THE "UNEXPLAINED" HIGH ERYTHROCYTE SEDIMENTATION RATE

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Routine estimation of the erythrocyte sedimentation rate (E.S.R.) in new patients attending a rheumatism clinic sometimes reveals a value inexplicable in terms of the clinical diagnosis—for example, when the affliction is thought to be of a non-inflammatory nature, such as degenerative joint disease or "psychogenic rheumatism." Such cases often remain diagnostic problems, and we have therefore reviewed all these cases seen over a period of 3½ years. It seems to us important to document them, since medical literature in general neglects such patients (although they occur in every clinic) and tends to record only those who can be fitted into well-defined nosological categories.

Method and Material

Westergren's (1926) method was employed, and due precautions were taken with regard to contamination of the sample with skin-sterilizing alcohol (Sykes, 1948), to delay before setting-up of the sedimentation tube, to its verticality and cleanliness (Ham and Curtis, 1938), and to the room temperature (Romanus, 1944).

From February, 1952, until September, 1955, 51 out of approximately 900 estimations on new patients were found to be above 20 mm. per hour for no good clinical reason. Of these 51 cases 45 were re-examined and the E.S.R. was estimated again within one month of their first visit. In 14 it had returned to normal, so these patients were classified as having a transient rise in their E.S.R. and are designated group II. The E.S.R. in the remaining 31 patients remained abnormally high, and these are referred to as group I.

Another re-examination of these group I patients was made in the out-patient department, looking particularly for evidence of tissue destruction or inflammation. No abnormality which could account for the high E.S.R. was found. A chest x-ray examination, a full blood count, and a second urine examination were then done, with negative results. The initial diagnoses are shown in Table I.

TABLE I.—Initial Diagnosis in 45 Cases with Unexplained High E.S.R.

	Group I	Group II
Degenerative joint disease ..	18	4
Arthralgia ..	4	1
Cervical spondylosis ..	2	1
Phlebotrombosis ..	2	1
Psychogenic rheumatism ..	1	2
Oedema of an extremity ..	1	1
Postural backache ..	1	1
Osteoporosis of spine ..	1	0
Osteochondritis ..	1	0
Iritis and arthralgia ..	0	1
Acroparaesthesiae ..	0	1
Prolapsed intervertebral disk ..	0	1
Total ..	31	14

Since a raised E.S.R. may be the only sign of serious disease such as carcinoma or myelomatosis, further investigations, including for most patients electrophoresis of the serum for protein pattern, differential agglutination titre (D.A.T., Rose-Waaler), C-reactive protein, fibrinogen estimation, L.E. cells, antistreptolysin titre, and serum uric

acid, were made. According to the results of these, other investigations were then instituted, including barium meal, barium enema, intravenous pyelography, and electrocardiography. In all cases with joint symptoms a careful review of the x-ray films was undertaken, and in certain cases biopsy of the bone marrow or synovial membrane was made, and for these the patient was admitted to hospital.

Results

In only a small number of cases was it possible to establish the cause of the raised E.S.R. after preliminary investigations, but the subsequent follow-up has allowed us to make a diagnosis in 20 out of the 31 in group I and in 7 out of 14 in group II cases (Table II). It can be seen that

TABLE II.—Final Conclusion on the Cause of Unexplained High E.S.R.

	Group I	Group II
Rheumatoid arthritis ..	8 (+ D.A.T. 4)	2 (+ D.A.T. 1)
Probable rheumatoid arthritis ..	6 (+ D.A.T. 1)	1
Ankylosing spondylitis ..	0	1
Phlebotrombosis ..	2	1
Carcinoma of bronchus ..	1	0
Tuberculosis of knee ..	1	0
Myelomatosis ..	1	0
Presence of cold agglutinins ..	0	1
Diverticulitis ..	0	1
Chronic bronchitis ..	0	1
Unexplained { Persisting more than 1 year ..	5	0
{ Settled in 1 year ..	6	7
Total ..	31	14

in a large number of patients who were thought at first to have solely degenerative joint disease a final diagnosis of rheumatoid arthritis was made.

A final diagnosis of rheumatoid arthritis was made in patients with polyarthritides (1) with a positive D.A.T., or (2) with erosions on x-ray films, or (3) with low viscosity high-protein-containing synovial fluid without infection. The final diagnosis of probable rheumatoid arthritis was made in patients with neither a positive D.A.T. nor x-ray erosion, but in whom pain, swelling, and limitation were present in multiple joints over a period of at least six months, without evidence of other conditions such as Reiter's syndrome, psoriasis, rheumatic fever, tuberculosis, lupus erythematosus, etc.

Case Histories to Illustrate Particular Points

Case 1 (Group I): Initial Diagnosis—Oedema, Not Yet Diagnosed; Final Conclusion—Rheumatoid Arthritis.—A 50-year-old woman was first seen in 1953, when she gave a two-year history of bouts of arthralgia persisting for three to four days every few weeks, and now complaining of intermittent swelling of the dorsum of both feet for six weeks. Apart from pitting oedema of the dorsum of the feet there were no abnormal physical signs, x-ray films were normal, and the Rose test (Rose *et al.*, 1948) was negative, but the E.S.R. was persistently raised about 30 mm. in one hour. The oedema settled, but she continued to have arthralgia. Two years later she developed swelling of the joints, initially palindromic but later persistent, and associated with severe pain and limitation of movement in the shoulder-, wrist-, finger-, knee-, ankle-, and toe-joints; the Rose test was now positive, and erosions have shown on the x-ray pictures of the hands and feet.

Case 2 (Group II): Initial Diagnosis—Oedema ? Due to Lymphatic Obstruction; Final Conclusion—Rheumatoid Arthritis.—A 66-year-old woman presented with oedema of the dorsum of the left hand which was thought to be due to lymphatic obstruction secondary to a radical mastectomy. No other abnormal signs were found, but the E.S.R. was 42 mm. in one hour. Over the next two and a half years she had occasional swelling of the left hand, but the E.S.R. returned to normal. She then developed pain and stiffness in both wrists followed by soft-tissue swelling. Other joints have become involved, the E.S.R. has risen to 60 mm. in one hour, and numerous erosions show on the x-ray pictures.

Case 3: Initial Diagnosis—Degenerative Joint Disease; Final Conclusion—Rheumatoid Arthritis.—A 77-year-old man presented with pain and stiffness of the legs, worse after rest and improved by walking, for the preceding 12 months. There was minimal

limitation of full knee flexion and no other abnormal signs. The E.S.R. varied between 30 and 35 mm. in one hour, and C-reactive protein was persistently present in the blood. The D.A.T. was positive 1:32. The x-ray films showed only mild degenerative changes. With analgesics and physiotherapy he has shown slight improvement over the year. The E.S.R. has remained raised, but he has not developed any other evidence of disease. In this case the most likely diagnosis was thought to be "anarthritic" rheumatoid disease.

The diagnosis of mono-articular arthritis at any age may be difficult. In group I there were two patients, both middle-aged (56 and 63) and both known to have had degenerative joint disease for some time, in whom the development of an effusion was thought to be a traumatic synovitis. In view of the rise in E.S.R. further investigations were undertaken, although the x-ray films showed only degenerative joint disease. In one the synovial fluid showed a high-protein content with a low viscosity, while the D.A.T. was positive, and the subsequent course has been that of rheumatoid arthritis. The synovial fluid in the other patient was compatible with degenerative joint disease, but, as his symptoms persisted despite physiotherapy and the E.S.R. remained high, he was persuaded to have a synovial biopsy performed. Histologically this case was of tuberculous aetiology, later confirmed bacteriologically.

Difficulty in Establishing Cause of Raised E.S.R.

Case 4: Initial Diagnosis—Osteoarthritis of the Knees; Final Conclusion—Multiple Myelomatosis, Osteoarthritis of Knees, Chronic Bronchitis.—A 70-year-old woman was first seen in February, 1954, complaining of pain and swelling of both knees of five years' duration. Asthmatic bronchitis had rendered her dyspnoeic on exertion for many years. She was very obese and had poor movement of her chest with widespread rhonchi. Both knees showed degenerative joint disease. The E.S.R. was 30 mm. in one hour; haemoglobin, 12 g. per 100 ml. The urine showed albuminuria. Blood urea was 41 mg. per 100 ml. X-ray films showed degenerative joint disease in the knees and a large left ventricle with considerable unfolding of the aorta. She was treated as an out-patient for degenerative joint disease with analgesics and physiotherapy, and was given dietary advice. Because of increasing dyspnoea on exertion and at night, as well as persistent pains in the legs, she was admitted in June, 1954, when she had albuminuria; E.S.R., 83 mm. in one hour; D.A.T., 1:2; total serum proteins, 8.5 g.% (albumin 4.3 g., globulin 4.2 g.); blood cholesterol, 248 mg. per 100 ml.; haemoglobin, 14 g. per 100 ml.; W.B.C., 3,600 c.mm. In view of the high E.S.R. and abnormal proteins it was suggested that her joint symptoms might be due to rheumatoid arthritis. She was treated with physiotherapy and analgesics with good effect, but the E.S.R. rose to 110 mm. in one hour, the haemoglobin fell to 8.7 g., and the electrophoretic pattern of the proteins became more abnormal and suggestive of myeloma. A sternal marrow examination was performed which showed 60% myeloma cells. There was no evidence of Bence Jones protein in the urine and no radiographic bone changes. The E.S.R. has continued to rise and haemoglobin to remain low, but in spite of generalized limb pain no radiographic abnormality has been detected.

Rise in E.S.R. in Relation to Disease

When this study was first begun the possibility that a raised E.S.R. could result from malignant disease as yet asymptomatic was very much to the fore in our minds. However, only one of our cases has so far proved to have a neoplasm, and in this case the diagnosis was not made until necropsy.

Case 5: Initial Diagnosis—Degenerative Joint Disease of Lumbar Spine; Final Conclusion—Carcinoma of Bronchus With Secondary Deposit.—A 63-year-old woman was seen in 1952 with a left-sided sciatica of two weeks' duration. In 1945, because of cough and haemoptysis, she had had a chest x-ray examination which revealed a shadow at the right apex. Investigations for neoplasm, including bronchoscopy, were negative. At the time we saw her her chest symptoms and x-ray picture were unchanged. All other investigations were negative and she improved on bed rest. Nine months later she developed bronchopneumonia and was admitted elsewhere, where she died.

In a few cases the cause of the raised E.S.R. bore no relationship to the disease process which brought the patient to our clinic.

Case 6: Initial Diagnosis—Cervical Spondylosis; Final Conclusion—Cervical Spondylosis, Cold Agglutinins.—A 42-year-old woman complained of pain and paraesthesiae in the left shoulder and arm. She showed marked limitation of movement of the cervical spine, and x-ray examination confirmed the presence of osteoarthritis in the cervical spine, involving the fifth and sixth vertebrae. The E.S.R. was raised to 100 mm. in one hour. Full investigations were instituted and a high titre of cold agglutinins discovered, 1:8,102 (2–5° C.), 1:128 (20° C.), 0 (37° C.). It was felt these probably accounted for the E.S.R. abnormality.

Cases in Which No Cause for High E.S.R. was Found

If we consider the patients in whom no cause for the high E.S.R. could be found, these fall into two types: those in whom the rate fell to normal with remission of their symptoms but in whom no diagnosis was made, and those in whom it persisted at a high level. The following is an example of the first type:

Case 7: Initial Diagnosis—Arthralgia; Final Conclusion—Unexplained High E.S.R. Which Settled.—A 25-year-old man was seen in October, 1953, with a history of a sore throat one year previously, followed by fever and general arthralgia. He had been treated with various antibiotics, with no apparent response, subsequently improved, but then began to have bouts of intermittent fever and arthralgia lasting two to three days at a time. There were no abnormal physical signs apart from right axillary and bilateral epitrochlear lymphadenopathy. The E.S.R. was 28 mm. in one hour, and all other investigations, including L.E. cells, blood culture with CO₂ preparation, Coombs test, *Brucella abortus* agglutinations, D.A.T., plasma proteins, liver biopsy, E.C.G., x-ray examination of the joints and chest, and barium meal, were negative. While in hospital he continued to have pyrexial episodes spiking to 102° F. (38.9° C.), lasting for two to three days and remitting spontaneously; in some of these acute arthritis of the mid-tarsal joints developed, and on one occasion there was a small effusion into the right knee-joint. Occasionally he also had purpuric spots on the chest and limbs, although bleeding- and clotting-times and platelet counts were never abnormal. Salicylates caused symptomatic improvement; he gradually improved and the E.S.R. slowly returned to normal over a few months. He has remained well during the past 18 months with only occasional arthralgia.

It is of course possible that he had a mild rheumatoid arthritis which cleared completely, or Schönlein-Henoch purpura, or rheumatic fever, but these diagnoses could not be substantiated.

There have been some patients in whom the raised E.S.R. has persisted, whose general health has remained good, and in whom the E.S.R. was not apparently related to the patient's symptoms.

Case 8: Initial Diagnosis—Degenerative Joint Disease of the Knees; Final Conclusion—No Cause for High E.S.R., Degenerative Joint Disease, Knees.—A 75-year-old woman was seen in August, 1954, complaining of pain in both knees, particularly the right, for 20 years, which was getting worse. On examination, apart from obesity, she showed only degenerative joint disease involving both knees. The E.S.R. was 23 mm. in one hour and x-ray examination confirmed the presence of degenerative joint disease. She was treated by weight reduction, analgesics, and physiotherapy with an excellent response, but in the subsequent two years her E.S.R. has remained between 30 and 35 mm. in one hour; the D.A.T., 1:2; protein, 6.8 g.% (albumin 3.6 g., globulins 3.2 g.); haemoglobin, 13.7 g. per 100 ml.; L.E. cells negative; and no other changes have shown on x-ray films.

In other cases the E.S.R. appeared to be related to the disease process, but a diagnosis could not be established.

Case 9: Initial Diagnosis—Psychogenic Rheumatism; Final Conclusion—Not Yet Diagnosed, Persistently Raised E.S.R.—A 47-year-old man noticed in 1954 the sudden onset of difficulty in walking because of stiffness and tightness of the legs associated with some weakness. At this time he had reddish-blue discoloration of toes and blotching of the dorsa of both feet, but no true claudication and no superficial phlebitis. On three occasions he had a rash on his legs, which when seen in the last attack was of a macular type. In addition he complained of general malaise, tiredness, headache, but had not lost weight, nor had he any history of fever. On examination he was very introspective, but no abnormal physical signs were found, apart from the remains of a rash. His E.S.R. varied between 100 and 118 mm. in one

hour; haemoglobin, 12.9 g. per 100 ml.; W.B.C., 6,000 (normal differential); urine normal, no albumin or Bence Jones protein, no L.E. cells; W.R. negative; A.S.T., 75; D.A.T., 1:2; total protein, 7.3 g.% (albumin 4.1 g., globulin 3.2 g.); protein electrophoresis normal; no cryoglobulins or other abnormal protein, apart from fibrinogen, which was 616 mg. per 100 ml.; acid and alkaline phosphatase, normal; blood urea, normal; x-ray film of lumbar spine normal; x-ray film of the sinuses showed some opacity of the right antrum. He has been reviewed by Dr. Edwin Clark, who could find no neurological abnormality, and by Mr. Peter Martin, who could find no abnormality in the peripheral vessels. Over the past two years his symptoms have gradually subsided with reassurance and analgesics. The E.S.R. remains between 60 and 80 mm. in one hour, and he still has a high fibrinogen content of the blood.

Here one of the rarer collagen disorders, such as polyarteritis nodosa, was considered but not established.

Discussion

Although the E.S.R. is higher in women than in men and shows some day-to-day variation, particularly in women (Greisheimer, 1927) and quite apart from menstruation (Benson and Rogers, 1941) and pregnancy (Hamilton, 1953), in normal adults it does not exceed the value of 20 mm. in one hour, which we have taken as our upper limit of normal. As age increases, the sex difference is less obvious and the normal level tends to rise, showing a wider range (Reinbourne, 1952).

In group I 15 of our patients were over 60 years, 10 between 50 and 60, and six under 50. However, of those in whom we were unable to find an adequate explanation for the rise in E.S.R. only three were over 60, five being between 50 and 60, and three under 50. It does not seem likely to us that in the two cases (Nos. 13 and 17) of the oldest age group, who have remained in good health and have now been followed for three and two years respectively with the E.S.R. remaining between 20 and 30 mm. in one hour, the raised value is due solely to their age and random variation, since in a third similar case the E.S.R. settled under observation in five months. That it is important not to accept age as the reason for an E.S.R. between 20 and 30 until full investigations have been carried out is shown by other patients with a similar initial reading who have later developed obvious rheumatoid arthritis or been found to be suffering from such diseases as tuberculosis of the knee.

Out of 31 cases in group I a disease process was diagnosed in 20, although in some it did not become obvious for a period of time. These results are similar to those of Cutler (1932), although the actual final diagnosis differed from his, since his series showed a high incidence of chest diseases. Similarly, our results should not be strictly compared with those of Liljestrand (Liljestrand and Olhagen, 1955; Olhagen and Liljestrand, 1955), since our cases were selected by referral to a rheumatology clinic, whereas his came from a general medical clinic. However, we agree with him that carcinoma as a cause of this high E.S.R. is rare. In his series of 37 cases with a raised E.S.R. of obscure cause, no final explanation could be given in 21 cases, and these were all women. In our similar group of 11 cases, 8 were women, and the prognosis does not seem at this distance to be bad.

The high incidence of rheumatoid arthritis in patients of advancing years and the difficulty in establishing its diagnosis are of particular interest. Clinically, a fairly confident diagnosis was made in 14 of the patients, though only eight fulfilled the criteria described earlier. This problem has been discussed by Bagratuni (1956), who described what he calls "anarthritic rheumatoid disease." The entity, described sometimes as the fibrositic prodromal phase of rheumatoid arthritis, is well known (Ropes and Bauer, 1945); but whereas in his cases there was little evidence to suggest joint involvement, in all except one of ours there was ultimately definite evidence of arthritis. The value of a rise in E.S.R. in differentiating early arthritis from fibrositic pains has also been stressed by Slocumb (1936), and can be confirmed by us in cases not included in this series.

Summary

An unexplained rise of the sedimentation rate above 20 mm. in one hour was found in 51 new patients out of approximately 900 attending a rheumatology clinic over a period of 3½ years.

Thirty-one of these remained high over one month, and eight of them have developed typical rheumatoid arthritis, while six are probably suffering from this disorder. In eleven others no cause for the raised E.S.R. could be found, and their general health has remained good. In five it returned to normal within one year, while in six it has remained high.

The presence of a high E.S.R. should lead to a careful assessment and investigation of the patient, but, particularly in older people, it is not necessarily associated with a bad prognosis.

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THERAPEUTIC TRIAL OF AZACYCLONOL

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Azacyclonol ("frenquel") has been the subject of pharmacological study in America since 1954. Chemically it is related to pipradol hydrochloride ("meratran"), which is alpha-(2-piperidyl) benzhydrol hydrochloride, while azacyclonol is the gamma isomer, alpha-(4-piperidyl) benzhydrol hydrochloride. Azacyclonol has been shown to protect subjects against the experimental psychosis induced by lysergic acid diethylamide (Fabing, 1955). The central effect appears to differ from that of reserpine and chlorpromazine, which act on the mesodiencephalic activating system. Azacyclonol again differs in its effects from pipradol hydrochloride, which is believed to be a central stimulant without concomitant autonomic effects (Rinaldi, Rudy, and Himwich, 1955). Favourable clinical responses to azacyclonol in various psychotic states have been reported (Fabing and Hawkins, 1955; Cohen and Parlour, 1956; Browne, 1956). The best responses were obtained in toxic hallucinatory states (Proctor and Odland, 1956), whereas the results in schizophrenia have been somewhat variable. This paper presents the results of treatment with azacyclonol in 56 patients with schizophrenia and two patients with alcoholic hallucinatory states.