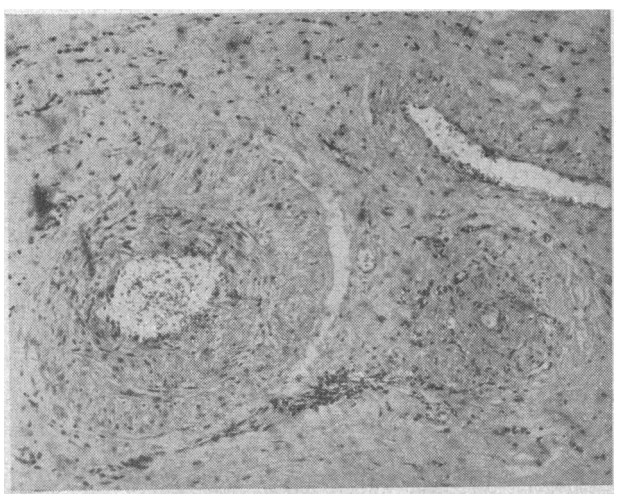

FIG. 7.—Case 4. High-power view (×78) of vessels from adventitia of thoracic aorta stained with haematoxylin and eosin, showing endarteritis and lymphocytic infiltration.

Microscopical Appearances.—The *aorta* (Figs. 6 and 7) showed intimal thickening and moderate atheroma, which was slightly calcified in places. The media was greatly thinned in the scarred areas and showed vascularization. The adventitia was greatly thickened with fibrosis and showed many small arterioles which were narrowed by endarteritis. In addition there were many areas of cellular infiltration, sometimes situated perivascularly. The cells were mainly lymphocytes, but there were also small numbers of plasma cells and occasional macrophage cells. The *left atrium* showed endocardial thickening with fibrous tissue which in places was 1 mm. thick. The myocardium showed slight diffuse replacement with fibrous tissue. The *cervix* showed a few mucous cysts and an erosion. The erosion was markedly vascular, but the subjacent infiltration with chronic inflammatory cells was slight. Sections of other organs confirmed the macroscopic findings.

Comment.—The macroscopic and microscopical lesions found in the cardiovascular system of this case show some features that are usually ascribed to the late effects both of syphilis and of rheumatic endocarditis. However, it seems probable that these changes are the late result of some other widespread cardiovascular disease.

Discussion

The incidence of serious valvular lesion of the heart arising in Reiter's disease is probably very low. Thus the possibility of this complication was suggested as early as 1917 by Stettner, yet no case with unequivocal valvular lesion has been reported to date. It is possible that such cases have been missed, as commonly the observation period was short and the subsequent cardiac status remained unknown. It is also likely that a patient with arthritis and valvular lesion of the heart is diagnosed as having rheumatic fever because the less prominent and often fugitive involvement of the urethra and the eyes is not inquired into.

Three patients previously described as having sustained attacks of pericarditis have been followed up by us and all have shown evidence clinically or electrocardiographically of further episodes of cardiac involvement. In one of the patients incompetence of the aortic valves has developed, and that this is not a chance finding is supported by the description of two further cases. The three men with aortic incompetence were found in a long-term study of 215 patients with Reiter's disease. The experience in ankylosing spondylitis is similar in this respect, as the two patients with aortic incompetence reported by Ansell *et al.* (1958) were diagnosed during a careful survey of 222 patients with classical ankylosing spondylitis. There is also similarity in the histological features of the cardiac lesions in Case 4 and those described in ankylosing spondylitis (Bauer *et al.*, 1951 ; Ansell *et al.*, 1958).

The difficulty in distinguishing the aortic lesions of ankylosing spondylitis from those caused by syphilis has been noted by several authors. In Reiter's disease, which may be closely linked with venereal infection, the exclusion of concomitant syphilis as an aetiological factor in the development of aortic lesions is clearly of importance. The recent advent of truly specific treponemal serological tests has made this task much easier, and it was possible to take full advantage of this in three of our patients.

It is noteworthy that iritis was present in three of our four patients, whereas in our experience of 215 consecutive cases of Reiter's disease it was found only in 17%. Radiographic evidence of sacro-iliitis was seen in two of the three male patients, but there was no suggestion of spinal involvement as found in classical ankylosing spondylitis.

The nature of the cardiovascular lesions described here is unknown, and, although potentially dangerous, they have not caused serious functional disability in three of the patients. One patient received prednisone therapy, during which time the erythrocyte sedimentation rate became normal, as did the previously prolonged P–R interval.

Summary

Three cases of Reiter's disease with aortic incompetence are described. The aortic lesion is believed to have developed during the course of Reiter's disease. This complication appears to be unusual, as no similar cases have been reported in the literature.

A fourth patient, a woman with iritis, transient arthritis, cervicitis, and aortic incompetence, came to necropsy and is also recorded, though the diagnosis of Reiter's disease could not be made with certainty.

A characteristic feature of the electrocardiogram was a prolonged P–R interval present at some time in all our patients.

The nature of the cardiac lesion is unknown.

Similar cardiac lesions have been described in a number of patients with ankylosing spondylitis, and this could give rise to some diagnostic difficulties.

We thank Dr. A. E. Wilkinson, director of the V.D. Reference Laboratory (M.R.C.), for carrying out the serological tests for syphilis. One of us (G. W. C.) received a grant from the U.S. Public Health Service under the aegis of the Medical Research Council Working Party on Non-Specific Urethritis.

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The *Hospitals Year Book, 1961*, has recently been published by the Institute of Hospital Administrators. The main change in this edition is that the directory of Northern Ireland Hospital Services has been revised and expanded to bring the information given about hospital management committees and their hospitals in Northern Ireland into line with that given in the sections for Great Britain. The *Year Book* is obtainable from the Institute, at 75 Portland Place, London W.1, price 59s. 6d., postage 2s. 3d.

FATAL DIABETIC KETOSIS

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There has been a marked reduction in the number of deaths from diabetic ketosis during the past 20 years. The low mortality of between 2 and 5%, in a series reported by Harwood (1951) and Joslin *et al.* (1959), has led to a general belief that fatal ketosis is now exceptional, and that when it occurs it is due to faulty treatment. However, mortality rates of about 15% reported from Melbourne (Greenaway and Read, 1958) and Cincinnati (Skillman *et al.*, 1958) do not support this. The absence of a published series from hospitals in this country in recent years has prompted the present study, in which 19 fatal cases are described.

Material

The results of treatment of 160 episodes of severe ketosis are considered. These were consecutive admissions to the General Hospital, Birmingham, in the five years between January, 1955, and December, 1959, and were contributed by 122 patients (2 patients had ketosis five times, 2 four times, 4 three times, and 16 twice). Fourteen of the patients had ketosis more than once in the same year. We have included in the series only those patients who showed obvious and visible air hunger on admission to hospital, for at this stage it can safely be claimed that ketosis has become severe and that coma is impending. The level of plasma bicarbonate was not regarded as a sufficiently reliable guide to be used as a criterion of clinical severity (Owens and Rockwern, 1939 ; Collen, 1942 ; Black and Malins, 1949 ; Harwood, 1951 ; Hudson *et al.*, 1960).

Results

Age, Sex, and Seasonal Incidence.—There were 60 episodes in males and 100 in females ; the series does not include those in children under 10. The Table shows the number of episodes in each 10-year age-group for both sexes, and Fig. 1 compares the incidence of ketosis in males and females with the prevalence of diabetes in all patients attending the hospital diabetic clinic. Thus the series is of comparable age and sex composition to those of Harwood (1951) and Cohen *et al.* (1960), but the mean age of admission is 10 years above that of the Joslin Clinic series (Joslin *et al.*, 1959). The significant excess in the incidence of ketosis in adolescent girls has been found before (Joslin *et al.*, 1937 ; Owens and Rockwern, 1939). Unlike the findings of most American authors (Danowski, 1957 ; Cohen *et al.*, 1960), Fig. 2 shows that the episodes of ketosis were seasonal, being especially common in November and December and uncommon in May and June. We consider the seasonal incidence to be associated with respiratory infection, which was a common precipitating cause of ketosis.