

severe insulin deficiency of an absolute type, as Bornstein and Lawrence (1951) have suggested. While others possess levels of insulin which are not very different from those of normal subjects in the post-absorptive state, this does not imply that the pancreatic islet tissue is normal in patients of this type. The islet tissue in this type of patient is in any case secreting insulin under the stimulus of a raised blood sugar, probably to a maximal extent. Indeed, such patients appear to be unable to respond to an additional glucose load by secreting additional insulin (Seltzer and Smith, 1959). Failure of blood pyruvate to rise after glucose ingestion in this class of diabetic patients (Smith and Taylor, 1956) may also be related to their inability to secrete insulin. It may be, therefore, that most patients in this group are suffering from some degree of impairment of islet-cell function.

This group ultimately seems to suffer a complete exhaustion of the islet cells, since insulin is not detectable in their pancreases at necropsy (Wrenshall *et al.*, 1952), nor does endogenous insulin (assayed by immunological methods) appear to be present in their serum some time after the beginning of insulin treatment (Yalow and Berson, 1961). Insulin is also present at very low levels in the protein fractions of serum from these patients when the blood is taken many hours after insulin injections (Taylor, 1963, unpublished).

This type of diabetes, associated at the time of onset with relatively high blood-insulin levels, shows some analogies with that induced in animals by growth-hormone administration (Randle and Young, 1956). Nevertheless, in this form of human diabetes (as opposed to that of the obese) growth-hormone levels do not seem to be raised (Erllich and Randle, 1961). It is uncertain, therefore, if growth hormone has any direct role in the genesis of this type of diabetes, though its presence might be necessary for the diabetes to develop.

In conclusion, it is suggested that severe diabetes presenting with loss of weight and ketosis is predominantly a disease in which insulin secretion is either deficient or becoming deficient. The high blood-insulin levels sometimes encountered in the early stages of this condition may reflect a stage of overstimulation of beta cells preceding final exhaustion. It is possible that in at least some of these patients the insulin antagonism is a consequence and not the cause of the insulin deficiency.

Summary

Serum from 22 cases of untreated diabetes presenting with ketosis has been examined for insulin activity.

Insulin was found in serum or protein fractions of many of these cases, though it was not detectable in a minority of cases with high blood sugars or in diabetic coma. Effects of this insulin in whole serum often appeared to be masked by insulin antagonists. One such antagonist, with its possible relation to diabetic ketosis, is discussed.

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PROGNOSIS IN THE ANARTHROTIC RHEUMATOID SYNDROME

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The anarthrotic rheumatoid syndrome (Bagratuni, 1953, 1956, 1957), or polymyalgia rheumatica as Stuart Barber (1957) named the condition, has now been accepted as a clinical entity under various names (*British Medical Journal*, 1957; *Lancet*, 1961). Todd (1961) has given the most recent survey of the disorder and presented 20 new cases.

The present article deals with the fate of 50 patients with this syndrome who have been followed up in the period 1945–61. The symptomatology and principal findings in 28 patients have already been described (Bagratuni, 1953, 1956) and the blood-protein changes analysed (Bagratuni, 1957).

By 1958 22 more cases had been collected and followed up. The principal findings in these 50 patients are shown in Tables I and II.

Follow-up

A comprehensive review of the 50 patients was undertaken in 1961 with recall for clinical reassessment of all patients who had not been regularly seen. Muscle tenderness, joint swelling or tenderness, limitation of joint movement, and rheumatic nodules were especially looked for.

TABLE I.—Data on 50 Cases

Age at onset, years:		Haemoglobin (lowest) (g./100 ml.):	
Male (12) { Mean .. 60.3		Standard .. 14.8	
{ Range .. 37-76		Mean .. 11.1	
Female (38) { Mean .. 60.5		S.D. .. ±1.9	
{ Range .. 19-78		Range .. 5.9-14.8	
Pain in:		White-cell count:	
Shoulder-girdle .. 44		Slight leucocytosis .. 12	
Cervical spine .. 42		Leucopenia .. 2	
Lumbar spine .. 37		Eosinophilia .. 4	
Other joints .. 31		Lymphocytosis .. 4	
Muscles .. 45		Abnormal white cells .. 6	
Chest .. 14		Bone-marrow (14):	
Abdomen .. 8		Plentiful or abnormal plasma cells .. 8	
Transient joint-swelling .. 37		Blood albumin (42) (g./100 ml.):	
Loss of weight .. 8		Mean .. 3.4	
Fever and sweating .. 29		S.D. .. ±0.7	
Headache .. 16		Range .. 2.2-4.4	
Cough .. 12		Blood globulin (42) (g./100 ml.):	
Abdominal symptoms (flatulence, vomiting, diarrhoea) .. 23		Mean .. 3.2	
Skin lesions:		S.D. .. ±0.5	
Nodules .. 7		Range .. 2.2-4.8	
Erythematous rash .. 4		Plasma fibrinogen (42) (mg./100 ml.):	
Eye lesions:		Mean .. 647	
Iritis .. 3		S.D. .. ±149	
Conjunctivitis .. 2		Range .. 297-1,240	
Punctate keratitis .. 1		Cryoglobulins (24) .. 10	
Lymphadenopathy .. 12		Electrophoresis of plasma proteins (24):	
Splenomegaly .. 2		Low albumin .. 23	
Heart: systolic murmur .. 10		Raised α-globulins .. 22	
Miscellaneous features:		Raised γ-globulins .. 9	
Sjögren's syndrome .. 2		Differential sheep-cell agglutination titre (34):	
Precipitating factor:		D.A.T. 128 .. 2	
Physical or emotional stress .. 17		D.A.T. 32 .. 5	
Family history:		D.A.T. 16 .. 7	
Rheumatic fever or rheumatoid arthritis .. 10		Negative .. 20	
"Arthritis" or "fibrositis" .. 6		L.E. cells (33) .. 0	
None .. 26		Urine:	
Not known .. 8		Trace of protein .. 9	
Chest radiography:		Cast and cells .. 2	
Indefinite shadows .. 3		Progressed to typical rheumatoid arthritis .. 2	
Joint radiography:			
Osteoarthritis .. 33			
E.S.R. (highest) (mm./hr. Westergren):			
Mean .. 96.7			
S.D. .. ±25.8			
Range .. 25-148			

TABLE II.—Age of Onset in Years, Age when Seen, and Duration of Anarthrotic Rheumatoid Disease in 50 Cases; "Anarthrotic" Implies no Joint-swelling; "Arthrotic" Implies Transient Joint-swelling

Type of Disease	No.	Age when Seen (Years)		Age at Onset (Years)		Duration (Years)	
		Mean	Range	Mean	Range	Mean	Range
Anarthrotic:							
Males	9	58.3 ± 12.9	37-76	57.3	37-76	8.0 ± 7.1	2'12-15
Females	33	59.5 ± 17.7	32-85	58.1	19-75	4.7 6.7 4.7	3 12-34
Total	42	58.9 ± 15.3	32-85	57.7	19-75	6.4 + 6.9 -6.4	2'12-34
Arthrotic:							
Males	3	67.0 ± 6.0	61-73	63.3	56-73	10.0 ± 8.0	2-18
Females	5	65.8 ± 10.7	51-79	62.8	51-78	5.4 + 7.1 -5.4	2'12-18
Total	8	66.8 ± 8.9	51-79	63.1	51-78	7.7 ± 7.5	2 12-18
All types	50	62.8 ± 12.1	32-85	60.4	19-78	7.1 ± 7.0	2 12-34

Laboratory investigations included estimations of the erythrocyte sedimentation rate (E.S.R.), haemoglobin, and the differential sheep-cell agglutination titre (D.A.T.). Blood films were examined and searched for L.E. cells. Plasma proteins, mucoproteins, and lipoproteins were also analysed. Many patients had further radiological studies of the peripheral joints and spine.

The recent protein studies and the radiological findings will be published elsewhere.

Assessment of improvement or deterioration in patients with myalgia is difficult, as the condition is so subjective; but terms such as symptomless, almost symptomless, and improved do convey degrees of change which are fairly specific and can be correlated with objective enhancement or limitation of movement and changes in the E.S.R.

Fate of the 50 Patients

Eleven of the 50 patients have died of various disorders unconnected with their rheumatic complaint. Nine patients last seen in 1958, when they were symptomless, could not be traced.

The remaining 30 were extensively re-examined and investigated. Two of these have progressed to frank rheumatoid arthritis.

The Dead

Of the 11 patients who died, three succumbed of congestive cardiac failure, one of pulmonary embolus and congestive cardiac failure, one of myocardial infarction, one of bronchopneumonia, one of miliary tuberculosis, one of secondary haemolytic anaemia, one of uraemia and chronic glomerular nephritis, one of purpura after gold therapy, and one of a suspected abdominal neoplasm (Table III).

Post-mortem examination, carried out in six patients, confirmed the cause of death. In these the joints and spine were carefully searched for signs of rheumatoid disease, and sections were cut from most organs for signs of "collagen disease," arteritis, or other pathology. Apart from changes associated with the immediate cause of death, no changes could be found of muscle, joint,

TABLE III.—Cause of Death and Post-mortem Results in 11 Patients Who Died

Sex and Age	Duration of Rheumatic Symptoms (Years)	Rheumatic Symptoms at Time of Death	Cause of Death	Post-mortem Findings
F 56	12	Slight myalgia	Bronchopneumonia	Nil
F 60	2	Nil	Miliary tuberculosis	Miliary tuberculosis. Generalized amyloidosis. Joints and spine normal
F 68	1.75	Slight myalgia	Myocardial infarction	Right coronary occlusion. Myocardial infarction. Basilar artery thrombosis. Atherosclerosis. Joints and spine normal
F 69	2.5	Nil	Congestive heart failure	Nil
F 72	5	"	Secondary haemolytic anaemia	Patchy fibrinoid necrosis of some afferent arterioles. Focal glomerular lesions with suggestion of "wire-loop" appearance at several points. No haematoxophil bodies, but appearances suggestive but not confirmative of systemic lupus erythematosus. Some oedema of soft tissue round right wrist, but this and all other joint surfaces normal. Spine normal
F 77	2	"	Congestive cardiac failure	Bronchopneumonia. Coronary and generalized atherosclerosis. Multiple cerebral thrombi. Joints and spine normal
F 78	0.25	"	"	Nil
F 84	7	"	? Abdominal neoplasm	"
M 66	12	Myalgia	Purpura after gold therapy	"
M 72	18	Nil	Uraemia. Chronic glomerular nephritis	Chronic diffuse glomerular nephritis. Generalized atherosclerosis. Osteoarthritis of knee- and ankle-joints. No active rheumatoid disease in these or other joints
M 73	15	Slight myalgia	Pulmonary embolus. Congestive cardiac failure	Senile generalized atherosclerosis. Aortic stenosis. Osteoarthritis both knees. Other joints and spine slight osteoarthritis only
Mean 70.5	7.1			
S.D. ±8.0	±6.1			
Range 56-84	0.25-18			

or vascular disease apart from degenerative osteoarthritic and atherosclerotic changes compatible with the age of the patients.

Two patients who had had transient swellings of various large joints during life, diagnosed radiologically as due to osteoarthritis, were confirmed at post-mortem examination to have osteoarthritic changes only in these and other joints.

The 72-year-old woman who died of secondary haemolytic anaemia did show a few focal glomerular lesions in the kidneys, and there was a suggestion of wire-loop appearance at some points. There were also patches of fibrinoid necrosis in some of the afferent arterioles, but no haematophilic bodies were present, and the changes were not sufficient to warrant a definite diagnosis of systemic lupus erythematosus. No L.E. cells were found in life and the D.A.T. was negative. Her rheumatic symptoms had almost cleared at the time of death apart from minimal sporadic aching around the shoulder muscles.

Only four patients were complaining of muscular discomfort at the time of death, and this was minimal compared with the original severity of their rheumatic symptoms.

The mean duration of symptoms in the 11 patients who died was 7.1 years. This was exactly the same as the mean duration of symptoms in the group of 50 patients as a whole (Tables II and III), suggesting that the natural history of the disease is fairly constant, that the disease is self-limiting, and that the eventual cause of death at the mean age of 70.5 years is unconnected with the rheumatic process, from which most had by this time recovered.

The Living

Two of the 50 patients have in recent months developed typical rheumatoid arthritis. A 65-year-old woman developed persistent classical polyarthritis of the hands five years after suffering from prodromal symptoms, without joint swelling, identical with the rest of the group. Her D.A.T. was negative.

A 57-year-old woman developed persistent polyarthritis of the hands, knees, and ankles after two years of prodromal symptoms also identical with the rest of the group. She required steroids for control of severe symptoms. Her D.A.T. was 128. Neither had L.E. cells in the peripheral blood.

The course of the illness as shown by the severity of muscular aching and stiffness is summarized in Table IV. The mean age at the time of onset of symptoms was 60.4 years (62.8 years when seen).

TABLE IV.—Progress of 50 Patients

Deaths	11 (22%)
Persistent symptoms	2 (4%)
Improved	17 (34%)
Almost symptomless	14 (28%)
Symptomless	15 (30%)
Progressed to frank rheumatoid arthritis	2 (4%)

Fifteen patients became quite symptomless; 14 became symptomless apart from occasional slight aching round the shoulder-girdle, upper arm, and thigh muscles; and 17 improved considerably.

In only two patients did severe muscular aching persist; in one for 34 years, in another for nine years. The clinical pattern in these patients differed in no way from that of the others. Neither had joint swellings or radiological signs of spondylitis. Their D.A.T. was negative.

Of the two patients with Sjögren's syndrome, one lost some of her rheumatic aching and improved considerably after 30 years of symptoms, but less so than the majority of the group, and there was little change in the dryness of the mouth and eyes. The other has had persistent severe symptoms for 34 years with remissions. These two patients have had the longest history of myalgia in the group. Neither has ever had any joint swellings and the D.A.T. was negative.

The mean duration of symptoms in 50 patients was 7.1 years (Table II).

Of the nine patients not seen since 1958, all were symptomless or much improved at that time.

The two patients who developed rheumatoid arthritis did so after two and five years of prodromal symptoms. This was a shorter period than the mean total duration of the illness in the remainder, suggesting that if rheumatoid arthritis is to develop it will do so before the mean total duration of symptoms of 7.1 years elapses.

None of the eight patients who had had transient slight joint swellings lasting a day or two in the past (Bagratuni, 1956) had recurrences of joint-swelling and none progressed to rheumatoid arthritis.

Biopsies

Seventeen biopsies were performed on 13 patients if the examination of organs removed at operation is included (Table V). No significant pathological changes were found except in organs removed at operation for specific diseases. Unfortunately, no biopsy was performed on the seven patients who had what appeared to be typical rheumatic nodules.

TABLE V.—Results of 17 Biopsies Performed on 13 Patients

Sex	Age	Organ	Result
F	32	Liver	Normal
F	49	Right pectoralis major	Dilated capillary in superficial dermis only. Muscle normal
F	51	Skin from anterior chest wall	Slight hyperkeratosis only
F	55	1. Right quadriceps 2. Synovial membrane from left knee	Normal
F	56	3. Right temporal artery Left pectoralis major	Medical calcification only Slight oedema. Scanty lymphocytic infiltration of superficial dermis. Insufficient to suggest earliest scleroderma. Not suggestive of any other disease. Muscle normal
F	56	Left pectoralis major	Normal
F	62	Skin from anterior chest wall	"
F	65	1. Liver 2. Skin from left eyelid papilloma	Squamous-celled papilloma only
F	67	Left temporal artery	Intimal fibrosis. Some atherosclerosis only
F	67	1. Left quadriceps 2. Gall-bladder (cholecystectomy)	Normal Chronic atrophic cholecystitis
M	56	Right pectoralis major	Some loss of striation and homogeneous faintly basophil staining of muscle fibres. Non-specific degenerative changes in a few muscle fibres
M	67	Gall-bladder (cholecystectomy)	Chronic hypertrophic cholecystitis
M	75	Prostate (prostatectomy)	Benign prostatic hyperplasia

Laboratory Investigations

E.S.R.—The improvement in clinical symptoms was reflected in a fall of the E.S.R. (Table VI). In the original 50 patients the mean highest E.S.R. was 96.7 mm./hour (Westergren). By 1961 the mean E.S.R. had fallen to 30.8 mm./hour (Westergren). Whereas originally only 12 (24%) patients had an E.S.R. below

70 mm./hour (Westergren), by 1961 this was below 50 mm./hour in 39 (78%), and in 17 (34%) the levels were below 20 mm./hour (Westergren).

TABLE VI.—*Erythrocyte Sedimentation Rates of Patients When First Seen and Recent*

E.S.R. at Onset (mm. hour, Westergren)			Recent E.S.R. (mm. hour, Westergren)		
Over 120 mm.	11	(22%)	Over 50 mm.	11	(22%)
" 100 "	24	(48%)	Under 50 mm.	39	(78%)
" 90 "	29	(58%)	" 20 " ..	17	(24%)
" 70 "	38	(76%)	10 mm. or under ..	7	(14%)
70 mm. or under ..	12	(24%)			
Mean 96.7. S.D. \pm 25.8. Range 25-148.			Mean 30.8. S.D. \pm 30.6. 19.2 Range 8-96.		

D.A.T.—This was determined, often repeatedly, in 34 patients (Table VII). It was negative in 20 (58.8%). Only two patients had a D.A.T. of 128, and one of these later developed rheumatoid arthritis. In one patient without peripheral joint-swelling or spondylitis the original D.A.T. of 128 reverted to 0 with loss of symptoms. The latex test, however, remained positive. In another patient the D.A.T. reverted from 16 to 0.

TABLE VII.—*Differential Sheep-cell Agglutination Titre in 34 Patients*

Negative ..	20 (58.8%) (1 developed rheumatoid arthritis)
D.A.T. 16 ..	7 (20.6%)
D.A.T. 32 ..	5 (14.7%)
D.A.T. 128 ..	2 (5.9%) (1 developed rheumatoid arthritis)
<i>D.A.T. Conversion</i>	
D.A.T. 128→0 ..	1 (latex test remained positive)
D.A.T. 16→0 ..	1

Plasma Fibrinogen.—One of the characteristic features of the anarthrotic rheumatoid syndrome is a very high plasma fibrinogen often reaching levels of 900-1,000 mg./100 ml. and associated with increases in the α_1 - and α_2 -globulin fractions (Bagratuni, 1957). The original mean level of fibrinogen in 42 of the 50 patients was 647 mg./100 ml. The fibrinogen was estimated in eight patients in 1961 and compared with the original levels in the same eight patients at the height of their illness. From the original mean of 712.8 mg./100 ml. it had fallen to a mean of 455.5 mg./100 ml. (Table VIII). Eight of the 10 patients who originally had cryoglobulins in their blood lost this abnormality with improvement in symptoms. The two patients with the longest histories and Sjögren's syndrome continued to show cryoglobulins. Thus the fall in the E.S.R. and plasma fibrinogen, and a return of the blood proteins to a more normal pattern reflected the clinical improvement observed.

TABLE VIII.—*Plasma Fibrinogen Levels in Original 50 Patients and Comparison Between Recent and Original Levels in the Same Eight Patients*

Plasma Fibrinogen (mg. 100 ml.)	Highest in Original 50	Highest in Original 8	Latest in Same 8
Mean	647	712.8	455.5
S.D.	\pm 149	\pm 202.5	\pm 167.7
Range	297-1,240	297-975	240-700

Radiological Findings.—Detailed radiological studies of the peripheral joints, bones, and spine, often with the help of several radiologists, failed to show any changes not compatible with the normal ageing process.

Indeed, in spite of the mean age of 62.8 years of the 50 patients when seen and the severity of the symptoms, it was remarkable how well preserved the spines and peripheral joints were in most, with only some patients showing slight osteoporosis or marginal lipping of the vertebrae.

Although osteoarthritic changes were sometimes found in the peripheral joints none showed the features of rheumatoid arthritis. Significantly the changes suggestive of rheumatoid arthritis described by Sharp *et al.* (1958) were absent, and the present group is similar to cases described by Ansell and Bywaters (1958) with a high E.S.R. and osteoarthritic changes only. The latter workers stressed the importance of rheumatic conditions as a cause of a high unexplained E.S.R. and made the important observation that patients with atypical rheumatic disease are often put aside and not followed up because they do not fit into an accepted but nevertheless arbitrary classification.

Treatment

All patients were treated with salicylates at some time during their illness and most responded well. In one patient phenylbutazone was tried and the response was better than with salicylates. In another patient who later developed rheumatoid arthritis, steroids had to be given, with good effect, for very severe muscle and joint pains.

One of the patients with Sjögren's syndrome was also given steroids, but this had no effect on the dryness of the mouth and eyes, and the myalgia was not severe enough at the time to warrant prolonged steroid therapy.

In general it was felt that salicylates alone were sufficient to control symptoms, and steroids with their accompanying hazards were not justified in a condition which may last for years with eventual spontaneous improvement.

Physiotherapy gave considerable relief to all patients who had it, and most patients volunteered the information that the muscle stiffness was at its worst at night or during rest and became less severe with movement and gentle exercise.

Discussion

The anarthrotic rheumatoid syndrome is thus a benign condition, on the whole self-limiting, and unlike systemic lupus erythematosus, dermatomyositis, scleroderma, periarteritis nodosa, and giant-cell arteritis, diseases which it superficially resembles, it does not shorten life. It is unlike rheumatic fever in that joints and heart are not necessarily involved and the age of onset is much later.

It does, however, closely mimic the prodromal symptoms of rheumatoid arthritis before joint involvement. The muscle aching without joint involvement, morning stiffness, alterations in the peripheral circulation, paraesthesiae, loss of weight, sweating, anaemia, Sjögren's syndrome, and a family history of rheumatic fever or rheumatoid arthritis in 20% of this series suggests there may be a link between the two conditions. This is borne out by the two patients who after two and five years of symptoms identical with the rest of the group developed rheumatoid arthritis.

Paulley and Hughes (1960, 1962) have suggested that this syndrome is giant-cell arteritis. Thirty of their 70 patients presented with eye symptoms and 32 had anarthrotic rheumatism. Three of the present series had iritis, two conjunctivitis, and one punctate keratitis, and their impairment of vision was due to these rather than to retinal or retro-ocular causes as in giant-cell arteritis. It seems remarkable, too, if this syndrome is giant-cell arteritis, that in a series of 50 patients not one had the visual disturbances characteristic of this form of arteritis.

Moreover, in only one of six post-mortem examinations in which an arteritis was specifically looked for was there a suspicion of an arteriolitis, and this, although not typical, was more suggestive of systemic lupus erythematosus. Seventeen biopsy specimens were normal or unremarkable.

To suggest that response to corticotrophin (MacGregor, 1961; Paulley and Hughes, 1962) in some way implies, without histological proof, that the lesion in such disorders is a giant-cell arteritis, fails to take into account that most cases of arteritis, of "collagen disease," and indeed of all inflammatory states will respond to corticotrophin or steroids.

Biopsy or post-mortem proof of giant-cell arteritis is the only valid reason for calling a disorder by that name or its synonyms. Without this evidence terms such as "anarthrotic rheumatoid disease" or "polymyalgia rheumatica" are non-committal and leave the field open for further study.

I can see no valid reason for MacGregor (1961) to assume that, because his 12 patients with a similar syndrome had no headache but occipital pain, the lesion was necessarily giant-cell arteritis of the occipital arteries. Careful clinical examination would have shown, I am sure, as in my cases, limitation of movement of the cervical spine, tenderness over the vertebrae, and tenderness of the periscapular muscles.

Forty-two of the present series had occipital and upper cervical aching and 16 had vertical, frontal, or temporal headache. These features, indeed, are characteristic of this syndrome, and it would be rash to assume the presence of giant-cell arteritis in the absence of histological proof.

The anarthrotic rheumatoid syndrome may be mild, moderate, or severe. In some acutely ill patients the period of intense muscle stiffness and aching may come on after an initial period of fever, loss of weight, and malaise, making early diagnosis difficult, although as a rule the stiffness precedes or accompanies the acute phase. Such spectacular acute cases, however, with an exceedingly high E.S.R., fever, rapid loss of weight, and intense stiffness are only at the extreme end of a range which includes patients with mild muscular discomfort around the shoulders and neck, with a normal or moderately raised E.S.R. and no loss of weight.

Slocumb (1936) and Race (1940), in their studies on "fibrositis," found most of their cases had a normal E.S.R., but in a few this was raised and these bore a closer resemblance to rheumatoid arthritis.

Short (1947), in an informative study of rheumatoid arthritis and myalgia in troops during the last war, stated that it was only possible to diagnose rheumatoid arthritis in troops with myalgia after they had developed joint swellings. Of his series, 87% suffered from fatigue, loss of weight, vasomotor instability, sweating, and paraesthesiae before the onset of any joint symptoms, and there were cases in which eventually only one joint would become involved. Those who did not develop joint swelling, in spite of the above symptoms, were simply classified as "fibrositis" or myalgia, and were thus similar to the cases described here.

The negative findings at necropsy and biopsy must leave the field open for several interpretations of the basic lesion. I favour the concept that this is a *forme fruste* of rheumatoid arthritis, but it would be unwise to give the condition a name which is already applied to a disorder whose pathology is known.

Kellgren (1952) noted the remarkable muscle wasting in rheumatoid arthritis with no gross histological change and suggested that the lesion occurred at the molecular level. Certainly the absence of pathology suggests this to be so in the anarthrotic rheumatoid syndrome also.

The examination of the spine, especially of the cervical spine, is very often overlooked when patients with unexplained malaise, loss of weight, and high E.S.R. are examined. Because of the frequency of mild myalgic symptoms, without constitutional changes, in the normal population, such pain in the cervical region of the more severely ill patient is often disregarded, even though there may be tenderness of the vertebrae and considerable limitation of movement.

The concept of arthritis is somehow inextricably associated with visibly swollen, tender joints. When no swelling is visible, as in the spine, even gross limitation of movement may be ignored or missed.

Many such cases may have rheumatoid arthritis of the spine. The frequency with which the shoulder-girdle and to a lesser extent the pelvic girdle are affected in the anarthrotic rheumatoid syndrome suggests that the disorder may be a *forme fruste* of rheumatoid arthritis of the spine or some other form of spondylitis. Up to now, however, in spite of detailed radiological and histological study, proof is lacking.

If, however, the initial change in rheumatoid arthritis and the other "collagen diseases" is an arteritis or a vasculitis, then it is not surprising that the symptoms and signs of these disorders should be like those in the more obvious forms of arteritis. This may explain why, in the absence of histological proof, it is so difficult to differentiate between these disorders clinically. Similar generalized pathological processes or their end-results would be expected to produce similar clinical pictures. Certainly if the anarthrotic rheumatoid syndrome does belong to this group it is the one with the best prognosis.

Summary

Fifty patients with the anarthrotic rheumatoid syndrome (polymyalgia rheumatica) have been followed up between 1945 and 1961. The mean age at onset of symptoms was 60.4 years. Eleven patients died of causes unconnected with their rheumatic complaint.

Six post-mortem examinations failed to show any significant pathology other than the primary cause of death.

One patient had slight renal changes suggestive but not diagnostic of systemic lupus erythematosus.

Seventeen biopsies were either normal or inconclusive.

The patients who died at a mean age of 70.5 years had all virtually recovered from their severe myalgia, which had lasted for a mean period of 7.1 years.

Of the 50 patients, 15 (30%) became symptomless, 14 (28%) became almost symptomless, and 17 (34%) improved. Only two patients had persistent severe symptoms.

The mean overall duration of symptoms in 50 patients was 7.1 years.

The fall in the E.S.R. and plasma fibrinogen reflected the clinical improvement.

The D.A.T. was negative in 58.8% and 32 or less in all but two.

Two patients have progressed to frank rheumatoid arthritis.

There is no evidence that the condition is giant-cell arteritis, a name which should be reserved for cases showing pathological proof of this condition.

The syndrome resembles the prodromal symptoms of rheumatoid arthritis more than other disorders and has an excellent prognosis.

Salicylate therapy was adequate in nearly all patients.

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BONE-MARROW HYPOPLASIA IN THE COURSE OF HAEMOLYTIC DISEASE OF THE NEWBORN

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Haemolytic anaemia due to incompatibility in Rh blood groups of mother and foetus affects 0.5% of newborn babies (Walker and Mollison, 1957). That the bone-marrow may not respond to this anaemia by increased red-cell production has been pointed out by Gasser (1955), Giblett, Varela, and Finch (1956), and Lindquist and Ryttinger (1959). Smith (1949) reported a case of pure red-cell hypoplasia in an infant, probably following haemolytic disease of the newborn, and a further case of proved haemolytic disease of the newborn in which there was some evidence of marrow hypofunction. Diamond (1948) suggested that most cases of haemolytic disease of the newborn show marrow hypoplasia at 2 or 3 weeks of age. Dillon and Krivit (1959), however, in a study of serial marrow specimens, could find no convincing cases of hypoplasia among 14 affected infants. They stated that in general the marrow shows increased erythroid cellularity in proportion to the severity of the anaemia. The case reported below showed marrow erythroid hypoplasia and persistence of Rh antibody in the infant's serum.

Case Report

The child was referred to Hammersmith Hospital 18 hours after birth, following the onset of cardiac failure after exchange transfusion. He was born to a 37-year-old Englishwoman who had had three previous pregnancies. Her blood group was A Rh-negative (*cde/cde*) and that of her husband O Rh-positive (*CDe/cde*). Her first two children were unaffected, but the third is recorded as showing slight jaundice during the neonatal period, although requiring no treatment. During the present pregnancy Rh antibodies were detected in the mother's serum at 34½ weeks' gestation at a titre of 32. The titre rose to 256 at 36½ weeks and to 2,000 at 38½ weeks, all these figures being obtained using an albumin technique.

At 38½ weeks labour began spontaneously and a male infant, weighing 3,060 g., was born. He was jaundiced at birth and the spleen was palpable. Investigations on the cord blood gave the following results. Haemoglobin, 6.7 g./

100 ml. Blood film, 207 normoblasts per 100 white cells. Direct antiglobulin (Coombs) test, strongly positive. Group A Rh-positive (*CDe/cde*). Serum bilirubin, 5.6 mg./100 ml.

An exchange transfusion was performed four and half hours after birth, using 450 ml. of packed red cells, group A Rh-negative. The infant developed heart failure, which responded to treatment with digoxin.

By the third day the serum bilirubin level had risen to 28.9 mg./100 ml. However, since the indirect-reacting fraction never exceeded 18.3 mg./100 ml., and it was realized that the jaundice was partly of the obstructive type (Oppé and Valaes, 1959), further exchange transfusion was not thought necessary.

After the original exchange transfusion the cord haemoglobin was 18.3 g./100 ml. (see Chart). Subsequent skin-prick blood samples showed a steady fall of haemoglobin, and after four weeks the following values were found: haemoglobin, 7 g./100 ml.; packed cell volume, 21.5%; red cells, 2,600,000/c.mm.; white cells, 5,000/c.mm.; platelets, 300,000/c.mm.; reticulocytes, nil. Rh antibody titre (indirect Coombs method), 32. Direct Coombs test,

