

endocarditis in usually seeking out valves which have been previously damaged by rheumatism or which are congenitally deformed. In nearly all the recorded cases, including the two previously described in England, old rheumatic valvulitis has been found. Our case is the fourth example of infection superimposed upon a congenital bicuspid aortic valve (Wechsler and Gustafson, 1942; Voth, 1949; Spink *et al.*, 1948).

Cases of bacterial endocarditis due to *Brucella* organisms have certain distinctive characteristics. These are well illustrated by our case, and may be summarized as follows:

1. The aortic valve is usually attacked. Occasionally the mitral valve is also involved, but in only two cases was the disease confined to it (Rennie and Young, 1936; Spink *et al.*, 1942).

2. There is a great tendency to produce ulceration. The valve cusps become perforated and there are often haematomata in the myocardium or in the auricular or ventricular septa. In the first case described by Call *et al.* (1944) the inflammatory process had ulcerated through the root of the aorta as far as the epicardium, but, unlike our case, rupture into the pericardium had evidently not occurred.

3. Aneurysmal dilatation of the aortic sinuses is common. Probably (see Jones and Langley, 1949) inflammation of the sinus wall causes separation of the annulus fibrosus from the aortic media, so that blood passes through the wall of the aorta and stretches the exposed muscle of atrium or septum. It then clots and eventually becomes organized, so giving rise to an aneurysm lined by fibrous tissue. That this is the correct explanation in our case is supported by the presence of the surrounding histiocytes filled with iron pigment.

4. A persistent leucopenia is common, but, unlike uncomplicated brucellosis, there is a relative neutrophilia rather than a lymphocytosis, apart from one exception (Steyrer, 1934).

5. Extremely low blood pressure, which was a prominent feature in this case—the systolic pressure being only once recorded as above 100 mm.—has also been found in other cases. In one of these (Gounelle and Warter, 1935) a pressure of 60/45 was recorded, and five others had pressures of 105 mm. systolic or less at one time or another. Furthermore, evidence of alteration in conduction of the heart muscle has been demonstrated in several cases, although not in ours. Both these factors may well be due to the severe myocarditis commonly present.

6. The accompanying bacteraemia often gives rise to a variety of focal lesions in the viscera, such as the granulomata, suppurative lesions, and focal necroses seen in our case (compare Matzdorff, 1933; Sprunt and McBryde, 1936; Rabson, 1939; Call *et al.*, 1944) as well as embolic lesions.

7. There may be improvement in symptoms and cessation of pyrexia for a period, even when infection remains active (Call *et al.*, 1944; Voth, 1949; Hart *et al.*, 1951), so that a patient with *Brucella* endocarditis may appear deceptively well—an important practical point, well illustrated by our case. There was little evidence of septicaemia, only slight pyrexia, no definite embolic manifestations, and no clinical enlargement of the spleen, at a time when the histological evidence suggests that the endocarditis was progressing.

The possibility of such rare complications reinforces the need for the early diagnosis of all cases of undulant fever and their treatment with full courses of antibiotics.

Summary

A case of *Brucella* endocarditis is reported. It was superimposed on a congenital bicuspid aortic valve and gave rise to aneurysms of the aortic sinuses. Terminal rupture of the heart resulted from a small abscess in the wall of one of these aneurysms.

The characteristics of this type of endocarditis are described in the light of this and previous cases.

The possibility of such a serious latent complication emphasizes the need for early diagnosis and treatment of all cases of brucellosis.

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OBSERVATIONS ON GOLD THERAPY IN RHEUMATOID ARTHRITIS

BY

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Gold salts have been widely used for the treatment of rheumatoid arthritis for about 20 years, and during that time many reports of the results have been published. Although some of these reports have been of small numbers of cases, others have been extensive; for example, Forestier (1935) reported on over 550 treated patients, and Hartfall *et al.* (1937) on 690. The general impression from these reports is that a favourable response may be expected in about 80% of cases. Thus Short *et al.* (1946) analysed the results of gold treatment in cases collected from 35 published reports. Making allowance for the different criteria adopted, they found that it was claimed that 84% of 1,943 cases showed definite improvement of any degree, 59.3% of 2,924 showed noteworthy improvement, and 22.6% of 1,825 were arrested. It is probably true to say that on this basis gold has become the most widely accepted single therapeutic weapon in the treatment of rheumatoid arthritis.

Need for Controlled Trials

Unfortunately, none of the results in the early series were controlled in any way, and even now the number of reports of controlled series is strikingly few. Control of results in rheumatoid arthritis is essential for two reasons. The first is that spontaneous improvement and arrest can occur at any time; it seems to occur more often in patients who have developed the disease at an earlier age and in earlier stages of the disease, and it is notable that it is for such patients that gold is said to give the best results. The exact course and the natural history of untreated rheumatoid arthritis are difficult to assess, as with such a prolonged and disabling condition it is impossible to keep patients entirely without treatment, either from their doctor or from friends. Few figures are available even for the results of simple and non-specific treatment, but Short *et al.* (1946)

assessed such results for 274 patients in 1937, after a period of six months to seven years. They found 52.9% with noteworthy improvement and 16.4% in which the condition was arrested. In a later paper (Short and Bauer, 1948), covering 250 cases followed for a further 10 years, 53.2% were found to be improved and 15.9% in remission, with 9% arrested for five years or longer. They did not consider that their own results for gold treatment in 35 patients were any better than this. They quote Furlong (1942) for the opinion that 60-70% of patients receiving general measures show improvement. Thompson *et al.* (1938) also claimed that various measures other than gold resulted in marked or moderate improvement in 76.5% of 274 patients, with 6% classified as being well.

The second difficulty in assessing results lies in the determination of objective improvement. In 1937 Hartfall *et al.* stated that they had been unable to eliminate the psychological effect of injection therapy, but thought that "most observers will no doubt agree that psychogenic factors do not play an important role in the majority of patients." In recent years the effect of the emotional state of the patient and of the emotional atmosphere on subjective tests of improvement has been increasingly noted. Clark (1951) has stressed the effect of placebo treatment, and Bedford (1951) has shown that the response to subjective tests may vary from hour to hour even in the absence of any therapy. There is as yet, however, no agreement on which tests may be considered objective. Quin *et al.* (1950) accept tenderness, power of grip, and speed of movement as suitable tests, and Janus (1950) accepts tenderness and grip. As Clark has pointed out, these tests depend on the co-operation of the patient, and changes in the emotional tone may, by varying the threshold of sensitivity to pain, cause variations in the results obtained. Strictly objective tests that may be used include the measurement of joint size, temperature, and blood flow; estimation of the E.S.R. and degree of anaemia; and estimation of plasma viscosity and C-reactive globulin. The difficulty of using many of these tests in routine assessment of improvement is obvious.

Results in the Literature

The first report of a controlled trial of gold salts was by Ellman *et al.* (1940). They treated 30 patients with large doses of gold salts and 30 with small doses; 30 patients were observed as controls. They claimed that in 14 of those on large doses, 8 on small doses, and 1 of the controls became inactive, and that 14, 20, and 22 respectively showed some improvement. These findings were supported by E.S.R. estimation and measurement of joint swelling. After one year the results in the treated cases remained better than in the controls.

Fraser (1945) carried out a carefully controlled investigation on 110 patients, 61 being treated with sodium aurothiomalate ("myocrisin") and 49 with control injections. The results were assessed after one year. He found that 82% of those on gold improved clinically, compared with 45% of the controls, although 75% of the latter claimed subjective improvement. He did not claim arrest in any cases, but 56% of those on gold were considered to show great improvement, compared with 33% of the controls. Fraser believed that, although gold was the best single form of treatment available at the time, the good results claimed by the majority of observers were unjustifiably high owing to the lack of adequate controls.

Waine *et al.* (1947) are quoted by Egelius *et al.* (1952) as having treated 58 of 120 patients with gold. After an average of 2.9 years they found 56.9% of the treated cases symptom-free or greatly improved, compared with 29.1% of those treated physically.

Adams and Cecil (1950) treated 106 of 189 patients with gold. After one year they claimed complete remission in 78.7% of cases on gold and in 29.8% of controls for cases of less than six months' duration, while in those in which the disease was present for a longer period remissions oc-

curred in 48.9% and 16.7% respectively. After an average of four years, 55.7% of gold cases and 36.1% of controls remained in remission. These figures are high for cases showing complete inactivation; by using the strict "therapeutic criteria" of the New York Rheumatism Association (Steinbrocker *et al.*, 1949) they are lowered to 44.8% for gold and 27.7% for controls; such figures indicate how varying criteria may affect the results obtained in uncontrolled series.

Merliss *et al.* (1951) treated 28 patients with aurothioglycanilide ("lauron") and 44 controls with saline, serum, or antireticulocytotoxic serum. They found no essential difference in the results of the two groups, and again stressed the great variation of results with a varying emotional atmosphere.

The introduction of cortisone has shown what effect can be achieved by a really potent remedy in suitable cases of rheumatoid arthritis, and has given a standard against which the results of gold therapy can be set. Since it is widely agreed that gold may produce dangerous toxic effects, it is essential to be sure that any benefit obtained is great enough to warrant its continued use. Gold treatment will not necessarily be discarded completely through the introduction of cortisone, and indeed its use to potentiate or prolong the action of cortisone is under investigation. In these circumstances, and considering the varying results reported, it seems essential that further controlled studies of the results of treatment should be carried out.

Present Investigation

A course of treatment lasting 13 weeks was given to 220 patients. All were treated in the out-patient department of the Glasgow Royal Infirmary and were seen once weekly for treatment and observation. The diagnosis of rheumatoid arthritis was based on the following criteria: polyarthritis; radiological confirmation or lack of evidence of other joint pathology; normal blood uric acid; negative Wassermann reaction; negative gonococcal complement-fixation test; negative serum agglutination test for abortus fever; acceptable clinical history and picture; and raised E.S.R. and raised plasma viscosity. The patients were assessed for improvement at the end of the course, again three months later, and, finally, one year after treatment had ceased. Assessment of subjective improvement was by pain, performance, well-being, and appetite; objective improvement by joint measurements, E.S.R., plasma viscosity, and degree of anaemia.

Treatment was as follows:—(1) Gold: weekly intramuscular injections of sodium aurothiomalate (total dose 0.8-1 g., divided over 13 doses). (2) Copper: weekly intravenous injection of "cuprelone" (1st dose, 10 mg.; 2nd and 3rd doses, 25 mg.; 4th and 5th doses, 50 mg.; 6th and 7th doses, 75 mg.; 8th and 9th doses, 100 mg.; 10th and 11th doses, 150 mg.; 12th and 13th doses, 200 mg.). (3) Saline: weekly intramuscular injections of 3 ml. of sterile normal saline. (4) Physiotherapy: weekly treatments of various forms of heat therapy and gentle massage. (5) Arsenic: weekly intravenous injections of nearsphenamine (1st dose, 0.15 g.; 2nd to 13th doses, 0.3 g.). (6) Aspirin: 10 gr. (0.6 g.) acetylsalicylic acid powder three times a day for 13 weeks; inter-viewed weekly.

The results at the end of the course for all patients are set out in Table I. These results are not, however, strictly comparable one with another, as the cases treated by gold and

TABLE I.—Results at End of Course; All Cases

Treatment	No. of Cases	% Symptomatically Improved	% Objectively Improved
Gold	38	75	50
Copper	60	50	33
Saline	60	42	33
Arsenic	21	70	50
Physiotherapy	22	50	33
Aspirin	19	50	25

arsenic had been selected in that they were all early and frankly active cases with an E.S.R. of over 40 mm. in one hour. The remaining groups included patients over 50 years of age and with advanced disease.

Table II shows the results adjusted by the removal of such patients from each group. The figures in this small series indicate that the results of a single course of treatment with gold salts are no better than those obtained by the other methods described.

TABLE II.—Results Adjusted to Exclude Elderly and Inactive Cases

Treatment	No. of Cases	At End of Course		At 3 Months		At 1 Year	
		A	B	A	B	A	B
Gold ..	38 (0)	75	50	62	28	53	30
Copper	40 (20)	77	52	66	32	50	33
Saline ..	38 (22)	74	53	60	36	55	30
Arsenic	21 (0)	70	50	60	30	50	29
Physiotherapy	16 (6)	70	43	58	29	48	30
Aspirin	13 (6)	77	38	59	25	60	25

A=Percentage symptomatically improved. B=Percentage objectively improved.

Figures in parentheses show the number of cases eliminated from each group to make the basis for selection comparable to that for gold therapy.

Summary

Attention is drawn once more to the small number of reports of controlled trials of gold therapy and to the variation in the results obtained.

A series of 220 patients have been treated by a variety of measures, 38 of them receiving gold. No appreciable difference in the results has been found, either immediately or after one year.

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Miss Patricia Hornsby-Smith, M.P., Parliamentary Secretary to the Ministry of Health, was the guest speaker at the annual general meeting of the Central Council for the Care of Cripples, which took place on April 10. She said she sympathized very much with the point of view of the council on the edict of the General Nursing Council preventing nurses from starting their training until they are 18, and thus eliminating the year of orthopaedic pre-nursing which many girls of 17 had been doing, but she hoped that some compromise might yet be reached in this matter. The Ministry of Health readily acknowledged and appreciated the voluntary work which the council was doing, and was glad to support the project being launched for the sale of goods made by cripples. A committee was being set up by the Ministry to inquire into the rehabilitation and training of all those physically handicapped. Miss Hornsby-Smith said that, following a circular to 129 local authorities asking them to submit schemes for the care of their physically disabled, 65 had already submitted schemes to the Minister. She thought local authorities had a difficult task in deciding which service to expand and which to create without increasing the rates.

DISSEMINATED ASPERGILLOSIS AND MONILIASIS ASSOCIATED WITH AGRANULOCYTOSIS AND ANTIBIOTIC THERAPY

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Pulmonary aspergillosis and local infections with monilia are not rare, but the disseminated forms are much less common. The use of antibiotics in the presence of these fungous infections is dangerous. The following case is of interest because both fungi were present in the lesions.

Case Report

A window cleaner aged 45 was seen on April 3, 1951, with an abscess of the thigh. He was treated with sulphonamides, and was admitted on April 18 for evacuation of the pus (culture, *Staphylococcus aureus*). He later developed consolidation of the right lung. This was treated with penicillin, 14 million units, and resolved slowly. Albuminuria developed on May 28 and persisted. The white-cell counts on April 26 and July 26 were 4,600 and 4,300 per c.mm., respectively. He was discharged on August 31, and shortly afterwards developed ulceration of the throat, which responded to chloramphenicol. He was readmitted on October 5 and agranulocytosis was found (white cells 1,800, polymorphonuclears 108 per c.mm.), and this persisted. Chloramphenicol was continued (total dose, 30 g.), with oral and intramuscular penicillin. Pyridoxine, 250 mg., "livadex" 20 ml., and three blood transfusions of 1 pint (570 ml.) were given. Consolidation of both lungs developed on November 1 (sputum culture, *Ps. pyocyanea*) and he died on November 7.

At necropsy on November 8 fibrinous pleurisy was present on both sides. A large infarct was found in the right upper lobe and a smaller infarct in the middle lobe; the pulmonary arteries to these areas showed thrombosis. In the left upper lobe was a pale area of consolidation 6 cm. in diameter, but no cavitation. A typical red infarct was present in the left kidney, and both kidneys showed several smaller dark-red areas in the cortex. The liver was enlarged (3,500 g.), pale, and firm, with numerous firm white nodules up to 1.5 cm. in diameter with some hyperaemia at the edges. There were a few similar areas in the spleen. The oesophagus was covered throughout with a ragged soft membranous exudate covering shallow ulcers. There was one small acute ulcer in the stomach. In the duodenum and jejunum there were numerous ulcers up to 1 cm. in diameter with a yellowish base and raised haemorrhagic border. A few ulcers were found in the ileum and one in the caecum. Red marrow was present in the sternum and vertebral bodies. Exploration of the left thigh showed fibrosis at the site of the abscess, but no pus or involvement of the femur.

Sections of the lesion in the left lung showed a central area of necrosis, in which only the outlines of the blood vessels could be distinguished. Surrounding this was a zone of inflammatory infiltration in which plasma cells and macrophages predominated. No polymorphonuclears or eosinophils could be seen. Branching mycelium was present throughout the necrotic zone, invading the inflammatory zone and large and small vessels at the edge. The left lung showed a typical infarct with mycelium in the thrombi. The kidney contained an infarct with mycelium in the lumen of the artery. Sections of liver and spleen revealed areas of necrosis similar to that in the lung, but with a very dense network of mycelium, which extended on to the peritoneal surface of the liver. The ulcers in the alimentary tract showed necrotic centres surrounded by the inflammatory reaction, and invasion of the muscularis and blood vessels by mycelium.