REGRESSION OF AMYLOIDOSIS SECONDARY TO RHEUMATOID ARTHRITIS

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The steady decrease in uncontrolled sepsis and tuberculosis in the last few decades has revealed rheumatoid arthritis to be important as a cause of amyloidosis. Extensive renal damage may result from the deposition of amyloid material in the renal arterioles and glomerular basement membrane. These changes often lead to proteinuria and the development of the nephrotic syndrome, while progressive renal failure and death in uraemia is a common termination (Abrami *et al.*, 1931; Rosenblatt, 1933; Gedda, 1955). Trasoff *et al.* (1944) noted a 91% mortality in recorded rheumatoid cases. We have seen uraemic death in four out of eight patients at Hammersmith Hospital (Missen and Taylor, 1956).

Recovery from secondary amyloidosis due to tuberculosis (Waldenström, 1928; Rosenblatt, 1936) or sepsis (Walker, 1928; Sherlock, 1945) has occasionally been described, but only two cases have been recorded with apparent recovery from amyloidosis secondary to rheumatoid arthritis. Trasoff *et al.* (1944) reported the development of heavy proteinuria, hypoproteinaemia, and gross anasarca in a 14-year-old girl with a three-year history of severe juvenile rheumatoid arthritis. Amyloidosis was suspected, and a 70% tissue retention of Congo red supported the diagnosis, although no histological proof was obtained. Treatment with liver extract and transfusions of plasma was accompanied by decrease in the activity of the arthritis and disappearance of the nephrotic syndrome. Five years later the arthritis was inactive and no evidence of amyloid disease was detected. The tissue retention of Congo red had fallen to 15%. The clinical course and changing Congo-red tests suggested the development and resolution of amyloidosis in this patient.

The case described by Kennedy (1935) followed a similar course, but again no histological studies were made and the follow-up was short. This 43-year-old man developed proteinuria and anasarca 18 months after the onset of severe generalized arthritis. The initial Congo-red test showed only 37% tissue retention, but this rose to 74% two months after the onset of proteinuria. Improvement occurred following treatment with an oral liver preparation, and six months later oedema was absent and proteinuria reduced to a trace. The Congo-red tissue retention had fallen to 27%, but no further follow-up was recorded.

These reports suggest that complete and prolonged control of rheumatoid activity might allow regression of secondary amyloidosis. The introduction of corticotrophin and steroid hormones raised the hope that adequate control of rheumatoid disease would become possible. Suppression of the clinical signs of rheumatoid activity is difficult to achieve with steroids, and the high maintenance dose required often results in the develop-

ment of troublesome effects. These hormones, however, produce considerable symptomatic benefit in patients with the nephrotic syndrome by abolishing proteinuria and oedema. On theoretical grounds at least these hormones might be expected to have a beneficial effect on amyloidosis secondary to rheumatoid arthritis, particularly in those patients developing the nephrotic syndrome.

Clinical evidence of the effect of corticotrophin and steroids on amyloidosis is conflicting and generally unfavourable. McCall and Fisher (1953) described improvement in two out of three patients with primary laryngeal amyloidosis treated with corticotrophin and cortisone respectively. Shuttleworth and Ross (1956) observed no increase in the incidence of amyloidosis in steroid-treated lepromatous leprosy, a disease frequently complicated by amyloidosis. They noted that these hormones did not influence established amyloid disease. However, West and Newns (1952) reported the case of a patient with rheumatoid arthritis with a normal liver biopsy prior to cortisone treatment, who after initial improvement on cortisone deteriorated, death occurring one year later. Amyloidosis was found at necropsy. Cortisone had failed to produce any favourable effect on the course of the disease in this case, and could have aggravated its development. Paulsen (1950), Bjørneboe *et al.* (1952), Schneckloth and Page (1955), and Goodman and Baxter (1957) report a total of seven cases of amyloid nephrosis treated with steroids. The amyloidosis was thought to be primary in four and secondary in three. The response was uniformly poor, and in Paulsen's two patients the proteinuria was increased.

Experimental evidence is conflicting. A number of workers have studied the influence of steroid hormones and corticotrophin on experimental amyloidosis produced in mice and rabbits by the injection of sodium caseinate. Grayzel *et al.* (1956) demonstrated a protective action of corticotrophin and cortisone in certain doses, while Latvalahti (1953) and Peräsalo and Latvalahti (1954) showed that these hormones increased the incidence of amyloidosis in treated animals.

There is also some clinical and experimental evidence suggesting an association between thyroid lack and amyloidosis. Myxoedema may be complicated by the development of amyloidosis, and Symmers (1956) mentions three such cases, one of which showed clinical recovery from the amyloidosis when treated with thyroid hormone. Experimental thyroidectomy increases the incidence of amyloidosis in mice injected with sodium caseinate, while thyroid hormone reverses this effect (Peräsalo and Latvalahti, 1954). While it is difficult to draw conclusions from experimental amyloidosis, these facts suggest that thyroid hormone may be of importance in protecting tissues from the deposition of amyloid material and might favour reabsorption.

The purpose of this paper is to describe the progress of two patients with rheumatoid arthritis complicated by amyloidosis in whom remissions of the rheumatoid disease were followed by apparent regression of the amyloidosis. The part played by steroid hormone in the treatment of these and other patients is discussed. Two patients received a course of treatment with triiodothyronine, and the results are described.

Case 1

In July, 1947, a girl, then aged 5 years, was first admitted to the Rheumatism Research Unit of the Canadian Red

Cross Memorial Hospital with severe generalized rheumatoid arthritis of two years' duration. At that time she was severely ill, with widespread active joint involvement, high fever, and a sedimentation rate between 43 and 68 mm./hour. The liver and spleen were not enlarged and no proteinuria was noted on repeated testing with salicyl-sulphonic acid over the next two and a half years. Serum proteins (8.5 g.%) showed an A/G ratio of 2.4. In this period she was gradually remobilized despite persistent disease activity. In June, 1950, an exacerbation of joint symptoms necessitated readmission: the liver edge was noted to be 5 cm. below the costal margin, the spleen was not palpable, and the E.S.R. had risen to between 60 and 120 mm./hour. Proteinuria was detected, about 300 mg./100 ml., and the daily urinary protein excretion was found to vary between 2 and 4 g. Intravenous pyelography showed no abnormality but a Congo-red test (September, 1950) showed 37% tissue retention in one hour, none being excreted in the urine. Gum biopsy was negative for amyloid but liver biopsy showed moderately severe amyloidosis maximal in the mid-zonal region.

On her third admission (July to November, 1951) with active joint disease, the liver had enlarged further and the spleen was now palpable. Proteinuria had increased further (3-5 g./day) and serum protein had decreased (4.6-6.8 g.% with an A/G ratio between 1.1 and 2.3). Cortisone given at 100 mg./day for a six-weeks period temporarily reduced the E.S.R. from its former level of about 100 mm./hour to 50 mm./hour but failed to affect fever, hepatosplenomegaly, or proteinuria: Congo-red tissue retention changed from 70% just before hormone therapy to 95% just after.

During 1952 the disease activity decreased, the E.S.R. fell (50 mm./hour), and the spleen was no longer palpable. Improvement continued during her fourth admission, July, 1953, to September, 1954: the E.S.R. fell from 26 to 10 mm./hour, the liver became smaller, and proteinuria was absent on repeated testing. With this the serum protein rose to a range of 7.5-8.6 g.% with an A/G ratio of 2-2.4. Congo-red tissue retention at one hour was still, however, 92%. In March, 1955, she appeared to be in remission, with spleen and liver impalpable, proteinuria absent, and E.S.R. 10 mm./hour.

A sudden exacerbation with fever occurred necessitating her fifth admission (November, 1955, to March, 1956) with E.S.R. 100 mm./hour, decrease in serum protein (5 g.%), and reappearance of protein in the urine (5-16 g./day). This gradually settled again and protein was absent in August, 1956, and March, 1957. In September, however, traces appeared (15 mg./100 ml.), and in November a renal exacerbation with oedema and massive proteinuria up to 20 g./24 hours led to her sixth admission. This nephrotic phase without rheumatoid activity, without liver or spleen enlargement, but with an E.S.R. of 100 mm./hour has lasted up to the time of writing, with concomitant fall in serum

protein. The blood urea has risen to 49 mg./100 ml. with a transient episode of retention up to 160 mg./100 ml.

Comment.—This child suffered from prolonged active rheumatoid arthritis and developed classical amyloid disease, the signs of which regressed completely during a prolonged remission of arthritis, only to return with a further exacerbation of rheumatoid activity. A short course of cortisone given in 1951 did not immediately influence the arthritis or the amyloidosis, and the only observed change during this time was an increase in the tissue retention of Congo red. The remission of the arthritic process appeared to occur spontaneously over the next six months following cortisone therapy. A shorter remission appeared subsequently. The development of the typical nephrotic syndrome in 1957 not associated with increased joint activity indicates that the underlying renal damage is extensive, and that reabsorption of the amyloid deposits did not occur in the period of clinical improvement.

Case 2

In 1948 a man, then aged 24, contracted pulmonary tuberculosis. A right-sided thoracoplasty was performed in 1950, since when the chest disease has remained clinically and radiologically inactive. In 1952 he developed polyarthritis of the rheumatoid type with fever, pain, swelling, and effusion of the small joints of the hands, wrists, elbows, knees, and ankles. No significant hepatosplenomegaly was detected and proteinuria was not found on repeated testing

TABLE I.—Treatment with Triiodothyronine

Case No.		Liver (cm.)	Spleen (cm.)	E.S.R. (mm./hr.)	Urea (mg.)	Urine Protein (g./24 hr.)	Alb./a ₂ Ratio
2	Before treatment	13.0	0	132	18	6.6	1.1
	After 30-480 µg. for 8 weeks ..	13.5	0	110	20	8.5	1.4
3	Before treatment	1	0	107	41	7.6	2.1
	After 30-120 µg. for 4 weeks ..	0	0	100	40	3.8	2.5

in the ward. The E.S.R. varied between 60 and 100 mm./hour. The Rose-Waaler sheep-cell test was negative, and x-ray films of the involved joints and spine showed only osteoporosis. Despite bed rest and treatment with salicylates, local heat, and splints, the disease remained active (see Fig. 2). Phenylbutazone gave some relief until dyspepsia prevented its further use.

Proteinuria was detected in May, 1953, and the patient was admitted for further investigation. Examination showed persistent rheumatoid activity in the hands, elbows, and knees. The spleen was not felt, but the liver edge was palpable 2 cm. below the costal margin. Proteinuria varied between 1 and 4 g. a day, the E.S.R. was 50 mm./hour, and blood urea 30 mg./100 ml. A Congo-red test showed 94% tissue retention at one hour. Biopsy of the buccal membrane was normal, but liver biopsy disclosed amyloid deposits.

Treatment with cortisone in doses up to 125 mg. daily failed to control the arthritic symptoms, and during the next ten months hepatosplenomegaly and proteinuria steadily increased. The patient was readmitted in March, 1954, when persistent effusions were present in the small joints of the hands, and x-ray films disclosed periostitis of the fourth metatarsals and erosions of the metacarpal heads. Corticotrophin was substituted for cortisone, and 20 units a day completely relieved the arthritic symptoms. A rising blood pressure to 210/120 mm. Hg necessi-

FIG. 1.—Case 1. Course and treatment.

tated discontinuation of corticotrophin, but a maintenance dose of cortisone relieved his symptoms and his protein pattern returned to normality.

This remission continued until 1956, when a relapse of the arthritis occurred, involving the wrists, knees, and ankles,

despite maintenance cortisone of 50 mg. a day. Hepatomegaly and proteinuria rapidly returned (Fig. 2). The cortisone dose was increased by increments to 150 mg. a day, but knee effusions persisted despite the addition of intra-articular hydrocortisone. Serum electrophoresis again

showed the changes seen in amyloid nephrosis (Fig. 3). While on this dose of cortisone a course of triiodothyronine was given for eight weeks in increasing doses up to a total of 480 μ g. a day, with little detectable effect on the symptoms or signs of the disease (Table I). The thyroid hormone was therefore withdrawn, and under cover of antituberculous drugs the cortisone dosage was raised to 200 mg. daily. The knee effusion slowly subsided and the E.S.R. fell. By May, 1957, the arthritis was less active, the liver smaller, and the proteinuria dropped to 0.9 g. daily. The blood urea was 30 mg./100 ml., and the serum electrophoretic pattern was again normal (Fig. 3). Maintenance cortisone dosage of 125 mg. daily has enabled the patient to return to full-time work, but the right knee has continued to show

mild rheumatoid activity and slight proteinuria has persisted. The liver enlargement is unchanged.

Comment.—This patient showed regression of the clinical signs of amyloidosis during a remission of rheumatoid disease, coincident with hormone therapy. Proteinuria disappeared and the liver edge regressed 11 cm. during 12 months. Biopsy of the liver and kidney, however, showed that reabsorption of the amyloidosis had not occurred, and relapse of the rheumatoid disease was closely followed by recurrence of massive hepatomegaly and proteinuria. Despite evidence of continued amyloidosis the patient remains in good health while taking a maintenance dose of cortisone.

FIG. 2.—Case 2. Course and treatment.

FIG. 3.—Case 2. Serial electrophoretic tracings of serum proteins.

Cases 3 and 4

Two further patients, both females, with amyloidosis secondary to rheumatoid arthritis were treated with steroid hormone in an attempt to reproduce the improvement noted in Cases 1 and 2, but in both of them the dose of prednisolone required to suppress the active joint symptoms gave rise to peptic ulceration and necessitated withdrawal of the hormone. The changes in their clinical and biochemical state during the hormone treatment were minimal (see Table II).

TABLE II.—Treatment with Prednisolone

Case No.		Liver (cm.)	Spleen (cm.)	E.S.R. (mm./hr.)	Urea (mg.)	Urine Protein (g./24 hr.)	Alb/a ₂ Ratio
3	Before treatment	0	0	55	41	4.5	4.0
	After 15 mg./d. for 6 months	0	0	32	46	5.5	4.6
4	Before treatment	1	0	120	25	3.0	1.5
	After 25–30 mg./d. for 3 months	0	0	42	22	4.0	1.45

We have observed the development of amyloidosis in four rheumatoid arthritic patients who had at some stage received treatment with corticotrophin or steroid hormone. In each case, however, the arthritis was of a severe generalized unremitting type, in which amyloidosis is most commonly seen, and at no time had the disease activity come under control with steroid hormone. It was not thought that the hormone had precipitated the development of the amyloidosis. The two patients died in renal failure. In one the cortisone was given only in the five weeks preceding death, when the patient was already in uraemia. In the second, cortisone was administered after the discovery of proteinuria, indicating that amyloidosis was probably already present. Post-mortem examination of both patients showed widespread amyloidosis, which did not differ in any way from that seen in patients not treated with steroid hormone.

In Cases 2 and 3 treatment with triiodothyronine failed to show clinical or biochemical changes suggesting any improvement of the amyloidosis (Table I) during this time.

Discussion

Regression of the clinical signs of amyloidosis during the prolonged remissions described in the above cases suggested that the amyloid deposits in the liver, spleen, and kidneys were undergoing resorption as described by Waldenström (1928). The biopsy from our patients failed to show this. It is known that amyloid is a somewhat inert substance, and both deposition and absorption of the material occur slowly. The rapid decrease in liver size in Case 2 during 1955 was not associated with histological evidence of resorption. Although liver biopsies are not necessarily representative, the apparent increase in amyloid in the second biopsy makes it unlikely that significant resorption had occurred. Peräsalo's (1948) experience is of interest in relation to this point. He reported a case of pulmonary tuberculosis complicated by amyloidosis proved by liver biopsy. Temporary improvement with regression of the signs of amyloidosis occurred and a further liver biopsy failed to show amyloid disease, but deterioration and death soon followed, and necropsy examination revealed extensive hepatic amyloidosis.

In both of our patients there is strong evidence that extensive renal damage has resulted from amyloidosis. Case 1 later developed a typical nephrotic syndrome after two remissions of three years and one year respectively, during which she was free from proteinuria, while in Case 2 the renal biopsy showed amyloid deposits at a stage when the clinical signs of amyloidosis had been absent for one year. During these remissions the Congo-red test remained abnormal in each patient. The exacerbations of the rheumatoid arthritis were in each case accompanied by the rapid reappearance of proteinuria. This is not unexpected in view of the irreversible ischaemic renal scarring seen in the later stages of amyloidosis. Richter (1954) has shown in rabbits that experimental splenic amyloid may be completely reabsorbed, with return to normal histological appearance, when the stimulus to amyloid deposition is withdrawn; however, the renal amyloid lesions remain unchanged.

Proteinuria is an extremely variable manifestation of renal disease and may fluctuate considerably from day to day in the absence of change in the underlying renal lesions. Corticotrophin and the steroid hormones may abolish or greatly reduce urinary protein loss in 60% or more of nephrotic patients (Lange *et al.*, 1957). Lauson *et al.* (1954) have produced evidence that corticotrophin decreases glomerular permeability to albumin in patients with the nephrotic syndrome. Steroid treatment of these patients may result in the disappearance of proteinuria, but, although there may be some improvement in the renal histological picture at biopsy (Galán and Masó, 1957), a considerable number of patients relapse, with reappearance of proteinuria, despite maintenance steroid treatment. It seems likely that the disappearance of proteinuria in our cases may have resulted from this non-specific effect of corticotrophic and steroid hormone on the renal clearance of protein.

The findings in these patients indicate that little reliance can be placed in changes in the clinical signs of amyloidosis. Disappearance of hepatosplenomegaly and proteinuria, with return to normal of electrophoretic patterns and sedimentation rate, may occur despite persistence of amyloidosis. All these signs may rapidly recur with exacerbation of the precipitating rheumatoid arthritis. Despite the failure to demonstrate the resorption of amyloid deposits in our patients there is no evidence that treatment with steroid hormone had a deleterious effect on the amyloid process. The development of this nephrotic state in a rheumatoid arthritic patient with active joint disease would fully justify a trial of these substances.

Summary

Despite experience in amyloidosis secondary to tuberculosis and sepsis, there does not seem to be any histologically proved case of recovery from amyloidosis secondary to rheumatoid arthritis. In two cases the disappearance of clinical signs of amyloidosis was unaccompanied by other evidence of amyloid resorption. Relapse of the rheumatoid disease was accompanied by return of splenomegaly and proteinuria, and biopsy confirmed the continued presence of amyloid in the liver and kidneys. Steroid hormones did not appear to influence the disease unfavourably, and may have induced remissions in the two patients reported.

Triiodothyronine did not influence the clinical or biochemical findings in two patients treated.

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INTESTINAL PERFORATION AND WIDESPREAD ARTERITIS IN RHEUMATOID ARTHRITIS DURING TREATMENT WITH CORTISONE

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Perforations of the small and large intestines in patients under treatment with cortisone have not often been reported, and the few cases recorded usually have had coexisting intestinal disease. Sloan, Briggs, and Halsted (1951) report one case of intestinal perforation, Tulin, Kern, and Almy (1952) three cases, Pessel, Beairsto, Edwards, Rathmell, and Wise (1953) one case, all in ulcerative colitis. Levin, Rivo, Scott, Figueroa, Fred, and Barrett (1953) describe a case of perforation in rheumatoid arthritis with widespread arteritis; Sauer, Dearing, and Wollaeger (1953) one case in ulcerative colitis and two in regional enteritis; Bradley (1954) one case of rheumatoid arthritis without arteritis; Palmer, Mason, and Adams (1955) two cases of diverticulitis; and Gumpel, Lewis, and Thomson (1957) one case of ulcerative colitis.

In the present paper three cases of intestinal perforation are described—one case with perforations in the jejunum and duodenum, one case in the caecum, and another in the sigmoid colon. All three were cases

of rheumatoid arthritis under treatment with cortisone, and at necropsy each showed a widespread arteritis.

Case 1

A 54-year-old man was admitted to hospital in May, 1956, for seven weeks for progressive stiffening of joints. In 1948 he developed pulmonary tuberculosis and was treated in a sanatorium until 1952 with resulting arrest of the disease. In January, 1956, he developed pain in the fingers and rheumatoid arthritis was diagnosed. In May, 1956, he was treated with prednisolone, 30 mg. a day. He was readmitted in December, 1956, and on an attempt to reduce the drug the arthritis became worse, so the prednisolone was discontinued. No lupus erythematosus cells were found. He was readmitted in August, 1957, because he had become bedridden, and was found to have the typical deformities of rheumatoid arthritis, with contraction of the hands, elbows, and knees, and many subcutaneous nodules. He was started on cortisone, 150 mg. a day, which was decreased to 70 mg. a day on September 1. On September 7 his third left finger became gangrenous. The cortisone was decreased to 60 mg. a day on September 10. On September 23 he developed severe abdominal pain, and on laparotomy was found to have a recent perforation 4 cm. in diameter of the sigmoid colon. His course was downhill, and after repair of the perforation he died on October 2.

At necropsy generalized peritonitis was found, with 150 ml. of thick yellow fluid in the abdominal cavity. The lungs contained numerous areas of fibrosis. The heart weighed 310 g., no pericarditis being present. The liver was pale and the kidneys appeared normal. The other organs showed no relevant changes. Microscopy revealed an acute arteritis in about half the small arteries in the heart, pancreas, small and large intestines, adrenals, and psoas muscle. The arteritis consisted (Fig. 1) of a deeply staining eosinophilic material (fibrinoid necrosis) extending through part or all of the artery wall and infiltration of its wall with inflammatory cells, mostly polymorphonuclear leucocytes. The heart, pancreas, small and large intestines, adrenals, psoas muscle, kidneys, liver, testes, and oesophagus showed a few small arteries (Fig. 2) with a grossly thickened fibrous intima and partial disruption of the internal elastic lamina; these vessels were thought to be a healed stage of the arteritis. The adrenals were depleted of fat.

Case 2

A 39-year-old man was admitted to hospital with perforation of the caecum in August, 1957. In 1942 he developed pain and stiffness in the joints of his hands and feet. A diagnosis of rheumatoid arthritis was made, and this pursued a chronic course. He was treated with cortisone in 1949 and was given several courses over the next few years, but details and dosage are not known. In 1955 he became short of breath, and was found to be anaemic, with an enlarged spleen. The spleen was removed and a diagnosis of Felty's syndrome was made. Cortisone was again given, and in August, 1957, he developed severe abdominal pain. Laparotomy was performed and a perforation of the caecum with surrounding abscess formation was found. He developed generalized peritonitis, and four days later a resection of part of his small intestine and caecum was performed. After this he was given cortisone, 50 mg. daily. A faecal fistula and subphrenic abscess supervened and he died one month later.

At necropsy there was generalized chronic peritonitis with an abscess measuring 10 cm. in diameter on the posterior aspect of the liver. The heart weighed 340 g. and there was a moderately acute pericarditis. The adrenals were atrophic. The other organs showed no relevant changes. Microscopy revealed an acute arteritis in the small and large intestines, testes, pancreas, kidneys, liver, and adrenals. A healed arteritis was seen in the heart, small and large intestines, pancreas, and kidneys. The adrenals were depleted of fat and atrophic, and about one-quarter of each was necrotic.

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