STUDIES IN RHEUMATOID ARTHRITIS

By

THOMAS N. FRASER.

From the Gardiner Institute of Medicine, University of Glasgow,

and the Western Infirmary, Glasgow.

INTRODUCTION

The work on which this thesis is based was carried out over the past ten years in the Gardiner Institute of Medicine, University of Glasgow, and in the Western Infirmary, Glasgow. Three sections, which are included in greater detail in the subsequent pages, have already been published under the following titles:-

(1) "Blood Cultures in Rheumatoid Arthritis"

in the Annals of the Rheumatic Diseases, 1943, 3, 181.

(2) "Gold Treatment in Rheumatoid Arthritis"

in the Annals of the Rheumatic Diseases, 1945, 4, 71.

(3) "Transmission of Acute Infective Hepatitis"

in the Glasgow Medical Journal, 1946, 27, 157, in association with Dr. J. Basil Rennie.

I wish to thank Professor J. W. McNee for the facilities which he has placed at my disposal for this research work.

TABLE OF CONTENTS

PART 1.

ON THE INFECTIVE NATURE OF RHEUMATOID ARTHRITIS

The problem of microbic infection in relation to the aetiology of rheumatoid arthritis has led to much discussion and experiment. Before going into the evidence for and against the infective nature of the disease, it would be advisable to define what we mean by infection. According to Topley and Wilson (1946), if we look at the problem as biologists, an infection should probably be regarded as any association of parasite and host in which the reaction between them involves any damage, however slight, to the host's tissues. Moreover, we should expect to find variations in the response of the host to the parasite according to the degree of shifting of the balance to the disadvantage of the host. Thus, we would see examples of clinically typical cases of the disease, whether mild, severe or fatal; of atypical cases not falling clinically into their correct category; and of cases of latent infection with no clinical signs or symptoms.

What evidence must we produce to show that a particular disease is

caused by a particular bacterial parasite? A series of conditions must be fulfilled to establish the relationship between the two, and these are generally referred to as "Koch's Postulates". Briefly, they are as follows:-

(1) The organism must be constantly present in all cases of the disease;

(2) The organism must be isolated and cultivated outside the body in successive generations;

(3) The isolated organism must be able to reproduce the disease in other susceptible animals.

We have today, however, additional criteria which help us to form an accurate judgement as to the relationship of a suspected bacterium to a given disease, e.g. the presence of specific antibodies in the blood or appropriate skin reactions. It is obvious, too, that certain technical difficulties may prevent us from fulfilling all the postulates in every case; for instance we may be unable to cultivate or stain the organism or, again, we may be unable to demonstrate its presence, as in the case of the filterable viruses. Nevertheless, it is true to say that the fulfilment of Koch's postulates is the only complete and absolute proof that a given organism causes a given disease. One of the best known examples of a disease which satisfies these postulates is diphtheria.

There are a number of diseases where the postulates appear to have been fulfilled, but where some special form of immunity or allergy in animals introduces a mechanism which is not, as yet, duplicated in man. The classical example of this group is tuberculosis. Although Koch

discovered the tubercle bacillus in 1882, yet today the course of the disease is so far from being understood that we do not know the epidemiology, the prognosis or the treatment.

Then there are those diseases where the story is even less complete and the evidence against a particular organism is, at most, circumstantial, e.g., the streptococcus in rheumatic fever, the mechanism of how the streptococcus brings about the disease being a complete mystery. Blood cultures have been consistently negative, but clinico-pathological investigations have, however, shown an indirect relationship to the streptococcus haemolyticus (Lancefield Group A). It is well known that the onset, an exacerbation or a recurrence of rheumatic fever is often preceded by a haemolytic streptococcal upper respiratory infection. Coburn and Pauli (1935) reported the results of an epidemic of sore throats due to a single type of haemolytic streptococcus in a convalescent home for children with heart disease. Of 17 patients proven to be infected with this organism, 14 rheumatic subjects developed acute rheumatism, while 2 rheumatic subjects and one with congenital heart disease escaped. These 14 rheumatic attacks were associated with a rise in the antistreptolysin titre of the blood which coincided with the onset of symptoms. They concluded that the outbreak of rheumatic fever was caused by a haemolytic streptococcus of a single strain. In addition to the rise in the antistreptolysin titre there is also an increase in antifibrinolysins and precipitins to the streptococcus haemolyticus in rheumatic fever. Coburn (1936) stressed the fact that patients with rheumatic fever develop group-specific and type-specific antibodies to the haemolytic streptococcus with the same regularity that

they develop changes in the blood sedimentation rate, and that a specific antibody response is a pre-requisite to the development of rheumatic activity. Furthermore, he pointed out that the maximum levels of anti-streptolysin and type-specific precipitin are not reached until the blood sedimentation rate and symptoms are subsiding.

In rheumatic fever, therefore, the indirect evidence against the haemolytic streptococcus as being the causative agent is very strong, but, so far, direct proof has been lacking. In the probably related condition of rheumatoid arthritis, however, the relationship to any organism has never been proved, although many attempts have been made to inculcate the streptococcus.

Is there any evidence for infection in rheumatoid arthritis? Most of the evidence to date suggests that infection does at least play a part in the production of the disease. In favour of this are the low-grade fever during the active phase, the tachycardia, the raised blood sedimentation rate, the anaemia, the loss of weight, the lymphadenopathy and the inflamed joint structures. However, it has often been pointed out that some of the clinical features which suggest that rheumatoid arthritis is an infectious disease are also exhibited by gout, which is considered to be a metabolic disorder. Those who support the bacterial theory of aetiology suggest that there is either a bacterial invasion of the joints via the blood stream from a septic focus, damage to joint structures as the result of toxins emanating from a septic focus and circulating in the blood, or an allergic response in hypersensitive joint tissues to focal infection.

This investigation was undertaken in an attempt to prove or disprove

the first variation of the bacterial theory, viz., that rheumatoid arthritis is a blood-borne infection, and direct evidence of infection was sought by blood cultures.

Historical

About a quarter of a century elapsed between the birth of the germ theory of human disease by Pasteur in 1864 and its concrete application to chronic arthritis. Three men are variously accredited with launching the microbic theory of chronic arthritis; Bouchard in France (1891), Schüller in Germany (1892) and Bannatyne in this country (1896).

From the joints of patients with various forms of arthritis Bouchard had isolated a variety of bacteria, but from the joint fluid of 11 patients with chronic non-suppurative arthritis he recovered a staphylococcus albus which, he said, "Seems to be the characteristic microbe of this form of rheumatism". It is, however, very probable that these patients did not have rheumatoid arthritis as we know it today, for the disease which Bouchard described was of the monarticular variety. For this reason, therefore, Schüller is more often referred to as "the father of the microbic theory of chronic polyarthritis". In 1892 he recovered his "dumb-bell bacillus" from synovial fluid and tissues in all of 116 cases (Schüller, 1893) of what he called "chronic rheumatic inflammatory joint disease". As the result of these findings he changed the name to "chronic villous bacillary arthritis". These bacilli produced non-suppurative lesions in the synovial membrane of rabbits. Schüller put forth the claim that chronic inflammation of joints with hyperplastic villous outgrowths,

which had hitherto been looked on as rheumatic in origin, were produced by "the influence of the bacilli first discovered by myself".

In this country Bannatyne, honorary physician to the Royal Mineral Water Hospital, working with Wohlman and Blaxall (1896), reported the recovery from the synovial fluid of patients with rheumatoid arthritis of a bacillus resembling a diplococcus, and claimed that it must be regarded as specific for that disease until it had been disproved.

Since the days of these three pioneers many arguments for the theory of infection have been put forward from clinical observations of the disease, from its pathology, cytology and chemistry, and from its response to various types of therapy, but mainly from bacteriological and serological data. At first a variety of organisms, e.g., bacilli, staphylococci, diplococci were isolated from various tissues and regarded as the causal agents, but it is now generally regarded that the bacteria then isolated were probably contaminants or saprophytes of no significance.

Attention was next turned to the bacteriaemic variant of the microbic theory, which presupposes a direct infection from a septic focus, through the blood, to the affected joints. This was in the nature of obtaining direct evidence of an infective process. Bannatyne, Wohlman and Blaxall (1896) were the first to report the recovery of organisms from the blood of patients with rheumatoid arthritis, and were able to demonstrate the presence of a minute bacillus with marked polar staining in 3 cases. Since then much work has been done on blood cultures in this disease, but the percentage of positive cultures has been variable and the organisms isolated have been of different types.

Gram negative bacilli were recovered from the blood by Jordon and Boland (1930) in about one third of their patients. Moon and Edwards (1917), Hadjopoulos and Burbank (1927), Bernhardt and Hench (1930), Dawson et al. (1932), Wetherby and Clawson (1932), Ashworth (1932), Wainwright (1934) and Angevine et al. (1940) were able to demonstrate the presence of staphylococci of the albus and aureus groups in a small percentage of cases. These organisms, however, are regarded by most workers (Hadjopoulos and Burbank, 1927; Bernhardt and Hench, 1930) as contaminants, although some (Munro 1925; Key, 1935) believe them to be aetiologically significant, since certain strains have been shown to be arthrotropic to rabbits. Crowe (1913) considered that the staphylococcus albus, which he called the Micrococcus deformans, was the chief cause of the disease, and used a vaccine from the organism in the treatment of his patients, claiming cures in 70 per cent.of cases. There is, nevertheless, little or no serological evidence to show that the staphylococcus is responsible for the disease.

The case against the streptococcus as the causative agent of rheumatoid arthritis is very much stronger, but here again its culpability is weakened by the fact that the evidence is divided between the streptococcus viridans and the streptococcus haemolyticus. The former has been recovered from the blood by a number of workers (Richards, 1920; Surányi and Forró, 1928; Cecil et al., 1929; Rosenow, 1929; Margolis and Dorsey, 1930; Nye and Waxelbaum, 1930; Klugh, 1931; McEwen and Bunim, 1936), while the latter has also been frequently isolated (Hadjopoulos and Burbank, 1927; Cecil et al., 1929 and 1931; Gray and Gowen, 1931;

Klugh, 1931; Dawson et al., 1932; Clawson et al., 1932; Strauss, 1932; Ashworth, 1932; Lichtman and Gross, 1932; Steinfeld, 1932; McEwen and Bunim, 1936). Indifferent streptococci have occasionally been recovered from the blood (Moon and Edwards, 1917; Cecil et al., 1929 and 1931; Margolis and Dorsey, 1930; Shands, 1930; Lichtman and Gross, 1932; McEwen and Bunim, 1936).

A number of observers have been able to isolate diphtheroids from the blood (Margolis and Dorsey, 1930; Klugh, 1931; Strauss, 1932 and Traut, 1933). The significance of these micro-organisms is not definitely established, but they are generally regarded as contaminants (Bernhardt and Hench, 1930). Klugh (1931) and Strauss (1932), however, consider that they may be of some aetiological significance, and are possibly mutation forms of the streptococcus.

The observations on blood cultures which undoubtedly attracted the greatest attention, both in Britain and in America, were those of Cecil, Nicholls and Stainsby (1929), using a complicated technique in which the possibilities of contamination are clearly abundant. They claimed that positive blood cultures were obtained in 69 per cent. of 78 patients with rheumatoid arthritis. The great majority of the organisms recovered were attenuated haemolytic streptococci and were named "typical strains" by the authors. Others have repeated this work, but the majority have failed to confirm the high incidence of positive cultures obtained by Cecil. Support was received from Gray and Gowen (1931), Ashworth (1932) and Strauss (1932), and condemnation from Bernhardt and Hench (1930), Dawson, Olmstead and Boots (1932), and Wainwright (1934). Recently (1940), since

the present bacteriological investigations were completed, Cecil has retracted his previous results admitting the probability of contamination.

The present work was begun in 1937, before Cecil had withdrawn from his earlier position, and to constitute a direct control the same technique as that used by Cecil was carried out in its entirety. This was essentially a modification of Clawson's method (1925), and this technique, or modifications of it, has been used by many other workers as shown in table 1 which summarizes the results of blood cultures in arthritis.

Technique of Blood Culture

The technique of Cecil (1929) was followed in the strictest detail, and may be summarized as follows:-

Blood is withdrawn from the antecubital vein, and 10 c.c. are placed in each of two sterile centrifuge tubes, thus providing duplicate samples for the culture. After centrifuging, the supernatant serum is removed by a sterile pipette. Each tube containing blood clot is now treated in the following manner. The clot is broken up by means of a piece of hollow glass tubing, and the fragments of clot are drawn up in the same glass tube and transferred to a 3-ounce culture flask containing 50 c.c. of beef-heart infusion broth with a pH of 7.6 (0.5 per cent. sodium chloride, 1 per cent. peptone). The flask is then incubated at 37°C. and left unopened for five days.

At the end of this time subcultures are made. A tube containing 8 c.c. of a 1.5 per cent. beef-heart infusion agar is placed in a water-bath

TABLE 1. - SUMMARY OF RESULTS OF BLOOD CULTURES IN RHEUMATOID ARTHRITIS

Observer	Year	Type of Arthritis	No. of Cases	Positive Cases	Positive %	Cases Yielding Streptococci: Haem. %	Viridans %	Non-haem. %	Other Organisms	Remarks
Bannatyne, Wohlman and Blaxall	1896	Rheumatoid	?	3	-	-	-	-	Minute bacillus with marked polar staining	-
McCrae	1904	Arthritis deformans	?	0	0	-	-	-	-	-
Bannatyne and Lindsay	1911	Rheumatoid	2	2	-	-	-	-	Gram-positive micrococcus	-
Greene	1912	Arthritis deformans	1	1	-	-	-	-	A bacillus and a diplococcus	-
Jones	1913	Chronic	8	0	0	-	-	-	-	-
Rosenow	1914	Chronic	?	?	?	Occasional streptococcus			-	-
Crowe	1914	Acute	1	1	-	-	-	-	Micrococcus deformans	-
Rowlands	1916	Rheumatoid	?	0	0	-	-	-	-	-
Moon and Edwards	1917	Acute	40	19	48	2.5	-	32.5	Diphtheroid bacillus	Rosenow's technique.
		Chronic	83	25	30	-	-	21.6	B. mucosus Staph. aureus	-
Richards	1920	Chronic	104	14	13	-	13	-	-	-
Munro	1922	Rheumatoid	?	2	-	Steptrococcus brevis			-	Cultures almost uniformly negative.
Hadjopoulos and Burbank	1927	Chronic	145	29	20	6.2	4.1	-	Diphtheroid bacillus Staph. aureus Colon bacillus	- -

TABLE 1. - SUMMARY OF RESULTS OF BLOOD CULTURES IN RHEUMATOID ARTHRITIS - Continued

Observer	Year	Type of Arthritis	No. of Cases	Positive Cases	Positive %	Cases Yielding Streptococci Haem. %	Viridans %	Non-haem. %	Other Organisms	Remarks
Rowlands	1927	Rheumatoid	?	0	0	-	-	-	-	-
Suránÿi and Forró	1928	Polyarthritis	25	17	68	-	68	-	-	-
Cecil, Nicholls and Stainsby	1929	Chronic infectious	78	54	69	51.3	7.6	2.5	Diphtheroid bacillus	Modification of Clawson's technique.
		Controls	54	0	0	-	-	-	M. zymogenes	
Rosenow	1929	Chronic	19	7	37	-	37	-	-	Modification of Cecil's technique.
Margolis and Dorsey	1930	Chronic	89	10	11	-	6.7	3.3	Diphtheroid bacillus	Various methods, including Cecil's.
Jordon and Boland	1930	Acute polyarthritis	32	12	37	-	-	-	Gram-negative bacilli Other bacilli	Modification of Cecil's technique.
Nye and Waxelbaum	1930	Acute and chronic infectious	26	5	19	-	3.9	-	Diphtheroid bacillus Gram-positive bacillus	Cecil's technique and whole blood.
Bernhardt and Hench	1930	Chronic infectious	20	5	25	-	-	-	Diphtheroids Staphylococci	Three methods, including Cecil's.
Cecil, Nicholls and Stainsby	1931	Chronic infectious	154	96	62	62	-	-	Diphtheroids	Modification of Clawson's technique.
Gray and Gowen	1931	Arthritis deformans	+110	41	37	37	"Similar to Cecil's typical strains"		-	Modification of Cecil's technique.
		Controls	74	6	8	8			-	

+ refers to samples of blood rather than to cases

TABLE 1. - SUMMARY OF RESULTS OF BLOOD CULTURES IN RHEUMATOID ARTHRITIS - Continued

Observer	Year	Type of Arthritis	No. of Cases	Positive Cases	Positive %	Cases Yielding Streptococci: Haem. %	Viridans %	Non-haem. %	Other Organisms	Remarks
Kracke	1931	Chronic	-	-	30	-	-	-	Diphtheroids	-
Klugh	1931	Infectious arthritis	74	58	78	6.7	71.6	-	-	-
Dawson, Olmstead and Boots	1932	Chronic polyarthritis	+204	58	28	1.4	Streptococci		Gram-positive bacilli Diphtheroids Staphylococci Gram-positive cocci Moulds	Cecil's technique. - - -
Wetherby and Clawson	1932	Chronic arthritis	57	32	56	1.7	42.1		Staphylococci	Clawson's technique.
		Controls	50	1	2	2				
Strauss	1932	Chronic infectious	31	17	55	6.4	Streptococci		Diphtheroids	Cecil's technique.
Ashworth	1932	Rheumatoid	138	56	40	28.2	"Similar to Cecil's typical strains"		Gram-positive diplococci Staphylococci	Modification of Cecil's technique.
Lichtman and Gross	1932	Rheumatoid	48	4	8	-	-	4.1	Gram-positive cocci	Several methods, including Cecil's.
Steinfeld	1932	Chronic	10	2	20	10	-	-	Haemolytic diplococcus	-
Traut	1933	Chronic	38	27	71	-	-	-	Bacillary or diplococcal forms Coccoid forms	Similar to Clawson's technique.
		Controls	20	0	0	-	-	-		

+ refers to samples of blood rather than to cases

TABLE 1. - SUMMARY OF RESULTS OF BLOOD CULTURES IN RHEUMATOID ARTHRITIS - Continued

Observer	Year	Type of Arthritis	No. of Cases	Positive Cases	%	Cases Yielding Streptococci Haem. %	Viridans %	Non-haem. %	Other Organisms	Remarks
Wainwright	1934	Rheumatoid	91	12	13	-	1	-	Diphtheroids Staphylococci Gram-positive bacilli	Similar to Cecil's technique.
McEwen, Alexander and Bunim	1936	Rheumatoid	35	7	19	3	9	5	Diphtheroids	Several methods, including Cecil's.
Angevine, Murray and Cecil	1940	Rheumatoid	+61	12	20	1 Alpha prim. strept.			Large Gram-positive diplococcus Staph. albus Staph. aureus B. subtilis	Aerobic clot method.
Fraser	1938	Rheumatoid	61	3	5	-	-	-	Diphtheroids	Cecil's technique.
		Controls	61	5	8	-	3	-	Diphtheroids	

and heated until the agar is completely melted. The agar is then partially cooled; 0.5 cc. of whole rabbit blood, taken direct from the ear, and 0.1 cc. of broth from the primary culture is added to it, and the contents poured into a petri dish. This subculture in a solid medium is allowed to incubate for twenty-four to forty-eight hours, and is then examined. Similar subcultures are made every three to five days until the primary culture has been in incubation for thirty days. If at the end of this time the subcultures are still sterile, the sediment in the primary culture flask is removed with a glass tube and centrifuged. Part of the sediment is examined by making stained smears, while the remainder is incubated both in fresh blood broth and in blood-agar plates. If these final subcultures show no growth, the blood culture is considered to have been sterile.

Personal Observations

1. Rheumatoid Arthritis.- For the investigation blood cultures were made from sixty-one patients. Fifty-one of these were women and ten were men. Their ages varied from 15 to 93 years; thirty-two were under 50 years of age and twenty-nine were 50 or over. In seventeen of the patients the disease had been present for less than a year; in twenty, from one to five years; in seven, from six to ten years; and in fourteen, for more than ten years. In three, all of whom were over 75 years of age, the duration was not obtained, but each stated that she had had the condition for many years (table 2).

TABLE 2.

Duration of Disease in 61 Cases of Rheumatoid Arthritis

	Duration of R.A. in Years			
	-1	-5	-10	10+
No. of patients	17	20	7	17

All patients presented the clinical syndrome of pain, stiffness and swelling of several joints. In all but three the joints of the fingers were involved and showed the characteristic fusiform swelling associated with the disease. In two of the others the knees were affected, and in the third the elbows and shoulders. In addition to pain, stiffness and swelling of the joints the majority showed some degree of deformity or ankylosis. As in Cecil's series, the patients were free from fever in all but two instances at the time the cultures were made. Forty-five patients were confined to bed and sixteen were ambulatory. In eleven cases the blood was taken from the patient while in the actual process of undergoing some form of physiotherapy, such as massage or passive movements, to test whether such treatment might tend to liberate organisms into the blood stream and increase the chance of obtaining positive blood cultures.

Streptococci were never isolated. No organisms of any kind were recovered from the blood of fifty-eight of the sixty-one patients after thirty days incubation. In the remaining three, diphtheroid bacilli were isolated. In none of the eleven patients from whom the blood was

removed during physical treatment (massage or passive movements) was a positive culture obtained.

2. Controls.- Blood cultures were made by Cecil's technique in sixty-one control patients. A large proportion of these were suffering from diseases due to chronic bacterial infection - e.g., chronic cholecystitis, chronic osteomyelitis, etc. A complete list of the series is given in table 3.

Following Okell and Elliott (1935), blood cultures were also taken after single or multiple dental extractions from twenty patients with apical infection or pyorrhoea alveolaris who were otherwise healthy, the blood being withdrawn within ten minutes of the dental operation. These workers found that a transient bacteriaemia developed in 61 per cent. of patients after dental extractions, due to the trauma. In the majority of these the organism was a streptococcus of the viridans type. Of more importance was the fact that in 11 per cent. of patients with septic mouths a streptococcal bacteriaemia was found irrespective of any operative interference. It was suggested that in these patients the brushing of the teeth or the act of chewing might act as a trauma and cause a "leak" of relatively non-pathogenic organisms into the general circulation, followed by their rapid removal by the phagocytic action of the body.

Organisms were recovered from the blood of five of the sixty-one controls during thirty days incubation. In three of these the streptococcus viridans was isolated and in two a diphtheroid bacillus. The former was obtained, after dental extraction for apical abscess, from the blood of three otherwise healthy patients, and the latter from

patients with osteo-arthritis and fibrositis respectively.

TABLE 3.

Control Series

	No. of Cases
Dental cases	20
Chronic sinusitis	7
Chronic cholecystitis	6
Fibrositis	6
Osteo-arthritis	5
Chronic osteomyelitis	4
Peptic ulcer	4
Chronic endometritis	2
Chronic pyelitis	2
Chronic abscesses of buttocks	1
Spondylitis ankylopoietica ..	1
Chronic pelvic cellulitis ...	1
Chronic empyema	1
P.U.O.	1
Total	61

As each blood culture in both groups of patients in this series was performed in duplicate, a total of 244 primary cultures and over 1,700 subcultures were done.

Discussion

The results of studies on blood cultures in patients with rheumatoid arthritis have been tabulated. From this sufficiently accurate data are available for a short analysis of the findings to be given. Including my own figures, details are given of blood cultures on 1,785 samples of blood

taken from 1,619 patients. Of these, 1,159 (65 per cent.) were found to be sterile, and from the remaining 626 (35 per cent.) a variety of organisms was recovered. In 418 instances (23 per cent.) the blood yielded a streptococcus, and in the remaining 208 (12 per cent.) non-streptococcal organisms were found, the most frequent of which were the diphtheroid bacillus and the staphylococcus albus.

From table 1 it will be noticed that the percentage of positive cultures obtained by various investigators varies considerably. Moreover, even among those who have obtained positive results there is a marked discrepancy in the type of organism recovered. The result of all this body of work remains entirely inconclusive, and I cannot claim that my findings in any way lessen this confusion.

Why should there be this disparity in the results obtained by various investigators? There are some (Nye and Waxelbaum, 1930; Wainwright, 1934) who view all positive results with suspicion and consider that the organisms recovered, including the streptococci, are contaminants. The possibilities of contamination in Cecil's technique are obviously numerous, and as Dawson, Olmstead and Boots (1932) pointed out, each subculture is subjected on an average to eighteen manipulations. In this connection, however, it is only fair to say that since the completion of this investigation Cecil (1940) has gallantly admitted that his "typical strains" were probably contaminants, and that he was sceptical of them from the first, but that he had been misled by the discovery of specific agglutinins to the streptococcus in the blood. He felt that the organisms had gained access to the culture medium by being blown down the pipettes in spite

of the use of cotton plugs. He repeated his previous work in a dust-free and air-filtered room, using rubber bulbs on the pipettes in place of the oral method, and was unable to recover the streptococcus; he found that 80 per cent. of the cultures were sterile. He concluded by saying, "From my stand-point this report is in the nature of a retraction. I hope that a few years from now I shall not have to retract the retraction. I do not think that is likely".

There are those, on the other hand, who attach significance, not only to the streptococci, but to the diphtheroid bacilli and staphylococci which they recovered from the blood. Klugh (1931), Kracke (1931), and Strauss (1932) were all of the opinion that the diphtheroid bacillus was an involution form of the streptococcus. Callow (1933), in her work on rheumatic fever, noted that 51 per cent. of the organisms isolated from the blood were pleomorphic bacilli.

Many of the positive results obtained are rendered invalid by the absence of control cultures. Lichtman and Gross (1932) stressed the necessity of providing adequate controls and included a large number in their work. In my series blood cultures were made from sixty-one controls. These included several diseases due to chronic bacterial infection, such as chronic cholecystitis and chronic osteomyelitis. In none of these was a positive blood culture obtained.

From the evidence so far available, and from blood culture findings in particular, it is not justifiable to conclude that rheumatoid arthritis is a disease of infective origin, streptococcal or otherwise. It may be, however, that some as yet unidentified organism plays a role in its

aetiology. It is suggested, following Okell and Elliott (1935), that bacteriaemia, due to trauma or treatment - e.g., massage - may occur and give rise to a positive blood culture; but the organisms reaching the blood may, or may quite well not, be aetiologically associated with rheumatoid arthritis.

Gray (1940) sums up the position fairly by saying that the presence of bacteria in the blood stream does not prove the microbic aetiology of rheumatoid arthritis, nor does the absence of bacteria disprove it.

Summary

Part 1 opens with a discussion on infection in general. This has been followed by arguments for and against the infective nature of rheumatoid arthritis, and includes an historical review of blood cultural studies in this disease.

The special technique of blood culture employed in the present investigation is then described in detail, and the results of my personal observations on 61 patients with rheumatoid arthritis and 61 control patients are given. No organisms of any kind were recovered from the blood of fifty-eight of the sixty-one arthritic patients, while in the remaining three diphtheroid bacilli were isolated. In the control series, the streptococcus viridans was recovered from the blood of three patients and a diphtheroid bacillus from two; fifty-six cultures were sterile. In all, 244 primary cultures and 1,700 subcultures were made using the complicated technique of Cecil (1929).

A discussion then follows on the results of blood cultural work in

rheumatoid arthritis, and an attempt is made to explain the disparity in the findings obtained by various investigators. It is concluded that, from the evidence so far available, there is no direct proof that rheumatoid arthritis is a blood-borne infection, but that it is possible that some as yet unidentified organism may play a part in its aetiology.

PART II.

ON THE BLOOD CHEMISTRY IN RHEUMATOID ARTHRITIS

1. Plasma Proteins

A considerable amount of work has been done on the relationship of the erythrocyte sedimentation rate to the various plasma protein fractions. Fahreus (1921), whose work forms the basis of modern E.S.R. studies, showed experimentally that both the fibrinogen and globulin percentage had an important bearing on the sedimentation rate. In order to ascertain what the position was in the blood itself Westergren, Theorell and Widestrom (1931) made a large scale investigation on clinical material derived from patients suffering from various diseases, including rheumatoid arthritis, and found that fibrinogen and, to a lesser extent, globulin showed a significant positive correlation with the E.S.R., while albumin showed a slight negative correlation.

On the basis of these facts, certain investigators proceeded to study the pathological changes in the plasma protein fractions in the rheumatic diseases. Aldred-Brown and Munro (1935), who were the first in this field,

were able to show wide variations in the values of the proteins between individuals in each of three groups, viz.-

(a) Healthy young adults.

(b) Subjects suffering from chronic rheumatic disorders.

(c) Non-rheumatic persons whose ages and economic stresses resembled the preceding group of chronic rheumatics.

They found that a large percentage of cases with rheumatoid arthritis had albumin values below the minimum of the healthy young adults and globulin, fibrinogen and total protein values above the maximum. Moreover, they were able to demonstrate that the means of the individual proteins in the non-rheumatic group with similar ages and economic stresses lay between the means of the normal healthy controls and those of the rheumatic group, and somewhat nearer the latter than the former. From these findings they inferred that several factors, of which increasing age and economic stress may be two, cause the plasma proteins to deviate from the normal.

Other investigations on the changes in the plasma proteins in rheumatoid arthritis followed. Davis (1935) demonstrated that the globulin, more especially the euglobulin, showed a considerable increase, and the fibrinogen to a lesser extent. The albumin percentage was lower than normal. Rawls, Weiss and Collins (1937) found a slight reduction in the total serum protein and a reversal of the albumin-globulin ratio. Schull, Bach and Pemberton (1939) were able to confirm the findings of Davis. Swedin and Bengtsson (1944) studied the relationship between the E.S.R. and the plasma protein fractions in rheumatoid arthritis, and found that

there was no absolute correlation between the two findings. They felt that a truer indication of the gravity of the disease was undoubtedly given by analysis of the protein fractions in the plasma, and in particular the fibrinogen percentage, which in the majority of cases was raised. This rise was maintained even after clinical improvement and a reduction in the E.S.R. had occurred. They suggested that this finding indicated that there was still some activity present.

The present investigation was undertaken in order to study the variations in the plasma proteins in rheumatoid arthritis, and to correlate, if possible, the findings with other factors and with the results of treatment.

The estimation of the plasma proteins was carried out by employing the method of Howe (1921), as modified by Hawke and Bergeim (1938).

Results

(1) Normal Controls

The plasma protein values found in fifty healthy blood donors are shown in table 1.

Table 1

Plasma protein values in fifty healthy blood donors

	Mean g. per 100 ml.	Standard deviation	Standard error
Total Protein	7.13	0.56	0.08
Albumin	4.91	0.37	0.05
Globulin	1.87	0.42	0.07
Fibrinogen	0.39	0.14	0.02

(2) Rheumatoid Arthritis

The plasma protein values were estimated in one hundred unselected cases of rheumatoid arthritis and the results are shown in table 2.

Table 2

Plasma protein values in one hundred cases of rheumatoid arthritis

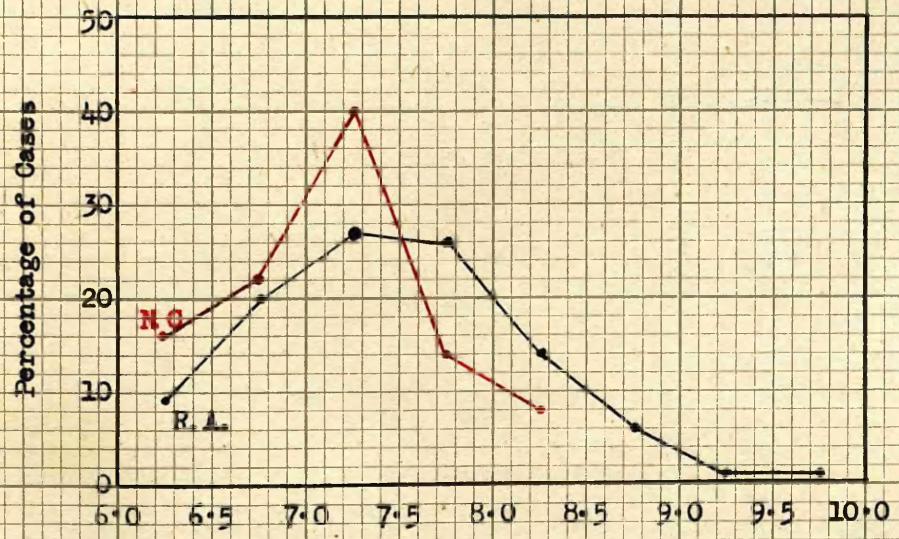
	Mean g. per 100 ml.	Standard deviation	Standard error
Total Protein	7.46	0.73	0.07
Albumin	4.10	0.34	0.03
Globulin	2.94	0.47	0.04
Fibrinogen	0.44	0.11	0.01

From tables 1 and 2 it will be seen that in rheumatoid arthritis the plasma protein values vary considerably from the normal. The greatest differences are seen in the globulin and albumin levels, the former being noticeably increased and the latter lowered in rheumatoid arthritis. The fibrinogen and total protein values are raised to a lesser extent. These findings are recorded graphically in figures 1 - 4 and the statistical significance of the results is shown in table 3.

Fig. 1.

Plasma Total Protein

in Normal Controls and in Rheumatoid Arthritis



N.C. = Normal Controls.

R.A. = Rheumatoid Arthritis.

Fig. 2.

Plasma Albumin

in Normal Controls and in Rheumatoid Arthritis.

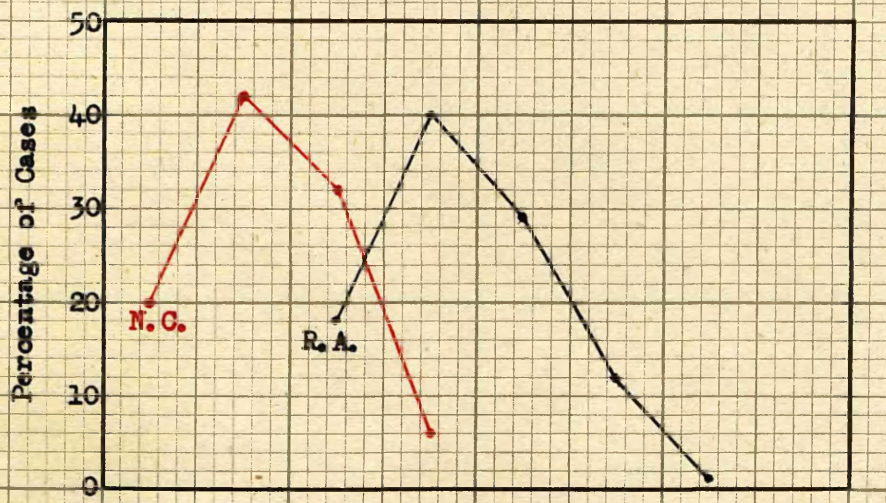
N.C. = Normal Controls.

R.A. = Rheumatoid Arthritis.

Fig. 3.

Plasma Globulin

in Normal Controls and in Rheumatoid Arthritis



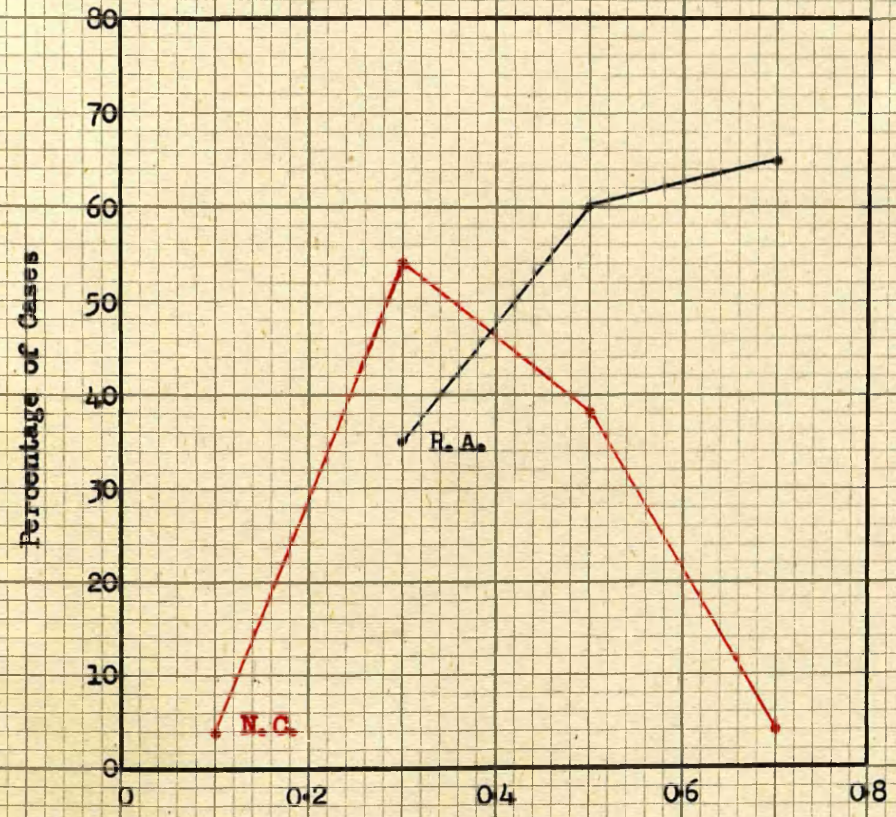
N.C. = Normal Controls.

R.A. = Rheumatoid Arthritis.

Fig. 4.

Plasma Fibrinogen

in Normal Controls and in Rheumatoid Arthritis



N. C. = Normal Controls.

R. A. = Rheumatoid Arthritis.

Table 3

Statistical comparison of plasma protein values in rheumatoid arthritis with normal controls

	Total Protein		Albumin		Globulin		Fibrinogen	
	Normal Controls	R.A.	Normal Controls	R.A.	Normal Controls	R.A.	Normal Controls	R.A.
Mean	7.13	7.46	4.91	4.10	1.87	2.94	0.39	0.44
D.M.	-	0.33	-	0.82	-	1.07	-	0.05
S.E.D.M.	-	0.13	-	0.06	-	0.08	-	0.02
$\frac{\text{D.M.}}{\text{S.E.D.M.}}$	-	2.50	-	13.60	-	13.30	-	2.50

Mean = g. per 100 ml. D.M. = Difference between Means.
S.E.D.M. = Standard error of difference between Means.

It is difficult to see why there should be such a marked variation from the normal in the plasma protein fractions in rheumatoid arthritis. An attempt was made to correlate the findings with numerous factors - shown in detail in table 18 (p. 38) - with the following results.

(a) Age.- The ages of the patients varied from 12 to 73 years. The age-groups are shown in table 4. There was no correlation between the age of the individual and any of the plasma protein values (table 18).

Table 4

Age-groups of 100 patients with R.A.

	Years							Total
	10-	20-	30-	40-	50-	60-	70-	
No. of patients	3	4	25	33	25	9	1	100

(b) Sex.- Thirty-two of the patients were males and sixty-eight were females. The sex of the individual did not have any bearing on the plasma protein results (table 18).

(c) Duration of R.A.- As it has often been stated that the plasma protein values are altered in chronic diseases as a whole, an attempt was made to correlate the variations in the plasma protein levels with the duration of the disease (table 5).

Table 5

Relation of plasma proteins to duration of arthritis

		Duration of R.A. in years						
		-1	-2	-3	-4	-5	-10	10+
No. of Cases		25	14	8	6	13	28	6
Mean (g. per 100ml.)	Total Protein	7.29	7.85	7.14	7.37	7.70	7.47	7.56
	Albumin	4.04	4.20	3.88	4.05	4.20	4.20	4.02
	Globulin	2.76	3.15	2.68	2.75	3.01	2.87	3.15
	Fibrinogen	0.49	0.50	0.58	0.57	0.49	0.40	0.39

It will be seen that there was no relation between the duration of the disease and any of the plasma protein fractions. In the case of the plasma globulin, for example, the lowest mean value (2.75 g.) was found in those patients who had had the disease for 4 - 5 years, and the highest (3.15 g.) was common to two groups, viz. 1 - 2 years and over ten years.

(d) Degree of Arthritis.- It was thought that the variations in the plasma protein values might be related to the degree of arthritis, and an attempt was made to correlate these two factors (table 6). The patients were divided radiologically into three groups according to the degree of involvement of the joints - mild, moderate and advanced.

Table 6

Relation of plasma proteins to degree of arthritis

		Degree of Arthritis		
		Mild	Moderate	Advanced
No. of cases		46	33	21
Mean (g.per 100ml.)	Total Protein	7.49	7.48	7.48
	Albumin	4.25	4.13	4.01
	Globulin	2.80	2.96	3.03
	Fibrinogen	0.44	0.39	0.44

From the table it would appear that the more advanced the rheumatoid arthritis, the lower the albumin and the higher the globulin values seem to be. The difference in the values in the three groups, however, is small and, statistically, the findings are insignificant.

(e) Previous gold therapy.- A little less than half of the patients had received at some time prior to the investigation one or more courses of gold injections, and it was felt that this might have some effect on the

plasma protein values through damage to the liver, i.e. a toxic hepatitis. It was found, however, that the mean plasma protein values of those patients who had had chrysotherapy were similar to the values of those who had not received any (table 7).

Table 7

Relation of plasma proteins to previous chrysotherapy

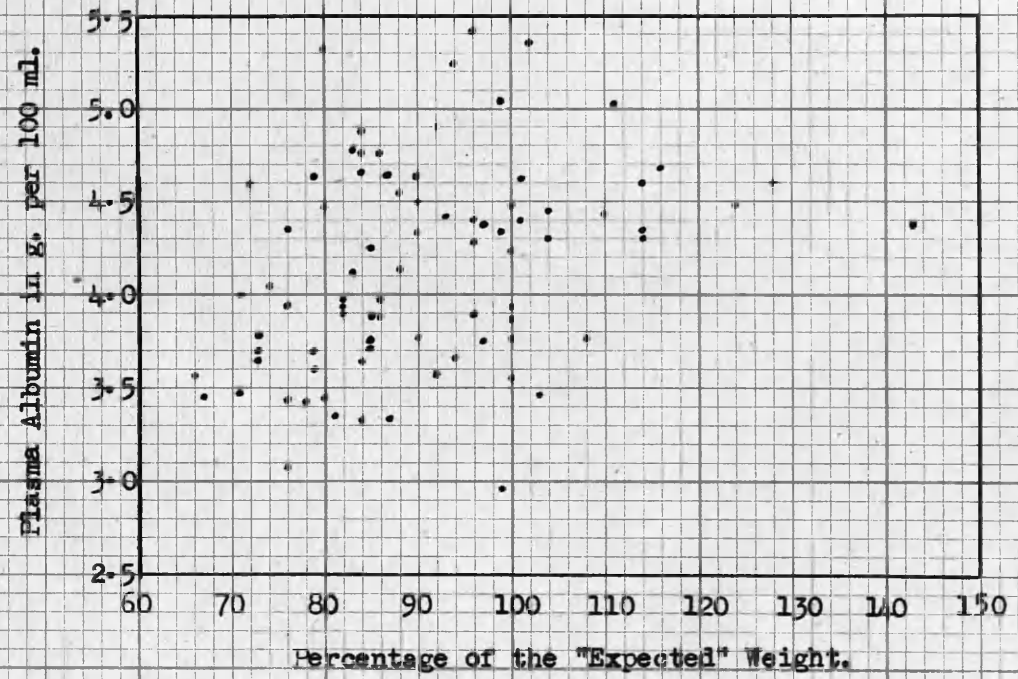
		Gold	None
No. of cases		44	56
Mean (g.per 100ml.)	Total Protein	7.47	7.46
	Albumin	4.15	4.11
	Globulin	2.89	2.90
	Fibrinogen	0.43	0.45

(f) Weight.- The weight of an individual may give some indication of his general nutrition. If there is a marked degree of under-nourishment there may be some disturbance of the plasma proteins, particularly the albumin fraction which may be appreciably reduced. It was, therefore, decided to compare the plasma albumin values with the respective weights of the patients. For this purpose the actual weight of each patient was calculated as a percentage of the expected weight estimated from the age and height of the individual (Lister's Tables). The results have been recorded as a "scatter" diagram, from which it will be seen that

Fig. 5.

To Show Absence of Relation

Between Plasma Albumin and Weight Percentage.



there is no correlation between the plasma albumin and the weight percentage (figure 5).

(g) Focal sepsis.- It was considered possible that the presence of focal sepsis might lead to an alteration in the plasma protein values. No correlation could be found, however, between these two factors. In 18 of the hundred patients with rheumatoid arthritis a septic focus was found, but the mean plasma protein values of this group did not vary in any way from those of the series as a whole.

(h) Temperature.- Only 5 of the patients were febrile at the time of the protein analysis. The plasma protein levels did not appear to be significantly affected by the rise in temperature.

(i) Other factors.- Comparison of the plasma protein values with the haemoglobin percentage and white cell count failed to reveal any correlation.

(3) Other forms of Rheumatism.

It was considered advisable to estimate the plasma proteins in other forms of rheumatism for comparison with the values in rheumatoid arthritis and the normal controls. The results are shown in tables 8 - 11.

Table 8

Total plasma proteins

	Normal Controls	Rheumatoid Arthritis	Osteo-Arthritis	Rheumatic Fever
No. of cases	50	100	20	12
Mean (g.per 100ml.)	7.13	7.46	7.65	7.51

Table 9

Plasma albumin

	Normal Controls	Rheumatoid Arthritis	Osteo-Arthritis	Rheumatic Fever
No. of cases	50	100	20	12
Mean (g.per 100ml.)	4.91	4.10	4.52	4.10

Table 10

Plasma globulin

	Normal Controls	Rheumatoid Arthritis	Osteo-Arthritis	Rheumatic Fever
No. of cases	50	100	20	12
Mean (g.per 100ml.)	1.87	2.94	2.75	2.91

Table 11

Plasma fibrinogen

	Normal Controls	Rheumatoid Arthritis	Osteo-Arthritis	Rheumatic Fever
No. of cases	50	100	20	12
Mean (g.per 100ml.)	0.39	0.44	0.37	0.50

A glance at the tables shows that the plasma protein values in rheumatic fever are very similar to those in rheumatoid arthritis and are therefore of statistical significance. The values in osteoarthritis tend to lie in a mid-position between these and the normal controls. The variations from the normal in the total protein, albumin and globulin values in osteoarthritis are themselves statistically significant (table 12), and are recorded graphically in figures 6 - 9.

Table 12

Statistical comparison of plasma protein values in osteoarthritis with normal controls

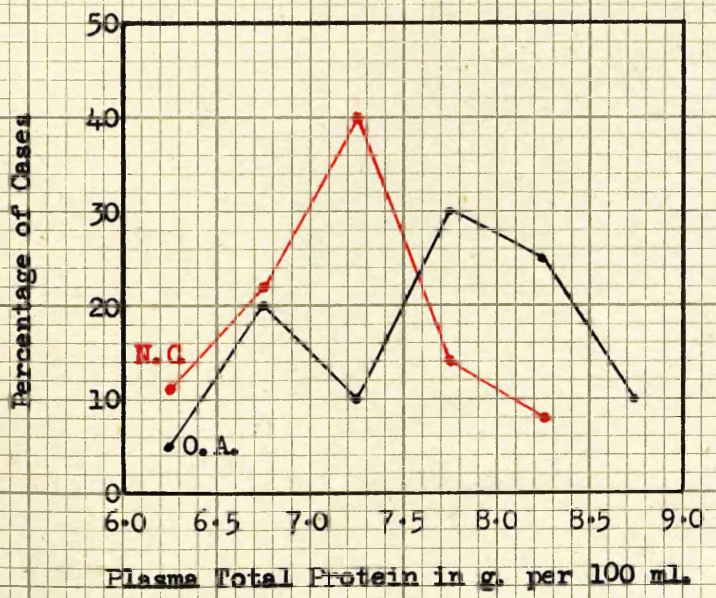
	Total Protein		Albumin		Globulin		Fibrinogen	
	Normal Controls	O.A.	Normal Controls	O.A.	Normal Controls	O.A.	Normal Controls	O.A.
Mean	7.13	7.65	4.91	4.52	1.87	2.75	0.39	0.37
D.M.	-	0.52	-	0.39	-	0.88	-	0.02
S.E.D.M.	-	0.09	-	0.12	-	0.12	-	0.03
$\frac{\text{D.M.}}{\text{S.E.D.M.}}$	-	5.7	-	3.2	-	7.3	-	0.6

Mean = g. per 100 ml. D.M. = Difference between Means.
S.E.D.M. = Standard error of Difference between Means.

It was felt that a comparison of the plasma protein values in rheumatic fever and in osteoarthritis with similar age-groups in rheumatoid arthritis would be of interest. The twelve patients with rheumatic fever were 35 years of age or under, and their plasma protein values were compared with those of the twenty-one patients with rheumatoid arthritis of the same

Fig. 6.

Plasma Total Protein Values in Normal Controls and in Osteoarthritis.



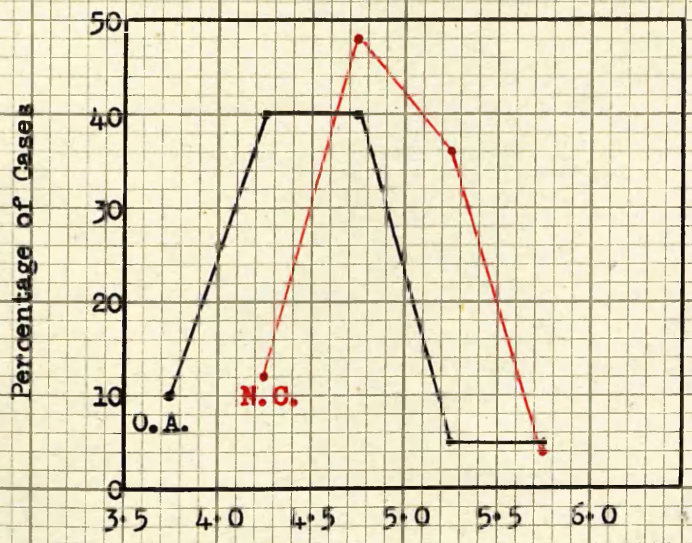
N.C. = Normal Controls.

O.A. = Osteoarthritis.

Fig. 7.

Plasma Albumin Values

in Normal Controls and in Osteoarthritis.



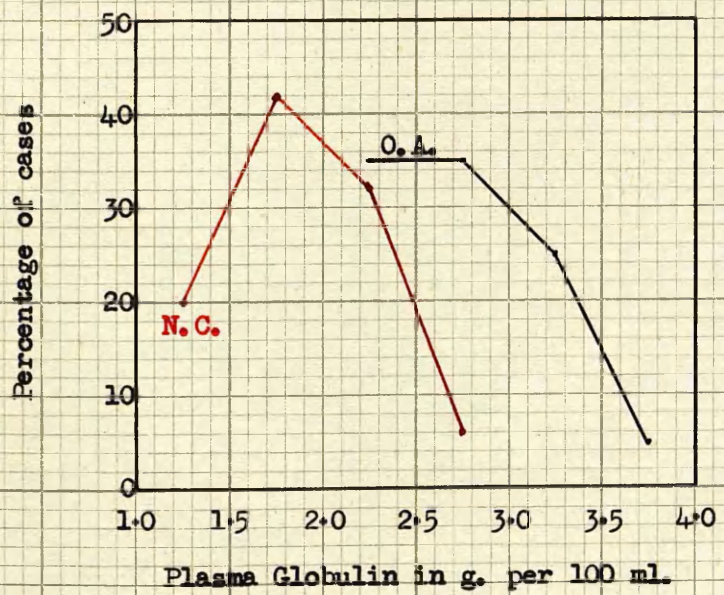
N.C. = Normal Controls.

O.A. = Osteoarthritis.

Fig. 8.

Plasma Globulin Values

in Normal Controls and in Osteoarthritis.



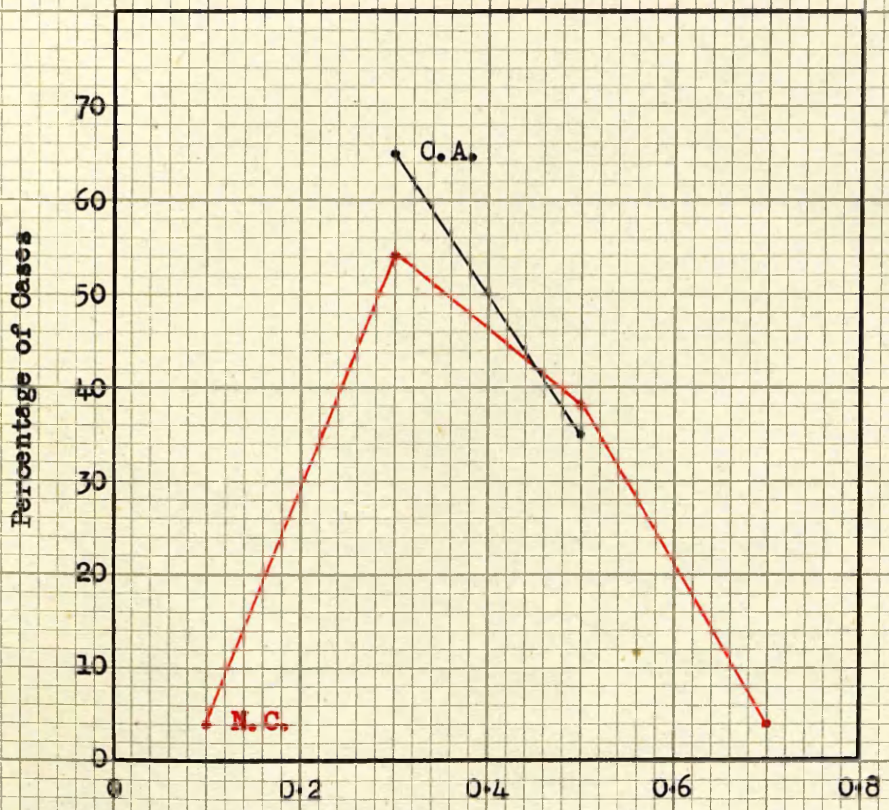
N.C. = Normal Controls.

O.A. = Osteoarthritis.

Fig. 9.

Plasma Fibrinogen Values

in Normal Controls and in Osteoarthritis.



N.C. = Normal Controls.

O.A. = Osteoarthritis.

age-group. The results are shown in table 13.

Table 13

Comparison of plasma protein values in rheumatic fever with similar age-group in rheumatoid arthritis

	No.of Cases	Average Age	Mean values in g.per 100ml.			
			Total Prot.	Alb.	Glob.	Fib.
Rheumatic fever	12	27	7.51	4.10	2.91	0.50
Rheumatoid arthritis	21	28	7.55	4.15	2.96	0.44

Table 14 shows the values in twenty patients with osteoarthritis and the thirty-five patients with rheumatoid arthritis of the same age-group, i.e. 50 years and over.

Table 14

Comparison of plasma protein values in osteoarthritis with similar age-group in rheumatoid arthritis

	No.of Cases	Average Age	Mean values in g.per 100ml.			
			Total Prot.	Alb.	Glob.	Fib.
Osteoarthritis	20	60	7.65	4.52	2.75	0.38
Rheumatoid arthritis	35	57	7.37	3.99	2.93	0.45

It will be seen from table 13 that the plasma protein values in rheumatic fever and rheumatoid arthritis of the same age-group are similar. It is, therefore, possible that the same factor may be responsible for the

alteration in the plasma protein values in the two diseases. On the other hand, the values for osteoarthritis are nearer to the normal values than those of rheumatoid arthritis of the same age-group. These findings would suggest that, while advancing age may play a part in the variations in the plasma protein levels in the older cases of rheumatoid arthritis, it is by no means the full explanation.

Out of interest the plasma proteins were estimated on six patients with fibrositis (table 15) and two with ankylosing spondylitis. The number of estimations is too small to draw conclusions from, but in the main the values for fibrositis were within the normal limits, whereas those for ankylosing spondylitis approached the figures found in rheumatoid arthritis.

Table 15

Plasma protein values in 6 cases of fibrositis

	Total Proteins	Albumin	Globulin	Fibrinogen
Mean (g. per 100 ml.)	7.22	5.12	1.85	0.25

(4) Effect of Gold Therapy

An investigation into the effect of gold therapy on the plasma protein values in rheumatoid arthritis was undertaken. Thirty patients were given a course of myocrisin (total = lg.), and the plasma proteins

estimated before and at the end of the course. The results are shown in table 16 and figures 10 - 13.

Table 16

Plasma protein values in 30 cases of rheumatoid arthritis before and after gold therapy

	Total Protein		Albumin		Globulin		Fibrinogen	
	Before	After	Before	After	Before	After	Before	After
Mean	7.30	7.65	3.88	4.35	2.95	2.92	0.43	0.42
D.M.	-	0.45	-	0.47	-	0.03	-	0.01
S.E.D.M.	-	0.18	-	0.14	-	0.16	-	0.03
$\frac{\text{D.M.}}{\text{S.E.D.M.}}$	-	2.50	-	3.30	-	0.18	-	0.33

Mean = g. per 100 ml. D.M. = Difference between Means.
S.E.D.M. = Standard Error of Difference between Means.

From the table it will be seen that, whereas the globulin and fibrinogen values remained unchanged as the result of treatment, the total protein and albumin levels were increased. The increase in both is shown to be of statistical significance.

The next step was an attempt to correlate the increase in the plasma albumin values following on gold therapy with the clinical results. For

Fig. 10.

Plasma Total Protein Values Before and After Gold Therapy in 30 Cases of Rheumatoid Arthritis.

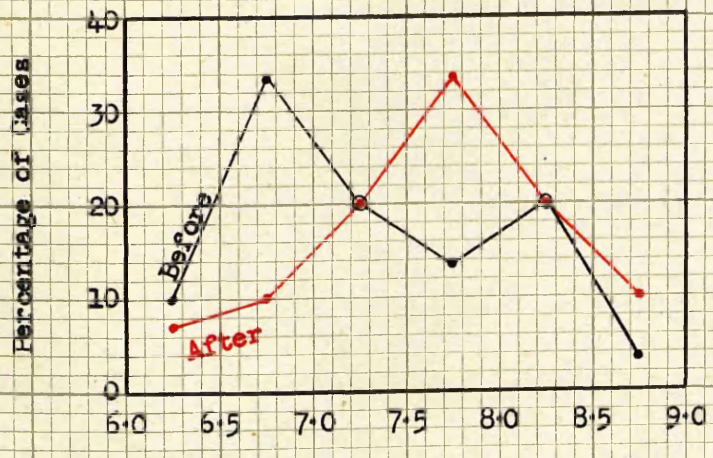


Fig. 11.

Plasma Albumin Values Before and After Gold Therapy in 30 Cases of Rheumatoid Arthritis.

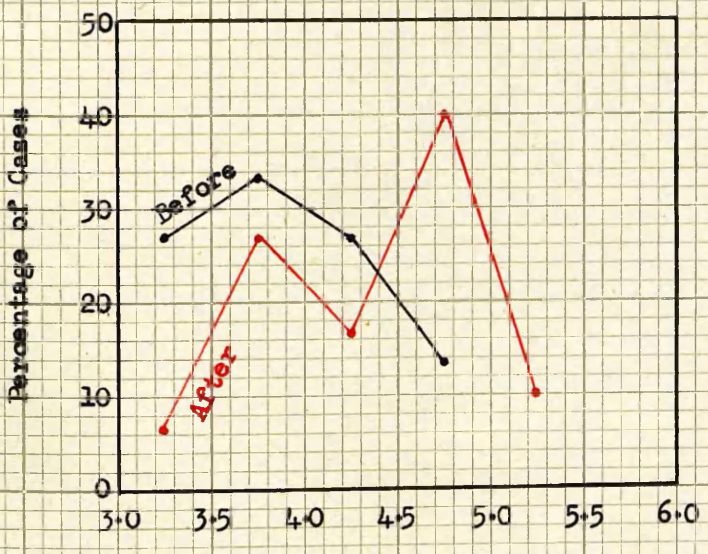


Fig. 12.

Plasma Globulin Values Before and After Gold Therapy in 30 Cases of Rheumatoid Arthritis.

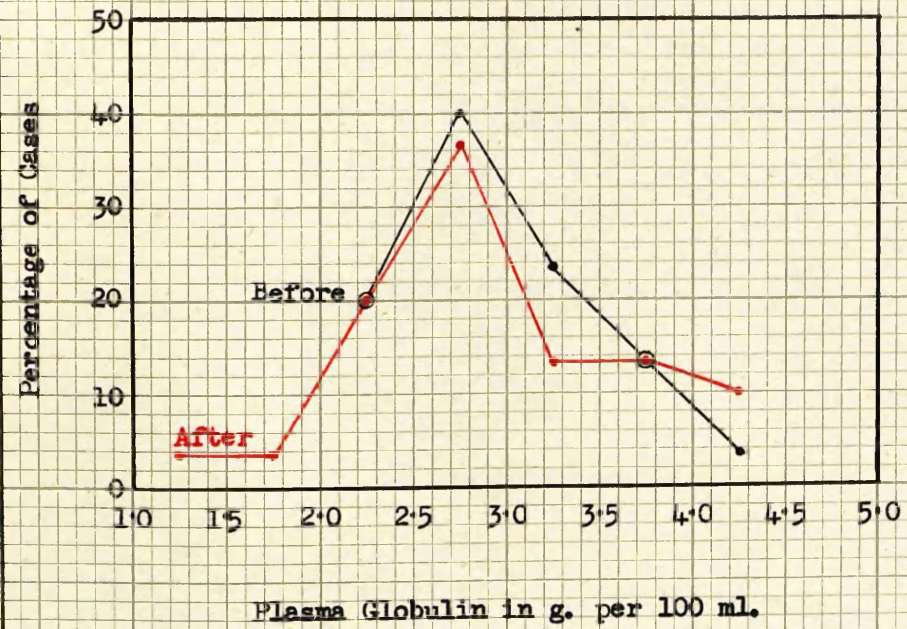
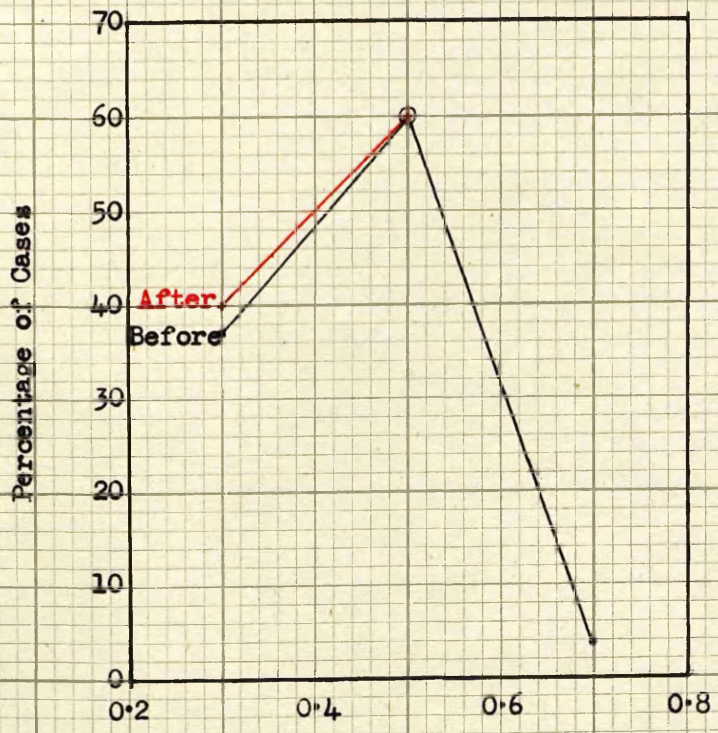


Fig. 13.

Plasma Fibrinogen Values Before and After Gold Therapy in 30 Cases of Rheumatoid Arthritis.



the purposes of assessing the latter the patients were divided into four groups - great, moderate, slight and no improvement - according to the changes in the clinical signs, e.g. general condition, weight, joint swelling, E.S.R., etc. The results are shown in table 17.

Table 17

Relation of changes in plasma albumin to clinical results after gold therapy

	No Improvement		Slight Improvement		Moderate Improvement		Great Improvement	
	Before	After	Before	After	Before	After	Before	After
No. of cases	5	5	6	6	11	11	8	8
Mean (g.per 100 ml.)	3.56	3.86	4.04	4.28	3.85	4.40	4.13	4.31

Of the 30 patients who received chrysotherapy 25 showed clinical evidence of improvement, and in 5 there was no obvious change in the arthritis. While the mean values for the plasma albumin were increased in all four groups, the increase was not proportional to the degree of clinical improvement.

(5) Relation to Erythrocyte Sedimentation Rate.

An opportunity was afforded of comparing the plasma protein values with the E. S. R. (Westergren). One hundred and thirty-three observations were made on one hundred patients with rheumatoid arthritis. The results are recorded graphically in figures 14 - 17 in the following manner. The protein fractions are arranged in groups and the average for each group found; the corresponding E. S. R. values in these groups are also averaged. The number of observations at the ends of the curves are in some instances few and therefore the figures have been "smoothed".

From figure 14 it will be seen that there is no apparent relationship between the total proteins and the E. S. R. Figure 15 shows a partial inverse relationship between the plasma albumin and the E. S. R., while figures 16 and 17 show a direct relationship between the plasma globulin and fibrinogen respectively and the E. S. R. The closest relationship is seen to be between the plasma globulin and the E. S. R.

Fig. 14.

Relation Between Erythrocyte Sedimentation Rate and Plasma Total Protein.

(No. of observations shown in brackets.)

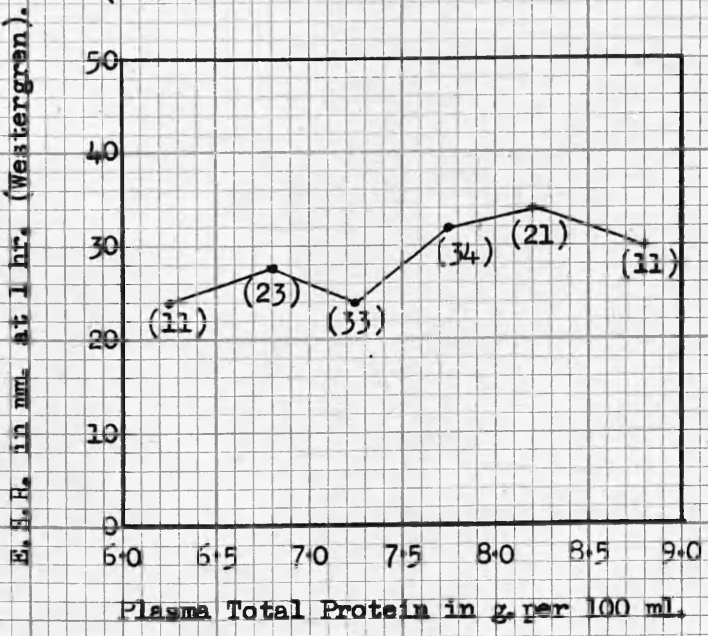


Fig. 15.

Relation Between Erythrocyte Sedimentation Rate and Plasma Albumin.

(No. of observations shown in brackets.)

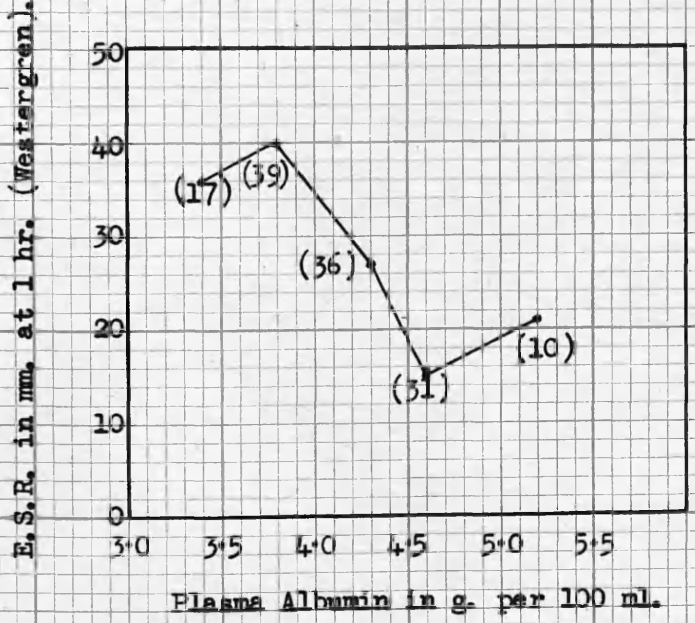


Fig. 16.

Relation Between Erythrocyte Sedimentation Rate and Plasma Globulin.

(No. of observations shown in brackets.)

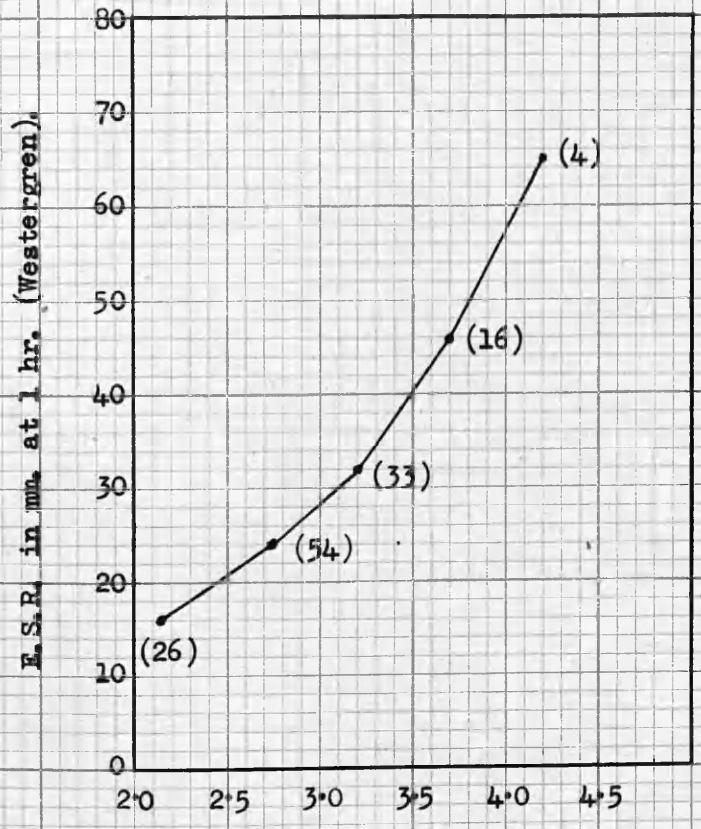


Fig. 17.

Relation Between Erythrocyte Sedimentation Rate and Plasma Fibrinogen.

(No. of observations shown in brackets.)

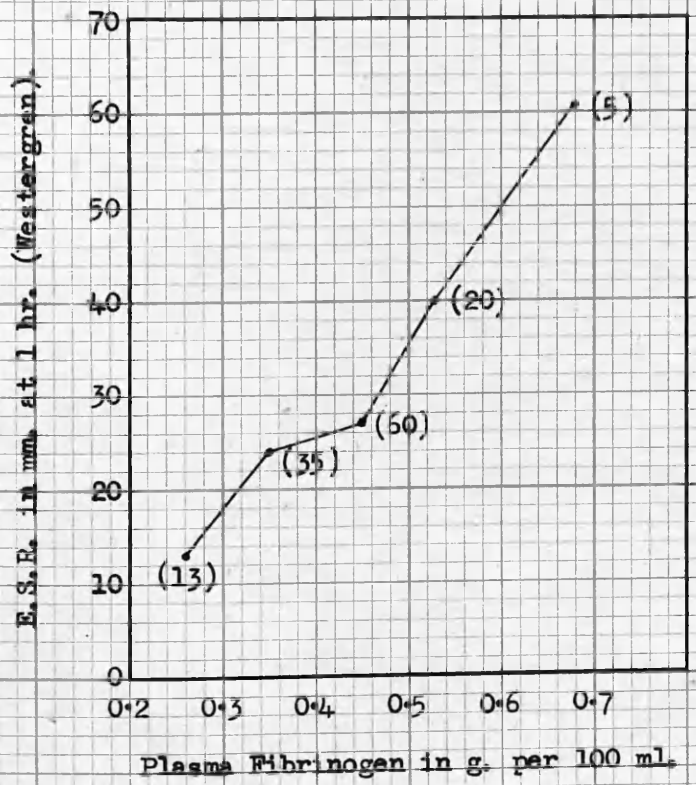


TABLE 18.

CLINICAL AND BIOCHEMICAL DATA IN 100 CASES OF RHEUMATOID ARTHRITIS

Case No.	Sex	Age Yrs.	Date	Coll. Gold	Ceph. Chol.	E.S.R. m.m.	g. per 100ml.				N.P.N. mg.%	Duration of R.A.	Degree of R.A.	Weight		Previous Gold
							Total Prot.	Alb.	Glob.	Fib.				Actual lbs.	Expected lbs.	
1	F.	57	18.9.46.	-ve	-ve	27	8.31	4.36	3.50	0.45	30	9 years	Mild	140	144	Yes
			18.12.46.	-ve	-ve	7	6.58	4.00	2.38	0.20	37					
2	F.	58	17.6.46.	4	-ve	38	6.02	3.37	2.30	0.35	28	5 years	Moderate	112	138	No
			13.12.46.	2	-ve	30	7.58	4.26	2.90	0.42	33					
3	M.	43	22.8.46.	-ve	-ve	9	7.58	4.55	2.55	0.48	40	4½ mths.	Mild	177	201	No
			11.12.46.	-ve	-ve	8	7.37	4.38	2.57	0.42	26					
4	F.	49	9.9.46.	4	-ve	31	7.98	4.43	3.16	0.39	31	2 years	Mild	166	151	No
			11.12.46.	4	-ve	13	7.97	4.76	2.78	0.43	31					
5	F.	45	8.8.46.	5	+++	54	6.28	3.44	2.50	0.34	30	8 mths.	Mild	112	140	No
			6.12.46.	5	+	20	7.28	3.93	2.99	0.36	22					
6	F.	36	29.8.46.	3	+	14	7.83	4.65	2.70	0.48	31	9 mths.	Moderate	109	129	No
			30.11.46.	-ve	-ve	17	8.46	5.19	2.99	0.28	32					
7	F.	33	18.6.46.	-ve	-ve	27	8.01	4.60	3.00	0.41	32	8 mths.	Mild	93	128	No
			20.11.46.	-ve	-ve	5	7.53	4.52	2.66	0.35	31					

TABLE 18. (Continued)

Case No.	Sex	Age Yrs.	Date	Coll. Gold	Ceph. Chol.	E.S.R. m.m.	g. per 100ml. Total Prot.	Alb.	Glob.	Fib.	N.P.N. mg.%	Duration of R.A.	Degree of R.A.	Weight Actual lbs.	Weight Expected lbs.	Previous Gold
8	M.	57	8.8.46.	4	-ve	35	6.91	4.01	2.36	0.54	31	8 mths.	Mild	116	162	Yes
			18.10.46.	-ve	-ve	35	6.25	3.58	2.10	0.57	30					
9	M.	62	6.8.46.	1	-ve	20	7.13	4.55	2.15	0.43	37	6 years	Moderate	-	-	Yes
			9.10.46.	-ve	-ve	6	8.20	4.55	3.19	0.46	37					
10	F.	54	8.8.46.	-ve	-ve	20	6.04	3.44	2.29	0.31	25	6 mths.	Mild	105	138	Yes
			9.10.46.	-ve	-ve	42	7.83	4.78	2.56	0.49	25					
11	M.	45	17.6.46.	5	++++	39	6.73	3.70	2.54	0.49	29	3 years	Moderate	116	158	No
			18.9.46.	4	-ve	31	8.43	4.38	3.61	0.44	34					
12	M.	41	30.6.46.	2	-ve	28	6.60	3.41	2.66	0.53	39	6½ years	Mild	124	159	No
			18.9.46.	2	-ve	20	8.77	4.65	3.70	0.42	35					
13	F.	40	13.6.46.	4	-ve	40	6.70	3.79	2.51	0.40	28	6 years	Mild	166	145	Yes
			20.9.46.	5	-ve	30	8.66	4.28	3.91	0.47	24					
14	F.	35	25.3.46.	4	+++	22	8.16	3.98	3.86	0.32	31	5 years	Moderate	121	140	No
			11.9.46.	4	-ve	23	6.87	3.58	2.86	0.43	31					
15	F.	36	17.4.46.	1	+++	12	7.34	3.89	3.14	0.31	28	1 year	Moderate	146	152	No
			11.9.46.	3	-ve	13	7.31	4.54	2.41	0.36	27					
16	F.	54	15.5.46.	5	+++	90	6.97	3.36	3.12	0.49	30	5 years	Moderate	-	-	No
			5.9.46.	5	-ve	52	7.75	3.10	4.10	0.55	25					

TABLE 18. (Continued)

Case No.	Sex	Age Yrs.	Date	Coll. Gold	Ceph. Chol.	E.S.R. m.m.	g. per 100ml.				N.P.N. mg.%	Duration of R.A.	Degree of R.A.	Weight		Previous Gold
							Total Prot.	Alb.	Glob.	Fib.				Actual lbs.	Expected lbs.	
17	M.	58	29.5.46.	2	-ve	38	7.18	4.12	2.57	0.49	28	7 years	Advanced	122	160	Yes
			4.9.46.	3	-ve	46	7.70	3.08	4.10	0.52	48					
18	F.	58	6.3.46.	4	++++	42	6.97	3.98	2.55	0.44	28	5 years	Advanced	116	141	No
			23.8.46.	5	-ve	70	8.19	4.55	3.10	0.54	31					
19	F.	30	15.3.46.	-ve	-ve	6	7.28	4.21	2.72	0.35	40	1 year	Mild	129	128	No
			23.8.46.	-ve	-ve	6	8.05	4.89	2.74	0.42	33					
20	F.	41	17.6.46.	4	-ve	75	7.14	3.96	2.79	0.39	22	6 mths.	Mild	91	136	No
			16.8.46.	4	-ve	76	8.60	3.58	4.47	0.55	25					
21	M.	51	10.3.46.	5	++	32	7.20	3.56	3.25	0.39	31	6 years	Mild	154	167	Yes
			5.6.46.	5	-ve	40	8.10	5.14	2.59	0.37	41					
22	M.	50	20.3.46.	1	-ve	60	8.15	4.31	3.30	0.54	34	2 years	Mild	169	153	No
			26.6.46.	-ve	-ve	6	7.77	4.58	2.84	0.35	42					
23	F.	47	5.3.46.	5	++	85	8.30	3.72	4.12	0.46	37	15 mths.	Advanced	105	142	No
			12.5.46.	4	-ve	80	7.80	3.52	3.89	0.39	38					
24	F.	39	27.2.46.	2	-ve	44	8.66	4.38	3.98	0.30	49	13 mths.	Mild	117	136	No
			13.6.46.	1	-ve	20	6.49	3.88	2.40	0.21	29					

TABLE 18. (Continued)

Case No.	Sex	Age Yrs.	Date	Coll. Gold	Ceph. Chol.	E.S.R. m.m.	g. per 100ml. Total Prot.	Alb.	Glob.	Fib.	N.P.N. mg.%	Duration of R.A.	Degree of R.A.	Weight Actual lbs.	Weight Expected lbs.	Previous Gold
25	F.	60	12.3.46.	-ve	-ve	24	6.92	4.20	2.29	0.43	42	17 years	Advanced	172	148	Yes
			19.6.46.	-ve	-ve	10	7.43	4.67	2.30	0.46	33					
26	F.	48	27.2.46.	-ve	-ve	21	7.92	4.34	2.86	0.72	59	8 years	Moderate	128	142	Yes
			26.6.46.	-ve	-ve	22	8.00	4.50	3.10	0.40	32					
27	M.	50	25.3.46.	2	-ve	30	7.09	3.74	2.86	0.49	29	8 years	Mild	137	160	No
			26.6.46.	-ve	-ve	14	7.35	4.50	2.59	0.26	35					
28	M.	53	6.3.46.	1	+	20	6.58	3.36	2.72	0.50	35	3 years	Moderate	141	162	No
			29.5.46.	1	-ve	5	7.53	4.66	2.42	0.45	31					
29	F.	21	8.5.46.	1	++++	11	7.61	4.90	2.45	0.26	32	1 year	Mild	114	123	No
			7.8.46.	3	-ve	12	7.17	5.42	1.46	0.29	36					
30	M.	40	1.4.46.	4	-ve	11	8.28	5.15	2.65	0.48	37	2½ years	Mild	132	146	No
			19.6.46.	3	-ve	12	7.43	4.63	2.51	0.29	31					
31	M.	37	10.3.46.	1	-ve	32	6.63	3.33	2.76	0.54	27	6 mths.	Mild	128	152	No
			20.6.46.	4	-ve	70	7.76	3.78	3.42	0.56	27					
32	M.	41	27.3.46.	2	-ve	53	8.05	3.93	3.58	0.54	40	9 mths.	Mild	121	159	No
			24.6.46.	1	-ve	24	6.77	4.39	1.94	0.44	28					
33	M.	44	3.4.46.	1	-ve	26	6.84	3.44	3.06	0.34	31	1 year	Mild	107	159	No
			24.6.46.	-ve	-ve	10	7.05	3.87	2.95	0.23	34					

TABLE 18. (Continued)

Case No.	Sex	Age Yrs.	Coll. Gold	Ceph. Chol.	E.S.R. m.m.	g. per 100ml.				N.P.N. mg.%	Duration of R.A.	Degree of R.A.	Weight		Previous Gold
						Total Prot.	Alb.	Glob.	Fib.				Actual lbs.	Expected lbs.	
34	F.	32	4	-ve	70	7.80	3.80	3.55	0.45	24	1 year	Moderate	112	125	No
35	M.	42	4	-ve	26	7.77	4.40	2.83	0.54	34	2 mths.	Mild	154	152	No
36	F.	43	5	++++	20	7.60	3.75	3.50	0.35	30	22 years	Advanced	129	133	Yes
37	F.	53	-ve	-ve	10	6.49	3.46	2.58	0.45	30	7 years	Advanced	105	148	Yes
38	F.	30	-ve	-ve	5	7.29	3.44	3.44	0.41	45	7 years	Moderate	137	132	Yes
39	F.	13	1	-ve	27	6.99	3.51	3.08	0.40	24	1 year	Moderate	91	115	No
40	M.	32	5	+	65	7.37	3.39	3.60	0.38	30	18 years	Advanced	-	-	Yes
41	F.	43	-ve	+++	8	8.11	4.60	3.18	0.33	32	5 years	Mild	167	147	No
42	F.	31	3	-ve	21	6.81	3.37	2.78	0.66	24	3 years	Mild	-	-	No
43	F.	40	-ve	-ve	42	7.01	3.48	3.08	0.45	30	6 mths.	Moderate	-	-	No
44	F.	31	1	-ve	21	6.47	3.57	2.44	0.46	23	3 years	Mild	-	-	No
45	F.	39	3	-ve	16	7.12	3.92	2.79	0.41	40	9 mths.	Moderate	-	-	Yes
46	F.	29	4	+	35	7.11	4.03	2.70	0.38	28	2 years	Moderate	-	-	Yes
47	F.	46	-ve	-ve	8	7.93	4.49	3.07	0.37	37	8 years	Advanced	112	139	Yes

TABLE 18. (Continued)

Case No.	Sex	Age Yrs.	Coll. Gold	Ceph. Chol.	E.S.R. m.m.	g. per 100ml.				N.P.N. mg.%	Duration of R.A.	Degree of R.A.	Weight		Previous Gold
						Total Prot.	Alb.	Glob.	Fib.				Actual lbs.	Expected lbs.	
48	F.	50	1	+++	15	7.87	4.61	2.71	0.55	28	3 years	Advanced	154	152	Yes
49	F.	30	4	-ve	25	7.89	4.34	3.22	0.33	25	7 years	Advanced	94	123	Yes
50	F.	51	-ve	-ve	12	7.77	4.49	2.77	0.51	32	9 years	Advanced	176	141	Yes
51	M.	47	-ve	-ve	11	6.50	4.06	2.09	0.35	29	9 years	Advanced	132	177	Yes
52	F.	47	1	-ve	40	7.82	4.20	3.02	0.60	35	16 years	Advanced	-	-	No
53	M.	73	5	-ve	44	7.34	3.98	2.92	0.44	41	9 years	Moderate	133	162	No
54	F.	48	1	-ve	40	7.44	4.14	3.02	0.28	33	14 years	Advanced	116	131	No
55	F.	56	-ve	-ve	16	6.96	3.92	2.53	0.51	38	1 year	Mild	145	146	No
56	M.	66	1	-ve	20	7.49	3.84	3.21	0.44	25	5 years	Advanced	-	-	No
57	M.	39	-ve	-ve	5	6.39	3.92	2.15	0.32	28	16 mths.	Mild	112	136	No
58	F.	35	-ve	-ve	20	6.74	3.71	2.61	0.42	27	3 years	Mild	116	136	No
59	F.	48	-ve	-ve	18	7.62	4.53	2.64	0.45	41	4 years	Mild	-	-	No
60	F.	64	-ve	-ve	77	7.79	3.77	3.55	0.47	28	1 year	Mild	130	131	No
61	F.	51	2	+	30	6.24	2.94	2.84	0.46	33	4 years	Advanced	142	144	No

TABLE 18. (Continued)

Case No.	Sex	Age Yrs.	Coll. Gold	Ceph. Chol.	E.S.R. m.m.	g. per 100ml.				N.P.N. mg.%	Duration of R.A.	Degree of R.A.	Weight		Previous Gold
						Total Prot.	Alb.	Glob.	Fib.				Actual lbs.	Expected lbs.	
62	F.	59	5	-ve	80	7.02	3.57	2.98	0.47	23	4 years	Advanced	-	-	Yes
63	F.	40	1	-ve	35	7.58	4.44	2.68	0.46	30	5 years	Moderate	-	-	Yes
64	M.	56	-ve	-ve	22	7.61	4.33	2.80	0.48	37	15 mths.	Moderate	150	153	Yes
65	M.	59	2	-ve	40	8.31	4.48	3.34	0.49	32	7 years	Mild	158	157	Yes
66	F.	50	5	-ve	47	8.56	4.60	3.50	0.46	34	6 years	Advanced	208	162	Yes
67	F.	24	-ve	-ve	8	6.98	4.50	2.05	0.43	31	6 years	Mild	109	120	Yes
68	F.	47	-ve	-ve	10	7.63	4.78	2.47	0.38	38	14 mths.	Moderate	118	139	Yes
69	F.	44	4	-ve	34	8.67	5.04	3.14	0.49	44	8 years	Moderate	164	147	Yes
70	M.	68	2	-ve	42	7.24	3.70	2.99	0.55	43	3 years	Moderate	124	157	No
71	F.	48	5	-ve	108	8.26	3.82	3.80	0.64	31	2 years	Moderate	-	-	No
72	F.	48	-ve	-ve	14	7.31	4.50	2.42	0.39	31	4 years	Mild	-	-	No
73	F.	60	-ve	-ve	52	7.69	4.05	3.11	0.53	19	6 years	Moderate	-	-	Yes
74	F.	45	-ve	-ve	20	6.99	3.66	3.02	0.31	27	5 years	Moderate	128	136	Yes
75	F.	62	3	-ve	26	6.55	3.39	2.73	0.43	56	4 years	Mild	-	-	Yes

TABLE 18. (Continued)

Case No.	Sex	Age Yrs.	Coll. Gold	Ceph. Chol.	E.S.R. m.m.	g. per 100 ml.				N.P.N. mg.%	Duration of R.A.	Degree of R.A.	Weight		Previous Gold
						Total Prot.	Alb.	Glob.	Fib.				Actual lbs.	Expected lbs.	
76	M.	31	-ve	-ve	17	8.69	4.88	3.33	0.48	35	2 years	Moderate	133	158	No
77	M.	51	-ve	++++	3	7.48	4.78	2.29	0.41	40	9 years	Mild	136	157	Yes
78	M.	35	-ve	-ve	36	8.44	5.05	2.80	0.59	40	9 mths.	Mild	138	140	No
79	F.	61	-ve	-ve	35	7.85	4.12	3.30	0.43	31	8 years	Moderate	127	152	No
80	F.	37	5	-ve	20	7.58	4.28	2.96	0.34	32	9 years	Mild	146	152	Yes
81	M.	63	3	++	30	7.91	3.68	3.76	0.47	38	7 years	Mild	126	172	Yes
82	F.	40	-ve	-ve	4	8.39	4.64	3.48	0.27	35	18 mths.	Mild	120	139	Yes
83	F.	41	1	++	8	7.30	4.25	2.76	0.29	30	5 years	Moderate	118	138	Yes
84	F.	39	3	-ve	21	7.39	4.30	2.74	0.35	24	5 years	Mild	150	144	Yes
85	M.	44	1	-ve	7	8.73	5.25	3.10	0.38	37	6 years	Moderate	146	154	No
86	M.	48	-ve	-ve	14	7.69	4.82	2.50	0.37	28	6 mths.	Mild	123	148	No
87	M.	57	-ve	-ve	18	7.14	3.86	2.92	0.36	33	10 years	Advanced	166	167	Yes
88	F.	54	-ve	-ve	12	8.71	5.37	2.87	0.47	44	3½ years	Moderate	137	133	Yes

TABLE 18. (Continued)

Case No.	Sex	Age Yrs.	Coll. Gold	Ceph. Chol.	E.S.R. m.m.	g. per 100ml.				N.P.N. mg.%	Duration of R.A.	Degree of R.A.	Weight		Previous Gold
						Total Prot.	Alb.	Glob.	Fib.				Actual lbs.	Expected lbs.	
89	F.	19	1	+++	17	9.88	5.41	3.99	0.48	37	5 years	Moderate	119	123	Yes
90	F.	27	1	+	21	9.01	5.33	3.15	0.53	42	5 years	Mild	102	127	Yes
91	F.	58	-ve	-ve	15	8.31	4.40	3.48	0.43	31	14 years	Advanced	151	157	No
92	M.	31	-ve	-ve	11	6.19	3.64	2.28	0.27	30	2 years	Moderate	133	158	No
93	F.	50	4	+++	20	8.19	4.36	3.46	0.37	29	2 years	Advanced	191	133	Yes
94	F.	34	-ve	+	16	6.22	3.79	2.02	0.41	27	6 mths.	Mild	135	124	No
95	F.	44	-ve	-ve	6	7.38	4.64	2.33	0.41	31	8 years	Mild	110	139	Yes
96	M.	37	1	-ve	7	7.02	4.41	2.24	0.37	25	4 mths.	Mild	154	165	No
97	F.	36	1	-ve	18	6.88	3.55	3.04	0.29	25	2 years	Mild	139	140	No
98	F.	12	-ve	-ve	116	7.71	3.88	3.06	0.77	30	5 mths.	Moderate	45	53	No
99	F.	46	5	-ve	40	6.95	4.44	2.03	0.48	41	9 years	Moderate	148	142	Yes
100	F.	36	-ve	-ve	18	7.14	4.11	2.62	0.41	32	5 years	Mild	-	-	No

2. Flocculation Tests

Apart from specific liver function tests, such as the synthesis of hippuric acid, laevulose tolerance and excretion of dyes, certain empirical tests have been devised which all depend mainly on excess of gamma globulin in the serum (Gray 1942; Kabat et al., 1943). The original object of these tests was threefold: (1) to distinguish between jaundice due to hepatitis and that due to obstruction of the bile-ducts; (2) to assist in the diagnosis of hepatitis in the early pre-icteric stage; and (3) to follow the course of hepatitis and aid in its prognosis. Two of these empirical tests - serum colloidal gold and cephalin-cholesterol - have been found to be particularly sensitive in parenchymatous disease of the liver.

According to Gray (1942), Zsigmondy (1901) laid the foundation for the diagnostic use of the colloidal gold reaction by observing that certain colloids, especially proteins, prevented the precipitation of colloidal gold suspensions by electrolytes. Lange (1912), with whose name is associated the colloidal gold reaction of the cerebro-spinal fluid, found, however, that proteins within certain dilutions did not prevent but actually caused precipitation. Sweet, Gray and Allen (1941) pointed out that when a colloidal gold suspension is added to certain dilutions of blood serum from patients with liver disease flocculation of the colloidal gold occurs in one or more of the first serial dilutions. Gray (1942) performed a series of electrophoretic studies on the serum proteins in all types of liver disease, which revealed that the most characteristic

and consistent alteration of the serum proteins was an increase in the gamma globulin associated with a decrease in albumin. He then studied the effect on the colloidal gold solution of the addition of purified protein fractions to normal serum and obtained the following results:

(a) The addition of pure gamma globulin to normal blood serum gave a positive colloidal gold reaction.

(b) The purified fractions with alpha and beta globulin had no effect.

(c) The albumin fraction inhibited the serum colloidal gold reaction.

As the result of these findings Gray suggested that the mechanism of the colloidal gold reaction in liver disease depended upon a relative increase in the gamma globulin of the blood.

According to Maclagan (1944) Gray's serum colloidal gold reaction presented certain difficulties, including standardization of the solution. Moreover, while the test gave positive results in 100 per cent. of cases of cirrhosis of the liver, it was also positive in 10 per cent. of normal subjects. To overcome these difficulties, Maclagan devised a modification of Gray's test; this was simpler to perform, requiring only one tube instead of ten. The sensitivity of the reaction in cirrhosis of the liver and hepatitis was unimpaired, and normal subjects gave uniformly negative results.

Thus, while the principal use of the serum colloidal gold reaction was in diseases of the liver, it was soon found that positive results were obtained in certain non-hepatic diseases such as malaria, glandular fever,

subacute bacterial endocarditis and rheumatoid arthritis. Carter and Maclagan (1946) found that the test was positive in 76 per cent. of a series of 34 patients with rheumatoid arthritis, the results varying from mild to strongly positive.

The cephalin-cholesterol flocculation reaction was first introduced by Hanger (1939) as a test of hepatic efficiency and was shown by several American workers (Hanger, 1939; Pohle and Stewart, 1941; and Mateer et al., 1942) to be extremely sensitive in the early detection of liver insufficiency. Like the serum colloidal gold reaction it, too, gives positive results with non-hepatic diseases including rheumatoid arthritis. The percentage of positive reactions in the latter disease, however, has been small. Dick (1945) obtained complete flocculation in only 2 out of 41 patients with rheumatoid arthritis, the remaining 39 failing to show any flocculation. Maizels (1946) noted a weakly positive result in one out of five cases of rheumatoid arthritis.

The present investigation was undertaken in order to determine whether either of the flocculation tests, more particularly the serum colloidal gold reaction, might be of value as an indicator of the activity or a guide in the prognosis of rheumatoid arthritis. Although the work of Carter and Maclagan (1946) gave promising results, it was felt that a much larger series of cases was necessary before forming any definite opinion about the value of the serum colloidal gold reaction. In addition, an opportunity was afforded for comparing the results of the flocculation tests with the plasma proteins, E.S.R. and other factors.

Maclagan's modification of Gray's serum colloidal gold test and Hanger's cephalin-cholesterol flocculation test were used throughout the investigation.

Results

(1) Normal Controls.

The serum colloidal gold and cephalin-cholesterol flocculation tests were performed on 100 healthy blood donors with uniformly negative results (table 19).

Table 19

Serum colloidal gold and cephalin-cholesterol tests in 100 healthy blood donors

	No. of cases	Positive %	Negative %
Colloidal gold	100	0	100
Cephalin-cholesterol	100	0	100

(2) Rheumatoid Arthritis.

One hundred and thirty-three observations with the serum colloidal gold and cephalin-cholesterol tests were made on 100 patients suffering from rheumatoid arthritis. Sixty-one per cent. of the former and 19 per cent. of the latter were found to be positive (table 20). In addition, it was found that in 17 per cent. both tests were positive.

Table 20

Serum colloidal gold and cephalin-cholesterol tests in rheumatoid arthritis. (133 observations on 100 cases)

	No. of observations	Positive	
		No.	%
Colloidal gold	133	81	61
Cephalin-cholesterol	133	25	19
Both tests	133	22	17

Table 21 shows the degree of flocculation present in both tests. It will be seen that complete flocculation was obtained in 18 instances in the case of the serum colloidal gold reaction and in only 5 in the cephalin-cholesterol flocculation test.

Table 21

Degree of flocculation of serum colloidal gold and cephalin-cholesterol tests in rheumatoid arthritis (133 observations on 100 cases)

	Colloidal Gold						
Cephalin-cholesterol	0	1+	2+	3+	4+	5+	Totals
0	49	16	9	8	16	10	108
+	1	2	1	1	1	2	8
++	0	1	0	1	0	2	4
+++	1	3	0	0	2	2	8
++++	1	1	0	0	1	2	5
Totals	52	23	10	10	20	18	133

An attempt was then made to see if the flocculation tests showed any correlation with the factors shown in table 18 (p. 38).

(a) Plasma Proteins.- The results of the two flocculation tests were compared with the total plasma proteins and the various protein fractions. The cephalin-cholesterol test did not show any relationship to the plasma proteins. On the other hand, while the serum colloidal gold reaction did not show any apparent relation to the total proteins and fibrinogen, there was a partial inverse and partial direct relationship with the albumin and globulin fractions respectively (figures 18 and 19). The method of depicting the results was as follows. The colloidal gold values were arranged and recorded in four groups only - viz., 0, 1+ and 2+, 3+ and 4+, 5+ - for this reason. While the results of the colloidal gold reaction are generally recorded in one of six groups - 0, 1+, 2+, 3+, 4+, and 5+ - considerable difficulty arose in many cases in distinguishing between a 1+ and a 2+ reading, and between a 3+ and a 4+, as the difference in the amount of flocculation between these two pairs of figures is small. The corresponding values of the protein fractions in the four groups were averaged.

(b) Other factors.- An attempt was made to correlate the colloidal gold and cephalin-cholesterol tests with various other factors, shown in table 18. No relationship was found between either of the tests and the age, sex, duration and degree of arthritis, weight, temperature, white cell count, haemoglobin, focal sepsis or previous gold therapy.

Fig. 18.

Relation Between the Serum Colloidal Gold Reaction and the Plasma Albumin.

(No. of observations shown in brackets.)

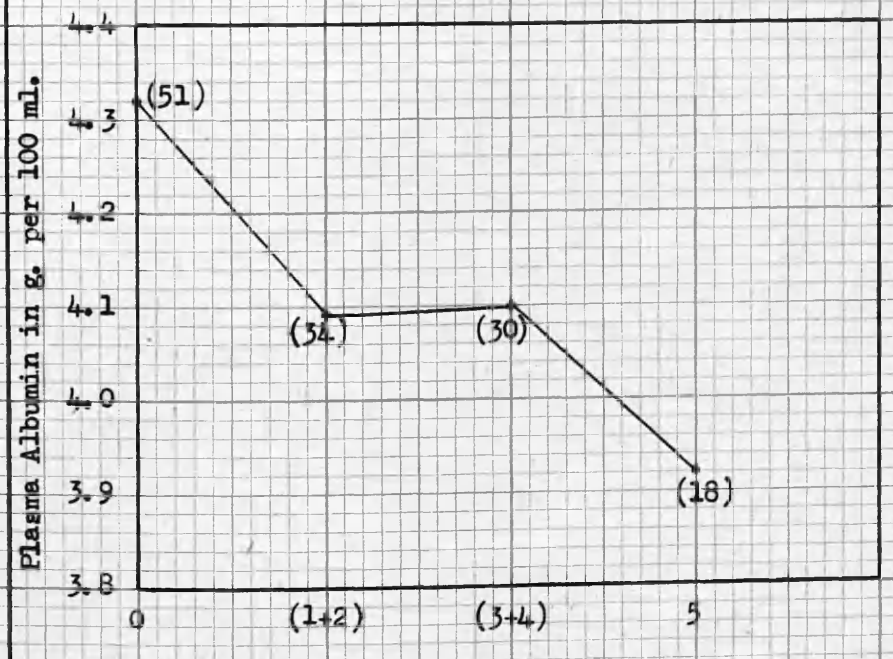
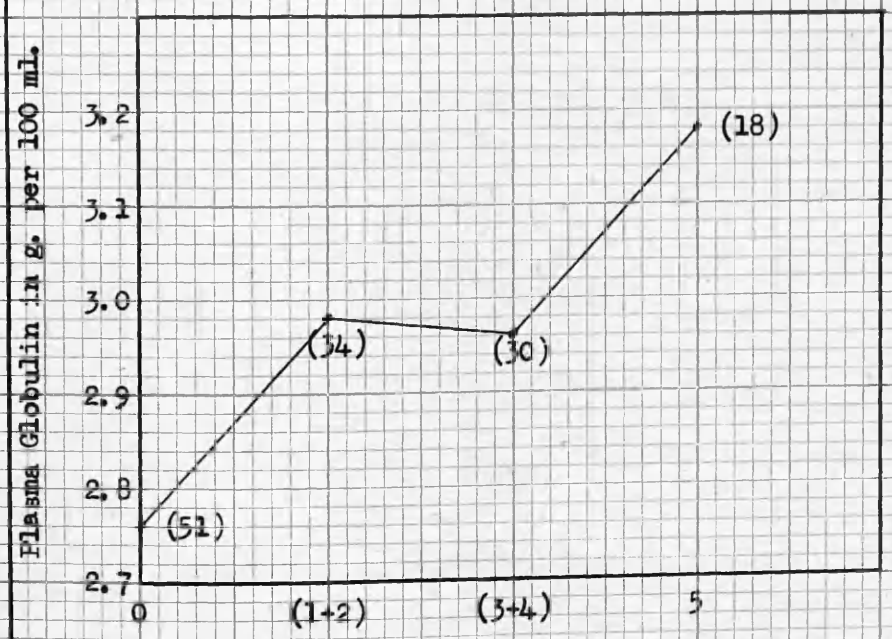


Fig. 19.

Relation Between the Serum Colloidal Gold Reaction and the Plasma Globulin.

(No. of observations shown in brackets.)



(3) Other Forms of Rheumatism

As an additional control series it was considered advisable to perform the colloidal gold and cephalin-cholesterol tests on patients with other forms of rheumatism. Observations were made on 20 patients with osteoarthritis, 15 with rheumatic fever, 6 with fibrositis and 2 with ankylosing spondylitis. The results are shown in table 22.

Table 22

Serum colloidal gold and cephalin-cholesterol tests in other forms of rheumatism

	No.of Cases	Colloidal Gold		Ceph. Chol.	
		Pos.	Neg.	Pos.	Neg.
Osteoarthritis	20	0	20	0	20
Rheumatic fever	15	6	9	2	13
Fibrositis	6	0	6	0	6
Ankylosing spondylitis	2	1	1	0	2

It will be seen from the table that in osteoarthritis and fibrositis the results of both tests were uniformly negative. One of the 2 patients with ankylosing spondylitis gave a mildly positive reaction (1+) with the colloidal gold test, while the cephalin-cholesterol test was negative in both. In the case of rheumatic fever, 6 (4o per cent.) of the patients had positive reactions with the colloidal gold test, and 2 (13 per cent.) with the cephalin-cholesterol test. The results are shown in greater detail in table 23.

Table 23

Serum colloidal gold and cephalin-cholesterol tests in rheumatic fever

Cephalin-Cholesterol	Colloidal Gold						
	0	1+	2+	3+	4+	5+	Totals
0	9	0	1	2	1	0	13
+	0	0	0	0	0	0	0
++	0	0	0	0	0	0	0
+++	0	0	0	0	1	0	1
++++	0	0	0	1	0	0	1
Totals	9	0	1	3	2	0	15

(4) Effect of Gold Therapy

The serum colloidal gold and cephalin-cholesterol flocculation tests were performed on 30 patients with rheumatoid arthritis before and after receiving one course of myocrisin injections (total = 1g.). The full details are shown in table 18, patients 1-33, omitting 3, 19 and 30 who only received physiotherapy.

Clinically, 25 of the 30 patients responded favourably to the gold therapy, the remainder showing no change in their condition. While the results of the serum colloidal gold reaction as a whole showed a change towards normal following therapy (table 24), the amount of improvement shown by the test, however, was only partially related to the degree of clinical improvement (table 25).

Table 24

Serum colloidal gold reaction before and after gold therapy in 30 cases of rheumatoid arthritis

		Colloidal Gold						Total
		0	1+	2+	3+	4+	5+	
No. of Cases	Before	5	7	5	1	7	5	30
	After	11	3	2	3	6	5	30

Table 25

Relation of serum colloidal gold reaction to degree of clinical improvement following gold therapy

Case No.	Clinical Result	Colloidal Gold		Case No.	Clinical Result	Colloidal Gold	
		Before	After			Before	After
1	Great Imp.	-ve	-ve	24	Mod. Imp.	2+	1+
4	"	4+	4+	27	"	2+	-ve
7	"	-ve	-ve	29	"	1+	3+
8	"	4+	-ve	32	"	2+	1+
9	"	1+	-ve	2	Slight Imp.	4+	2+
22	"	1+	-ve	6	"	3+	-ve
28	"	1+	1+	20	"	4+	4+
33	"	1+	-ve	23	"	5+	4+
5	Mod. Imp.	5+	5+	25	"	-ve	-ve
10	"	-ve	-ve	26	"	-ve	-ve
11	"	5+	4+	14	No Imp.	4+	4+
12	"	2+	2+	15	"	1+	3+
13	"	4+	5+	16	"	5+	5+
17	"	2+	3+	18	"	4+	5+
21	"	5+	5+	31	Worse	1+	4+

Clinical result is expressed as great, moderate, slight, no improvement or worse.

Eleven of the 30 patients who received gold therapy had a positive cephalin-cholesterol flocculation test prior to treatment. It is of interest to note that in ten of the eleven cases the test was negative at the end of therapy (table 26).

Table 26

Cephalin-cholesterol flocculation test before and after gold therapy in 30 cases of rheumatoid arthritis

		Cephalin-cholesterol					Total
		0	+	++	+++	++++	
No.of Cases	Before	19	2	2	4	3	30
	After	29	1	0	0	0	30

It was found that there was only a partial relationship between the change in the cephalin-cholesterol flocculation test and the degree of clinical improvement following on gold therapy (table 27).

Table 27

Relation of cephalin-cholesterol flocculation test to degree of clinical improvement following gold therapy

Case No.	Clinical Result	Ceph.Chol.		Case No.	Clinical Result	Ceph.Chol.	
		Before	After			Before	After
28	Great Imp.	+	-ve	6	Slight Imp.	+	-ve
5	Mod. Imp.	+++	+	23	"	++	-ve
11	"	++++	-ve	14	No Imp.	+++	-ve
21	"	++	-ve	15	"	+++	-ve
29	"	++++	-ve	16	"	+++	-ve
				18	"	++++	-ve

Clinical result is expressed as great, moderate, slight or no improvement.

It will be seen from tables 25 and 27 that, whereas 10 of the 11

patients who had positive cephalin-cholesterol flocculation tests prior to therapy gave negative reactions at the end of treatment, there is no comparable change in the results of the serum colloidal gold test in the same ten cases.

(5) Relation to Erythrocyte Sedimentation Rate

It was considered of interest to see whether the results of the serum colloidal gold test were related to the changes in the erythrocyte sedimentation rate in rheumatoid arthritis. The results have been recorded graphically in figure 20. As before, the colloidal gold values have been arranged into 4 groups as follows.- 0, 1+ and 2+, 3+ and 4+, 5+. The corresponding E.S.R. values in these groups have been averaged. There would appear to be a moderate degree of direct relationship between the serum colloidal gold reaction and the erythrocyte sedimentation rate.

As the cephalin-cholesterol test was positive in only 19 per cent. of the estimations the findings have not been recorded graphically, as it was felt that to do so would give an erroneous picture.

3. Van den Bergh

The plasma bilirubin was estimated in all the patients as a test of liver function. The method employed was that of Thannhauser and Andersen (1921), using the Lovibond Comparator. In all, 133 observations were made on 100 patients with rheumatoid arthritis and 40 on the patients with other forms of rheumatism. The results are shown in table 28.

Fig. 20.

Relation Between the Serum Colloidal Gold Reaction and the Erythrocyte Sedimentation Rate.

(No. of observations shown in brackets.)

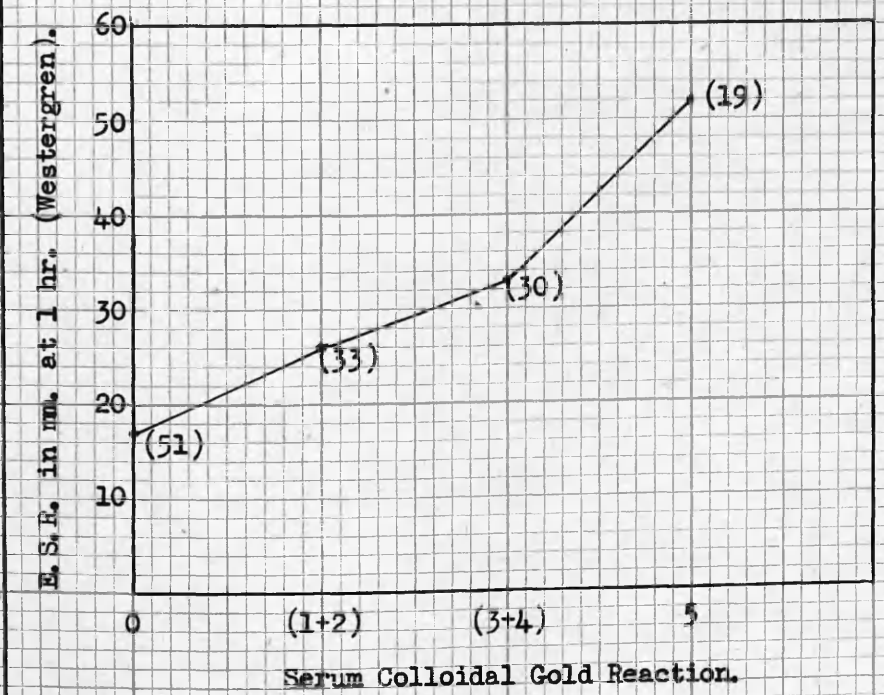


Table 28

Van den Bergh reaction in rheumatoid arthritis and other forms of rheumatism

	Van den Bergh (indirect). Plasma bilirubin in mg. per 100 ml.					Total
	- 0.2	- 0.3	- 0.4	- 0.5	- 0.6	
Rheumatoid arthritis	125	7	1	0	0	133
Osteoarthritis	12	1	4	1	2	20
Rheumatic fever	11	0	0	1	0	12
Fibrositis	3	2	1	0	0	6
Ankylosing spondylitis	1	0	0	0	1	2

It will be seen that the van den Bergh reaction was within the normal limits (up to 0.6 mg. per 100 ml.) in all the patients with rheumatoid arthritis and with the other forms of rheumatism.

Discussion

1. Plasma Proteins.

It has been recognised for some time now that the plasma albumin is usually decreased and the globulin increased in acute infective hepatitis. Sherlock (1946) attempted to correlate the alteration in the albumin-globulin ratio in this disease with the histological appearances of material obtained by liver puncture. She found that the extent of the hepatic damage was reflected in the serum albumin level. It is generally

agreed that the alteration in the protein values in acute infective hepatitis is due to liver damage, and that these return to normal levels on recovery. Changes of the same order, however, are also found in rheumatoid arthritis. These changes were first noticed by Aldred-Brown and Munro (1935) when they estimated the plasma protein values in 34 cases of rheumatoid arthritis, and ascribed the alteration in the protein levels to several factors, including increasing age and economic stress.

In the present series the plasma protein values were estimated in 100 patients with rheumatoid arthritis. In comparison with the results obtained in 50 normal healthy control patients, it was found that in rheumatoid arthritis there was considerable variation in the protein values. The greatest differences were seen in the globulin and albumin levels, the former being noticeably increased and the latter lowered. The total protein and fibrinogen values were raised to a lesser extent.

The explanation for the variations in the plasma protein values in rheumatoid arthritis is still unknown. From post-mortem examinations there is no evidence to suggest that these changes in the proteins are due to liver damage. Baggenstoss and Rosenberg (1943) studied at necropsy the pathological changes in the viscera in 30 patients with rheumatoid arthritis, and failed to observe any characteristic hepatic lesion which could be ascribed to the disease. In this connection, too, it was found that the van den Bergh reaction was normal in the 100 cases of rheumatoid arthritis in the present series.

It is generally accepted that albumin, fibrinogen and some of the

globulins are formed by the liver. It has, however, been shown by Enders (1944) that many circulating antibodies are associated with or actually consist of gamma-globulin. Furthermore, the formation of antibodies is considered a function of the reticulo-endothelial system, which is widely scattered throughout the body. It may be, therefore, that some other organ(s) or structure(s) in the body plays a part in the maintenance of the plasma protein levels in addition to the liver, and that the causative agent of rheumatoid arthritis may affect this non-hepatic source of the proteins.

An attempt was made to correlate the results of the investigation with several possible factors. It was shown that the age and sex of the individual bore no relation to the changes in the proteins. Other factors which did not appear to be related to the alteration in the protein values were the temperature of the patient at the time of the analysis, the haemoglobin percentage, the white cell count, the presence of focal sepsis and previous gold therapy.

It is widely accepted that there is an alteration in the plasma protein values in many chronic diseases. It was thought that, if this was true of rheumatoid arthritis the greatest changes in the protein levels would be found in those cases of the longest duration. This, however, was not the case as some of the greatest variations from normal were found in patients with early rheumatoid arthritis. Furthermore, one might have expected the degree of arthritis to be related to the changes in the plasma protein values, i.e. the more advanced the disease, the more

marked the deviation of these values from normal. The findings, however, did not bear this out, as the protein levels were very similar in mild and advanced cases alike.

It was considered advisable to estimate the plasma proteins in other forms of rheumatism and compare the results with those in rheumatoid arthritis. It was found that the protein levels in rheumatic fever were similar to the values obtained in rheumatoid arthritis. This finding does not give support to the view that the changes in the latter disease are due to its chronicity. It may well be that some, as yet unknown, factor is responsible for the alteration in the plasma protein values in the two diseases.

In osteoarthritis the total protein, albumin and globulin values also showed a variation from the normal. The results were compared with those of rheumatoid arthritis - of the same age-group - and it was found that the levels in osteoarthritis held a position almost mid-way between the normal controls and rheumatoid arthritis. These findings would suggest that, while advancing age may play a part in the variations in the plasma protein levels in the older cases of rheumatoid arthritis, it is by no means the full explanation.

The plasma protein values were estimated in 6 cases of fibrositis and 2 with ankylosing spondylitis. It was found that in the former condition the values were within the normal limits, and in the latter, as might be expected from the nature of the disease, the levels approached those seen in rheumatoid arthritis. The number of estimations in both groups,

however, was too small to be of any real significance.

Plasma protein estimations were made before and after one course of myocrisin injections (1g.) in 30 patients with rheumatoid arthritis. It was found that after the gold therapy the mean values for the total proteins and albumin fraction were increased, whereas the globulin and fibrinogen levels remained unchanged. Of the 30 patients 25 showed clinical evidence of improvement. As already shown, the increase in the plasma albumin was not definitely related to the degree of clinical improvement. In spite of this, however, one feels that the changes in the plasma albumin may be taken as a rough guide to the progress of the disease.

During the investigation an opportunity was afforded for comparing the plasma protein values with the erythrocyte sedimentation rate. One hundred and thirty-three observations were made on one hundred patients with rheumatoid arthritis. The findings were in keeping with those of the majority of observers (Westergren et al, 1931; Fraser and Rennie, 1941), and showed that a rise in globulin and fibrinogen and a fall in albumin were associated with rates above normal.

2. Flocculation Tests.

The serum colloidal gold and cephalin-cholesterol flocculation tests were first introduced as empirical tests of hepatic efficiency. Gray (1942), by performing a series of electrophoretic studies on the plasma proteins in all types of hepatic disease, was able to show that in parenchymatous disease of the liver a positive colloidal gold test was

associated with a relative increase in the gamma-globulin.

In 1946 Carter and Maclagan pointed out that the serum colloidal gold test gave positive results in certain non-hepatic diseases, including rheumatoid arthritis. In a small series of 34 patients suffering from the latter disease, they obtained a positive reaction in 76 per cent. of the cases. In the present investigation 133 observations on 100 patients with rheumatoid arthritis were made with the serum colloidal gold test; sixty-one per cent. of the results were positive, the reaction varying from mild to strongly positive.

What is the explanation of these changes in the serum colloidal gold test in rheumatoid arthritis? As already mentioned in the discussion on the plasma proteins, the evidence does not suggest that the high proportion of positive results is due to liver damage. It is possible, as Enders (1944) showed in other diseases, that an antibody associated with the serum gamma-globulin fraction may be responsible for the flocculating power of patients with rheumatoid arthritis. Nevertheless, an attempt to correlate the serum colloidal gold reaction with the total proteins and various protein fractions shows that there is a partial inverse and partial direct relationship with the albumin and globulin fractions respectively; there was no apparent relationship with the total proteins and fibrinogen.

An attempt was made to correlate the serum colloidal gold test with various other factors (table 18), but no relationship was obtained with any of these.

It was considered essential to see whether any of the other forms of rheumatism would give positive results with this test. Accordingly, estimations were made on 43 patients suffering from osteoarthritis, rheumatic fever, ankylosing spondylitis or fibrositis. Forty per cent. of 15 patients with rheumatic fever gave a positive reaction, while the patients with osteoarthritis and fibrositis had uniformly negative results; one of two patients with ankylosing spondylitis showed a mildly positive reaction. Thus it will be seen that the test is also positive in a fair percentage of cases of rheumatic fever. It may be that some factor common to both rheumatoid arthritis and rheumatic fever is responsible for this finding.

The serum colloidal gold test was also performed on 30 patients with rheumatoid arthritis before and after receiving a course of myocrisin. Clinically, 25 of the patients responded favourably to the chrysotherapy, and, while the results of the gold test as a whole showed improvement, there was only a partial relationship between these two factors. For instance, one would have expected those cases which showed the greatest clinical improvement to have had negative or only mildly positive colloidal gold reactions, but this was not invariably the case. This may, of course, be due to the fact that the test takes longer to return to normal in comparison with the clinical progress.

A comparison was made between the serum colloidal gold test and the erythrocyte sedimentation rate in rheumatoid arthritis (figure 20), and it was found that there was a definite direct relationship between the

two tests - e.g. there were 30 observations with normal sedimentation rates (up to 10 m.m.), the corresponding serum colloidal gold test being negative in all but 7 instances, and in these only a mild positive reaction was obtained (1+).

To sum up, one may say that the serum colloidal gold test is of value in rheumatoid arthritis, although, just as with the erythrocyte sedimentation rate, too much reliance should not be placed on it. As an indicator of the activity and as a guide to the progress of the disease it is probably a less sensitive test than the latter. It is useful, however, in the differential diagnosis between rheumatoid arthritis and osteoarthritis and fibrositis. Unfortunately, it is of no value in distinguishing between rheumatoid arthritis and rheumatic fever, as it is positive in an appreciable number of cases of the latter disease.

There is little to commend the use of the cephalin-cholesterol flocculation test in rheumatoid arthritis, as it was positive in only about one-fifth of the observations. There was one finding, however, worthy of note - viz., the change to a negative reaction following on gold therapy in 10 out of 11 previously positive cases.

Summary

The first section of Part 11 deals with the plasma proteins in rheumatoid arthritis, and is introduced by a survey of the literature on the subject. This is followed by the results of the present investigation

which include plasma protein estimations on 50 normal controls, 100 cases of rheumatoid arthritis (single observations), 30 of rheumatoid arthritis before and after gold therapy, 20 of osteoarthritis, 12 of rheumatic fever, 6 of fibrositis and 2 cases with ankylosing spondylitis.

It was found that there was an alteration in the plasma protein levels in rheumatoid arthritis. The most noticeable changes were seen in the albumin and globulin values, the former being diminished and the latter increased. The total protein and fibrinogen values were also increased to a lesser extent. All these changes were of statistical significance. Likewise, there were alterations in the plasma protein levels in rheumatic fever which were similar to those found in rheumatoid arthritis. In osteoarthritis there were also changes of statistical significance in the plasma protein levels, and these lay in a mid-position between those of rheumatoid arthritis and of the normal controls. Lastly, the plasma protein values in fibrositis were within the normal range.

An attempt was made to correlate the plasma protein findings in rheumatoid arthritis with numerous factors, including the duration and the severity of the disease, but without success except in the case of the erythrocyte sedimentation rate. It was found that an increase in the latter was associated with a rise in the globulin and fibrinogen and a fall in albumin levels.

The various theories which have been put forward to explain the alteration in the plasma protein levels in rheumatoid arthritis are then discussed. It is generally considered that the liver is not responsible

for these changes, although absolute proof of this view is still awaited. It is suggested that the increase in the globulin may be of extra-hepatic origin and associated with the reticulo-endothelial system, as Enders (1944) has shown that many circulating antibodies are linked with or actually consist of gamma-globulin.

It was found that, following on gold therapy, the plasma albumin level was statistically increased. It is felt that the changes in the albumin values may be used as a rough guide to the progress of the disease.

The van den Bergh reaction was performed on all the patients with rheumatoid arthritis and on all the control subjects, and was found to be within the normal limits in every case.

The second section of Part 11 deals with the serum colloidal gold and cephalin-cholesterol flocculation reactions in rheumatoid arthritis, and begins with a survey of the literature on the two tests. This is followed by the results of the present investigation which includes 133 observations with both tests on 100 patients with rheumatoid arthritis, observations on 20 cases of osteoarthritis, 15 of rheumatic fever, 6 of fibrositis, 2 of ankylosing spondylitis and on 100 healthy blood donors.

The serum colloidal gold test was positive in 61 per cent. of the observations in rheumatoid arthritis and in 40 per cent. of the cases of rheumatic fever. In osteoarthritis, fibrositis and the normal controls the results were uniformly negative.

The cephalin-cholesterol flocculation test gave a positive reaction in 19 per cent. of the observations in rheumatoid arthritis and in 13 per

cent. of the cases of rheumatic fever. Negative results were obtained in all the normal controls, in osteoarthritis, fibrositis and ankylosing spondylitis.

Attempts were made to correlate the results of the serum colloidal gold reaction in rheumatoid arthritis with various factors, including the plasma proteins and the erythrocyte sedimentation rate. While they did not show any apparent relation to the total proteins and fibrinogen, there was a partial inverse and partial direct relationship with the albumin and globulin fractions respectively. A moderate degree of direct relationship was observed between the colloidal gold test and the erythrocyte sedimentation rate.

A possible explanation of the flocculating power of patients with rheumatoid arthritis, as Enders (1944) has shown in other diseases, may lie in the fact that an antibody may be associated with the serum gamma-globulin fraction.

The serum colloidal gold test was performed on 30 patients with rheumatoid arthritis before and after receiving a course of myocrisin. The results of the gold test as a whole showed improvement after chrysotherapy, but were only partially related to the degree of clinical improvement.

It is felt that the serum colloidal gold test is a useful indicator of the activity of rheumatoid arthritis, and may also be used as a guide in the progress of the disease. It is of value in the differential diagnosis from osteoarthritis and fibrositis, but not from rheumatic fever.

The cephalin-cholesterol flocculation test would appear to be of little or no value in rheumatoid arthritis.

PART III.

ON GOLD THERAPY IN RHEUMATOID ARTHRITIS

In considering the treatment of rheumatoid arthritis,it is necessary to bear in mind that it is a systemic disease and not purely a disease of the joints. It follows, therefore, that therapy should be directed along general lines as well as against the local joint condition. There should be no hard and fast rules and each patient should be treated individually according to his needs. A definite programme should be formulated for the care of every case. The decision as to the appropriate treatment required should not be left in the hands of one individual, usually the physician, but should be dealt with by a team of experts consisting of the medical and orthopaedic specialists, the physiotherapists and the occupational therapists,and the almoner.

In the main, treatment should aim at giving the patient mental as well as physical rest; at building up his general resistance with a nourishing, well-balanced and high vitamin diet and with attention to the bowels; at eradication of any focal infection as a general health

measure; at the prevention of, or, when already present, the correction of deformities of the joints by splintage and other orthopaedic measures; at the maintenance of function by physiotherapy; and at symptomatic care as required, including analgesics, sedatives and iron medication.

There is at present no known specific remedy for rheumatoid arthritis. A study of the literature reveals the well known multiplicity of therapeutic measures said to produce satisfactory results but, apart from gold salts, none of these have stood the test of time. As Gold (1941) points out, there are few subjects in therapeutics which seem to be in a more unsettled and unsatisfactory state than the treatment of arthritis, and in few therapeutic fields has there to be found such sharp contrasts of views concerning matters which should be matters of fact.

This section is concerned with chrysotherapy in rheumatoid arthritis. As the cause of the disease is still unknown, the use of gold salts must of necessity remain empirical. On reviewing the extensive literature on this subject one would expect to find a valuable mass of information for comparison with one's own results, but this is not the case on account of the rather confusing state of methods of investigation and data in this field. On going over this material one is struck by the absence of generally accepted criteria whereby the results of one investigator may be compared with those of another.

Many of the treatises on the subject include patients with chronic arthritis who are not suffering from true rheumatoid arthritis. Some of these conditions are infective arthritis, atypical rheumatic fever,

arthralgias and many rheumatoid-like arthropathies. Unless precautions are taken to exclude them, inaccurate results are bound to be obtained. This failing was more noticeable in earlier papers on chrysotherapy, but recent authors appear to be taking more care in their diagnosis of rheumatoid arthritis and in their selection of patients for gold therapy.

Again, it is necessary to classify the patients according to the stage of the disease. Accurate information should be given as to the proportion of early, moderately advanced and greatly advanced cases with activity in the group, for it is generally acknowledged that spontaneous remissions are more common and the response to therapy more marked in early rheumatoid arthritis. Lack of observance of this important fact makes comparisons extremely difficult and misleading. A good classification which takes into account the stage of the disease has been suggested by Taylor (1937).

The different criteria adopted by observers in assessing the results of therapy add further to the confusion. Some use the objective clinical signs in estimating the response to treatment, some the subjective clinical signs, while others combine the two. Until definite basic standards for estimating the response to treatment are laid down and agreed to by all observers, the accurate evaluation of gold salts as a therapeutic measure is not possible. As I will show later, one has to reckon with a large psychological factor in this disease and, for this reason, too great a reliance should not be placed on the patient's statements. As a basis for assessing results joint swelling, restoration of

function, general condition, gain in weight and such laboratory aids as the blood sedimentation rate and haemoglobin estimation might be usefully employed. A good "yardstick" containing all these features has been devised by Baylis and Hall (1943). If some such measure was generally accepted, much useful and reliable information would be gained in therapeutic investigations.

It should be remembered, too, that rheumatoid arthritis is a disease in which spontaneous remissions are common, and that many patients will show temporary or permanent improvement, both general and local, to ordinary general therapeutic measures such as rest, constitutional treatment and physiotherapy. Gold salts are, as a rule, given to supplement this regime, and it follows, therefore, that in assessing the results of chrysotherapy the part played by these two factors should be borne in mind, otherwise the conclusions will be fallacious and misleading. The necessity for adequate controls in any experiment is obvious but, unfortunately, seldom carried out.

Yet another of the causes of confusion in any attempt to compare results is the mixed terminology employed without any explanation as to its definition. It is difficult to interpret such groups as "much improved", "greatly improved", "moderately improved" and other grades of improvement without an exact description of the author's meaning. In the majority of papers these categories are not defined. A uniform and internationally accepted classification of gradations of improvement is an essential need.

That rheumatoid arthritis shows a tendency in a high percentage of cases to relapse after apparently successful treatment there is no doubt. Unless results are checked after a reasonable lapse of time, conclusions as to the effects of therapy are unreliable. A follow-up period of five years would seem to be desirable, particularly in the arrested cases and those patients showing great improvement. Most of the extravagant claims made for the value of gold salts in rheumatoid arthritis would be rendered null and void. Unfortunately, few follow-ups have been reported, and only when the incidence of relapse among the "cured" or "greatly improved" is known can the usefulness of the drug be correctly ascertained.

The greatest need of all in assessing the results of any form of therapy is to control the investigation adequately. I cannot find any true control series in the numerous papers on chrysotherapy. Too little attention has been given to the psychological aspects of treatment. The mere act of "having an injection" stirs into action powerful suggestive forces. Or again, in large clinics, particularly if one of the patients happens to show a marked improvement from therapy, the general morale of the others immediately rises. This aspect of therapy must be taken into account in the final summing-up; it was one of the chief aims in the present investigation to neutralize the psychological effect. This auto-suggestion is neatly illustrated by Weiss and English (1943) who state, "Many magical shrines are famed for the piles of crutches that have been thrown away by cripples, who, for the moment, consider themselves cured but most of whom have to buy more crutches after they get home".

Mode of Action and Fate of Gold Salts in the Treatment of Arthritis

The mode of action of gold salts in rheumatoid arthritis is not known. Various theories have been put forward by different observers. Kling et al. (1939) showed that gold compounds were deposited in higher concentrations in organs with reticulo-endothelial cells, of which synovial membrane contains a large number. In a series of biopsies of synovial membranes and of aspirated synovial effusions from knees in rheumatoid arthritis, the presence of gold was detected in both the tissue and the fluid, even after the administration of such small amounts of gold salts as 350 mg. This finding supported their view that a higher concentration of gold salts was to be found in diseased synovial membranes and joint effusions. They concluded that, on the basis of experimental and clinical evidence, in rheumatoid arthritis the efficiency of gold compounds was considered to be due to the stimulation of the general reticulo-endothelial system, as well as to the effect of the local deposits of gold in the defence mechanism of the synovial membrane.

The bacteriostatic theory was advanced by Hartung and Cotter (1941), who reported that serum from patients with rheumatoid arthritis became bactericidal against a strain of haemolytic streptococcus when treated with gold salts, the effects being in direct proportion to the amount of gold given. Rothbard et al. (1941) found that sodium aurothiomalate was an effective therapeutic agent in the prevention of arthritis in rats produced by the haemolytic streptococcus, but that it did not cure the

disease once it was established. A third hypothesis was put forward by Tegner (1939), who suggested that the effect of gold salts was due to a mild shock therapy of prolonged action, and pointed out that those patients who developed toxic reactions found their arthritis very much improved. The general feeling among observers to-day is that gold compounds exert their effect by stimulating the cells of the reticulo-endothelial system, although this view is still only a hypothesis.

Much experimental work has been done in an effort to determine the fate of gold salts in the body. According to Rosenberg (1942) gold enters almost every cell in the body shortly after injection, the greatest concentrations being found in the liver, spleen, kidneys and skin. Freyburg et al. (1942) found that gold was absorbed very rapidly into the blood stream following intramuscular administration of the soluble crystalline salts in aqueous solution, such as myocrisin. Using a highly accurate photoelectric colorimetric method for the determination of gold in biological tissues and fluids (Block and Buchanan, 1940), they were able to show that the protein fraction of the plasma held most of the gold, while the blood cells only contained insignificant traces. There was a step-like increase in plasma gold corresponding to increase in dosage, but once the weekly dose remained constant the plasma level kept relatively steady. Thus they found that the plasma gold concentration was determined by the size of the weekly injection, and that there was no accumulation of gold in the blood with continued treatment, as the amount of gold in the plasma remained relatively constant between weekly injections.

Gold is excreted chiefly through the kidneys and to a lesser degree through the intestine and bronchial mucosa. Larger amounts are eliminated on the days of injection, and according to Freyburg and his colleagues this is due not to a higher concentration in the blood, but probably to a more readily excretable form on these days. They found that when 100 mg. of myocrisin is being given weekly only about 20 mg. is excreted, from which they concluded that large amounts are retained in the body. During a course of gold therapy, therefore, about 80 per cent. of the injected gold apparently remains in the tissues. This large retention of gold during its administration is an important point which must be remembered. After cessation of treatment the same observers found that gold could be recovered from the blood and urine for long periods, even up to one year. By and large, the smaller the weekly dose of gold the more rapidly does it disappear from the blood and urine. This retention of gold in the body is of the greatest importance where the advisability of subsequent courses of injections is under consideration.

Historical

In 1890 Koch stated that gold cyanide in dilutions of 1:2,000,000 inhibited the in vitro growth of the tubercle bacillus; since then many therapeutic trials have been carried out with gold salts. Junker (1913) gave gold cyanide intravenously to 11 patients with pulmonary tuberculosis, and stated that his general impression of the results was not unfavourable. Feldt (1917) introduced a complex organic compound of gold - krysolgan - which he used in experimental animal infections with tuberculosis. It

was not until 1924,however, that gold salts became recognised as a useful therapeutic agent, when Möllgaard used sanocrysin in the treatment of pulmonary tuberculosis and reported favourable results.

After the encouraging reports of the use of sanocrysin in tuberculosis, its effect was tried in other conditions. In 1926 Feldt introduced another new gold compound - solganal - which was used by Lewy and Freund (1926) with good results in streptococcal infections in man. Schmidt (1944) claimed that nearly twenty years ago he was among the first to employ gold in the treatment of the various types of arthritis and found that it had a very limited usefulness. In Stockholm, Hedenius (1926) reported good results with colloidal gold in septic polyarthritis, and Landé (1927) was favourably impressed with solganal in the treatment of chronic polyarthritis. Pick (1927), however, using triphal, found little or no improvement in his small series of patients. The use of gold salts in rheumatoid arthritis spread rapidly throughout Europe, and almost simultaneously Forestier (1929) in France, and Umber (1929), Zimmer (1930) and Feldt (1930) in Germany published independent results of chrysotherapy in this disease. Forestier stated that his attention was drawn to the use of gold salts in the treatment of some of the forms of chronic arthritis by the analogy of the clinical evolution of certain severe types of chronic rheumatism with that of tuberculosis; he (Forestier, 1935) reported that 70 - 80 per cent. of over 550 patients responded favourably to gold therapy.

In this country reports on the treatment of rheumatoid arthritis

with gold salts began to appear in 1934. Slot and Deville (1934) and Buckley (1934) used gold salts in two small series of cases with promising results. The latter felt that there was no greater risk with gold salts than with protein shock. The following year Pemberton (1935) published encouraging results in a series of 100 patients with varying types of chronic arthritis, and concluded that the response to gold salts was roughly inversely proportional to the duration of the disease. In subsequent years an increasing number of publications on this subject made their appearance. Crosby (1936), Bach (1936), Crawford (1937), Copeman and Tegner (1937), Hartfall et al.(1937), and Ellman et al.(1940) made valuable contributions to the literature. The most outstanding of these were the results of Hartfall and his co-workers at Leeds, who claimed that 80 per cent. of 750 patients with rheumatoid arthritis showed apparent cure or striking improvement.

In America gold therapy was not looked on with any great favour for a number of years. Philips (1936) used gold salts in 9 cases, but gave it up as he felt that, on account of its toxicity, he was "not competent to handle the drug to the advantage of the patient". In the same year, however, Oren (1936) found that 91 per cent. of 66 patients were improved. In more recent years many contributions on the subject have appeared, including favourable reports by Key et al. (1939), Snyder et al. (1939), Sashin et al. (1939), Dawson et al. (1941), Cecil et al. (1942) and Price and Leichentritt (1945). Snyder and his associates felt that they obtained better results in older patients, a view that is at variance with other reports. Cecil and his colleagues found that relapses,

usually milder than the original attack, were quite common in their series of 245 cases. Other work on gold therapy has been done by Secher and Gudiksen (1935), Parr and Shipton (1937), Sundelin (1941), and Graham and Fletcher (1943). Sundelin, in an excellent monograph from Scandinavia, gives a detailed account of the literature on gold therapy and reports the results of 730 cases of chronic inflammatory arthritis treated with a variety of gold preparations, some of the patients receiving as many as five courses of injections. He is very cautious in assessing his results, but he felt that 93 per cent. of the patients showed improvement, although it was marked in less than half of these.

To sum up the literature on the subject, the majority of observers have been favourably impressed with the use of gold salts in rheumatoid arthritis and most have found that 70 - 80 per cent. of their patients respond well to this treatment. As shown earlier in this discussion, however, in few instances has any attempt been made to control these observations, especially the psychological aspects of the treatment, in large clinics. One of the chief aims in this investigation was to neutralise the psychological effect usually associated with "having an injection". In every possible way an attempt was made to control the experiment adequately.

Clinical Material

The investigation, which extended over a period of one year, was concentrated on classical cases of rheumatoid arthritis in which clinical

activity was known to have been present for two to five years. In addition, women should have shown the first signs of the disease before the age of 40 and men before the age of 50.

Age and Sex.- Of the 110 patients falling into the category described, 28 were males and 82 females. Table 1 shows the patients in different age-groups at the onset of arthritis, but it should be remembered that no women over the age of 39 were included. Excluding the age-group 40-49 for this reason, the ratio of men to women in this series is approximately 1:5. It will be seen that more than half of the patients fall into the age-group 30-39.

Table 1

Age-group	Age-distribution at onset of arthritis No. of cases
0-9	0
10-19	10
20-29	29
30-39	59
40-49 (males only)	12
	Total 110

Previous Health.- Forty-nine of the patients had a history of rheumatic fever, scarlet fever or tonsillitis. Of these, 11 were known to have had rheumatic fever. Three patients were suffering from psoriasis, and this had been present before the onset of the arthritis.

Family History.- Fifty-eight (53 per cent.) of the patients stated that there was some form of "rheumatism" in the family and, of these, 28 (25 per cent.) had blood relations with rheumatoid arthritis. This figure is greater than that reported by Hartfall et al. (1937) in their large series of cases, when it was only 16.9 per cent.

Joint Involvement.- Bilateral and symmetrical involvement of the finger-joints was present in all the patients in the series.

Cardiac Involvement.- Valvular disease of the heart was present in 15 (14 per cent.) of the patients, and high blood-pressure in 2. Recently, Baggenstoss and Rosenberg (1941) have put the figure for cardiac involvement in rheumatoid arthritis as high as 56 per cent. They found at autopsy cardiac lesions indistinguishable from those of rheumatic fever in 14 out of 25 patients.

Previous Treatment.- The majority of patients had already had some form of treatment - e.g. eradication of septic foci, protein shock, salicylates, physiotherapy - with little or no improvement. None had been treated with gold salts.

Method of Treatment

All the patients, with one exception, had ambulatory treatment, and attended the clinic once a week for observation and injections. In addition, all received some form of physiotherapy, such as heat and massage. Before treatment was begun each patient was given a thorough clinical examination, including joint measurements, full blood count, blood sedimentation rate, blood uric acid, urine analysis, urea

clearance, and radiological examination; the findings were charted on special case sheets, supplied by the Empire Rheumatism Council for whom this investigation was done. The same procedure was adopted at the end of the period of observation - i.e. one year - while during treatment weekly urine analysis, fortnightly white blood cell counts and monthly blood sedimentation tests were carried out. A careful watch was kept for the first signs of intolerance to gold.

In order to control the investigation from the therapeutic aspect, the "blindfold" method of treatment was employed. The patients were divided roughly into two groups, one receiving myocrisin, an aqueous solution of gold sodium thiomalate containing 50 per cent. metallic gold, and the other an inactive control substance. The latter contained the same constituents as the myocrisin with the exception of the gold radical, had the same appearance, and was made up in identical ampoules. The patients who received the control substance were unaware of the fact, believing that they were having gold injections. For my part, it was not made known to me which patients had received myocrisin and which the inactive control substance until after I had completed and recorded my final observations on the progress of the disease. Both the myocrisin and the control substance were administered in the same way. Intramuscular injections were given into the buttocks at weekly intervals in the following doses: 1 x 0.01, 2 x 0.02, 1 x 0.05, and 9 x 0.1g., giving a total of 1.0g. in a course. If necessary, after an interval of three months a second course of 1.0g. was given in the same dosage. As

the period of observation was for one year only, it was not possible to give more than two courses of injections. Treatment was suspended temporarily when the milder forms of toxicity appeared, and permanently when the reactions were severe.

Results of Treatment

Of the 110 patients 61 had injections of myocrisin and 49 the inactive control substance. Owing to toxic reactions or to the patient's defaulting, 4 of the former and 3 of the latter are not included in the results of treatment. Thirteen of the patients on myocrisin and 28 on the control received two courses of injections, while the remainder received only one or part of one course.

As previously stated, it is difficult to decide what criteria to use in assessing the results of treatment. I have based the classification on my general impression of the progress made and on the change in the clinical signs - e.g. general condition, gain in weight, joint swelling, restoration of function, blood sedimentation rate, etc. The patients were divided arbitrarily into five groups: great, moderate, slight, and no improvement, and worse. No cures were claimed, as it is apparent that the patients were not observed over a sufficient period of time. The results of myocrisin are shown in table 2 and of the inactive control substance in table 3; the figures in parentheses in both representing the results as obtained from questioning the patient about his own opinion as to progress during the year.

Table 2

Results of treatment with myocrisin

Result	Cases	
	Number	%
Great imp.	24 (32)	42 (56)
Moderate imp.	12 (8)	21 (14)
Slight imp.	11 (6)	19 (11)
No imp.	5 (9)	9 (16)
Worse.....	5 (2)	9 (3)
Total.....	57	100

Table 3

Results of treatment with inactive control substance

Result	Cases	
	Number	%
Great imp.	4 (15)	8 (33)
Moderate imp.	6 (12)	13 (26)
Slight imp.	11 (6)	24 (13)
No imp.	10 (6)	22 (13)
Worse.....	15 (7)	33 (15)
Total.....	46	100

From these figures it will be seen that, while 82 per cent. of the patients who received myocrisin improved clinically, 45 per cent. of those on the control also showed some improvement. However, a closer study of the results shows that there is a considerable difference in the degree of improvement in the two groups. It is of interest to note that 72 per cent. of the control group felt that they had received some benefit from the injections, although only 45 per cent. showed clinical improvement.

In table 4 I have shown the relationship of the results of gold therapy to the number of courses of myocrisin given. It will be seen that 65 per cent. of those patients receiving one course only showed great or moderate improvement against 53 per cent. receiving two courses.

Table 4

Relation of results to number of courses of gold

Courses	Cases	Great Imp.	Mod. Imp.	Slight Imp.	No Imp.	Worse
		No. and %	No. and %	No. and %	No. and %	No. and %
1	44	20 (45)	9 (20)	8 (18)	4 (9)	3 (7)
2	13	4 (30)	3 (23)	3 (23)	1 (7)	2 (15)
Total	57	24	12	11	5	5

Graham and Fletcher (1943) pointed out that a good result following on gold therapy was related to a fall in the blood sedimentation rate - the better the clinical result, the greater the fall. An analysis of the clinical results in relation to the sedimentation rate in both groups in this series is shown in table 5.

Table 5

Relation of improvement to fall in blood sedimentation rate

Result	Sedimentation rate			
	Myocrisin		Control	
	Average initial	Average final	Average initial	Average final
Great imp.	23	7	47	11
Moderate imp.	20	9	27	17
Slight imp.	26	13	11	14
No imp.	10	9	22	17
Worse.....	15	7	19	31

Of the 57 patients who received myocrisin 19 were unable to continue with their work when first seen, while of the 46 patients on the control substance 14 were similarly incapacitated. By the end of the period of observation 17 of the former and 4 of the latter had been able to resume their original employment, which was in the majority of

cases of a moderately heavy or heavy nature (table 6).

Table 6

Capacity for work before and after treatment

Nature of Injection	No.of Cases	At Work			
		Before		After	
		No.	%	No.	%
Myocrisin	57	38	66	55	96
Control	46	32	69	36	78

As it had been suggested by a number of observers in America that not infrequently patients with gout were being labelled as cases of rheumatoid arthritis, it was decided to carry out blood uric estimations on all the patients in this series before and after treatment. The method described by Benedict (1922) was employed. Out of 110 patients 12 had initial levels above the normal (2 - 4 mg./100 ml.), the highest being 6.0 mg. (table 7). Of these, 7 received myocrisin and 5 the inactive control substance. The final levels were within normal limits in 11 of the 12 cases, and in the twelfth the blood uric acid fell from 6.0 mg. to 4.4 mg. after one course of myocrisin. In none of the twelve cases was there any evidence, clinical or radiological, to suggest that the condition was one of gout.

Table 7

Patients with blood uric acid levels above 4 mg./100 ml.

Case No.	Sex	Nature of Injection	Blood Uric Acid mg./100 ml.	
			Before Treatment	After Treatment
56	M.	G.	6.0	4.4
37	F.	G.	5.4	3.1
63	F.	G.	5.1	4.0
22	M.	G.	4.9	2.8
3	M.	C.	4.8	3.6
10	M	G.	4.8	4.0
51	F.	C.	4.7	4.0
13	M.	G.	4.7	4.0
2	F.	G.	4.5	3.9
17	F.	C.	4.3	3.6
4	F.	C.	4.2	3.0
1	F.	C.	4.1	3.2

G = Gold. C = Control.

Toxic Reactions

It is a well recognised fact that the use of gold salts in the treatment of rheumatoid arthritis is not without its dangers. The

incidence of toxic reactions is high, according to many observers appearing in about half the cases (Cecil et al., 1941; Dawson et al., 1941; and Graham and Fletcher, 1943). Unfortunately, there is no reliable method of predicting which patients will develop signs of toxicity or complications, the factors upon which the toxic reactions depend being unknown, nor is there any known method of prevention. According to Comroe (1945) patch tests with gold do not adequately reveal sensitivity to the metal. The fact that reactions may occur after even as small a dose as 0.01g. myocrisin rather suggests that in a number of cases the toxicity of gold is the result of an individual sensitivity, and not a heavy metal intoxication per se. In others, however, the question of dosage is important, the greater percentage of reactions occurring with larger doses of gold salts. Furthermore, toxic reactions may be delayed, many occurring two or three months after the cessation of therapy. Theoretically, they might be expected so long as gold can be recovered from the blood and urine, i.e. up to one year, according to Freyburg and his colleagues (1942).

Many attempts have been made to prevent the appearance of toxic reactions, but all have failed. Lintz (1941) suggested that large amounts of Vitamin C. should be given continuously during gold therapy. Like most other observers, I have found the results disappointing. Similarly, the treatment of complications has met with little success. Sodium thiosulphate and calcium salts are generally employed empirically to shorten the course of the toxic reactions, but in common with others, I

feel that they are of little or no avail.

The majority of toxic reactions are generally of a mild nature, but fatalities have been recorded from time to time (Forestier, 1935; Ellman and Lawrence, 1935; Hartfall and Garland, 1935 and 1936). These were usually associated with the larger dosages that were given in the earlier days of gold therapy. In the present series 75 per cent. of the 61 patients who received gold injections developed toxic manifestations (table 8) - a figure higher than that generally reported - but the majority of these were mild. Seven patients had multiple reactions. Most of the reactions occurred during the first course of injections, but some appeared in the second course, and a few were delayed, making their appearance some time after the cessation of treatment. It is of interest to note that 37 per cent. of the 49 patients who were given the control substance had "toxic reactions" (table 9).

Table 8

Toxic reactions following the use of myocrisin in 61 cases of R. A.

	No. of Cases
Skin (minor reaction)	35
Mouth	7
Kidney	5
General	4
Skin (major reaction)	2
Alimentary tract	1
Total	54 (75%)

Table 9

"Toxic reactions" following the use of an inactive control substance in 49 cases of R. A.

	No. of Cases
Skin	16
Kidney	2
Mouth	1
Total	19 (37%)

General Reactions.- These were noted in 4 of the patients who received myocrisin, and consisted of headache, vomiting and shivering immediately after each injection. In all, the upset became so severe that therapy had to be discontinued.

Skin Reactions.- These appeared in 37 of the 61 patients, but only 2 were of a severe nature and gave rise to some anxiety. These were cases of generalized exfoliative dermatitis. Both were admitted to hospital for a period of six weeks, but it was several months before the skin had returned to its normal condition. The remaining 35 patients had reactions of a minor character, 7 of them having pruritus only. Other skin lesions were simple erythema, macular, maculo-papular, papular, pustular, squamous and exudative dermatitis. Some of these were accompanied by fissuring of the palms of the hands, and others by desquamation of the skin. Treatment was discontinued only temporarily in most of these cases. There were several cases of delayed reactions; in one

instance a maculo-papular dermatitis of the back appeared six months after the cessation of gold therapy. Sixteen of the 49 patients who received the inactive control substance complained of skin lesions. Of these, 10 had pruritus only; 2 a papular dermatitis; and the other 4 an erythema, a pustular rash, a seborrhoeic dermatitis and a dermatitis infectiosa respectively. It should be pointed out that all the patients were made "skin conscious" before treatment started, and were instructed to report anything out of the usual.

Mouth Lesions.- These were noticed in 7 patients who had myocrisin injections. Five of these had ulceration of the gums, cheeks and lips, and 2 complained of soreness of the mouth without any lesions. One of the patients on the control substance stated that she had a metallic taste in her mouth during treatment.

Kidney.- A mild transient albuminuria appeared in about half of the patients in both the myocrisin and the control groups, but was not considered of sufficient importance to be included in the kidney reactions. Only 5 of the patients who received myocrisin showed any definite evidence of kidney damage. Albumin, red blood cells and casts were found in the urine and treatment was abandoned. Two of the control patients also developed albumin and casts in the urine. The urea clearance test (McIntosh et al., 1928) was performed in all the patients of both groups before and after each course of injections, but the results did not show anything of significance even in those cases in which blood and casts were found in the urine. Table 10 shows the blood urea level and the

urea clearance test of the 5 patients receiving myocrisin performed at the time of the renal complications.

Table 10

Blood urea and urea clearance test made at the time of renal complications in the 5 cases receiving myocrisin

Case No.	Blood urea mg./100ml.	Urea Clearance %
13	21	77
26	34	117
27	26	96
56	28	102
74	25	97

Alimentary Tract.- One patient developed a colitis with blood and mucus in the stools after receiving 0.6g. of myocrisin. This proved very resistant to treatment, and, when seen recently, 17 months after the onset, the patient stated that although the condition was much better he still had periodic attacks of diarrhoea without blood or mucus.

Blood.- Comroe (1945), in a survey of the literature, found that 50 cases of agranulocytosis (with 25 deaths) had been reported. In my series a decrease in the white cell count was noticed during treatment in the majority of patients receiving myocrisin, but in no instance did it fall below 3,000 per c.mm. The count returned to its original level shortly after the end of treatment. It was noticed that the haemoglobin generally rose in those patients who responded to gold therapy.

Other toxic reactions which have been recorded from time to time such

as acute yellow atrophy of the liver (Crosby, 1936), aplastic anaemia (Comroe, 1945), thrombocytopenic purpura (Price and Lichentritt, 1945), and polyneuritis (Leiper, 1946) were not seen in my series.

It has been the experience of most observers that those patients who develop toxic reactions generally have a marked, though usually temporary, alleviation of the joint condition. This was found to be true in the present series, especially with the more severe reactions - e.g. exfoliative dermatitis and colitis.

In table 11 I have listed the various toxic reactions following the use of myocrisin, excluding patients with pruritus or simple erythema only, in relation to sex, erythrocyte sedimentation rate and the total amount of myocrisin at the onset of complications. Snyder and Traeger (1943) found that toxic reactions following the use of sodium aurothiosulphate were eight times more common in women than in men. In my own series sex had no bearing on the frequency of reactions. Although twice as many women as men had complications, the ratio of women to men who received myocrisin was 2:1. As to the relationship of the erythrocyte sedimentation rate with the toxic reactions, Ellman and his associates (1940) showed that there was a greater risk of reactions developing when gold therapy was continued after the sedimentation rate became normal, and advised that the injections should be suspended for a month and then only resumed in small doses. My own findings tend to confirm this view. Lastly, it will be seen that toxic reactions occurred at any time between the first injection and six months after the cessation of therapy.

Table 11

Toxic reactions following the use of myocrisin in relation to sex, E.S.R. and total amount of gold salt received

Group	Case No.	Sex	E.S.R. at time mm.	Total amount of gold g.	Toxic reaction
Skin (minor reaction)	14	F.	8	1.0	S.D. arms 3 months after cessation of therapy.
	16	F.	23	0.01	M.P.D. legs.
	28	F.	5	1.0	Ex.D. right hand 2 months after cessation of therapy.
	37	F.	9	0.61	Generalised P.D.
	39	F.	7	0.5	Generalised M.P.D. with fissuring.
	46	F.	9	0.2	P.D. face and arms.
	48	M.	11	0.7	V.D. hands with fissuring.
	53	F.	28	0.1	P.D. face and chest.
	54	F.	25	0.1	Pust. D. of face.
	58	F.	4	0.7	Generalised M.P.D.
	60	F.	47	0.6	Pust. D. face and chest.
	66	F.	4	0.9	V.D. face.
	72	F.	60	0.01	Generalised M.D.
	75	F.	4	0.4	M.P.D. arms and legs.
	76	M.	26	0.5	M.P.D. chest.
	77	M.	1	1.0	M.P.D. back 6 months after cessation of therapy.

Table 11. (Continued)

Group	Case No.	Sex	E.S.R. at time mm.	Total amount of gold g.	Toxic reaction
Skin (minor reaction)	88	F.	22	0.9	M.D. neck.
	94	M.	13	1.0	M.P.D. legs.
	102	F.	3	0.7	M.P.D. chest.
	104	M.	5	0.6	P.D. legs.
	110	M.	12	1.0	Generalised M.D. and Pust. D. face.
Skin (major reaction)	5	M.	18	0.68	Generalised Ex. D.
	29	F.	8	0.3	Generalised Ex. D.
Stomatitis	29	F.	8	0.3	Ulceration of gums and cheeks.
	39	F.	7	0.5	Ulceration of gums.
	67	M.	15	0.7	Ulceration of gums.
	80	M.	5	0.8	Ulceration of gums and lips.
	86	F.	5	0.7	Gums sore; no ulcers.
	97	F.	19	0.1	Gums sore; no ulcers.
	106	F.	5	0.7	Ulceration of gums.
Renal	13	M.	21	0.8	R.B.C. in urine.
	26	M.	16	0.9	R.B.C. in urine.
	27	F.	22	0.8	Granular casts in urine.

Table 11. (Continued)

Group	Case No.	Sex	E.S.R. at time mm.	Total amount of gold g.	Toxic reaction
Renal	56	M.	15	0.7	R.B.C. in urine.
	74	F.	12	1.0	R.B.C. and granular casts in urine.
Alimentary Tract	76	M.	26	0.5	Colitis with blood and mucus.
General	8	F.	8	0.6	Headache, vomiting and shivering after injections.
	26	M.	16	0.9	Vomiting after injections.
	53	F.	28	0.1	Headache and fever after injections.
	101	F.	4	0.05	Headache and shivering after injections.

M.D. = Macular dermatitis.
M.P.D. = Maculo-papular dermatitis.
P.D. = Papular dermatitis.
S.D. = Squamous dermatitis.
V.D. = Vesicular dermatitis.
Ex.D. = Exfoliative dermatitis.
Pust.D. = Pustular dermatitis.
R.B.C. = Red blood corpuscles.

Discussion

Although the number of patients in this series is small and the period of observation for the purposes of the investigation - i.e. one year - is short, it is justifiable to draw certain conclusions. It

should be borne in mind, however, that treatment was confined to one small group of patients suffering from rheumatoid arthritis. In the first instance the patients had had the condition for 2 - 5 years. This choice was made in an attempt to eliminate, so far as possible, the inclusion of patients showing spontaneous remissions, which are most common during the first two years of the disease, and to exclude old-standing cases in which the disease might have burned itself out. Secondly, men should have shown the first signs of the disease before the age of 50, and women before the age of 40. In this way it was thought to avoid any complicating factor associated with the menopause. Thirdly, every patient had some form of physiotherapy, such as heat and massage. Lastly, I wish to stress again one important point - namely, that I was completely unaware of what each patient was receiving during his course of injections.

Of the 57 patients who received myocrisin, 82 per cent. showed clinical signs of improvement compared with 45 per cent. of the 46 patients on the control substance. At first sight these figures do not seem very encouraging, as there is only a 37 per cent. difference in favour of myocrisin; but on going into the results more closely (tables 2 and 3) it is found that, whereas 42 per cent. of the former showed great improvement, only 8 per cent. of the latter improved to this extent. Similarly, 21 per cent. of those on myocrisin were moderately improved as against 13 per cent. of the controls. Slight improvement was noted in 19 per cent. of the myocrisin cases and 24 per cent. of the controls;

and, finally, in 18 per cent. of the former and 55 per cent. of the latter the condition remained stationary or had deteriorated.

Why should the control patients have shown any improvement? The explanation probably lies in the fact that all the patients received some form of physiotherapy and, secondly, that spontaneous remission must have occurred in a number of cases. In the same way it would be reasonable to suggest that these two factors were responsible for the improvement shown in roughly the same percentage of cases in the myocrisin group. If this were so, the figures showing improvement as the result of gold therapy would be appreciably reduced - viz. to 34 per cent. great improvement and 8 per cent. moderate improvement. It should be explained, however, that only 13 of the 57 patients had more than one course of gold injections, and that, while the condition of many of those receiving only one course improved considerably during the treatment, it had regressed by the end of the period of observation. It was unfortunate that war work prevented many of the latter from attending for further therapy. As Hartfall and his colleagues (1937) felt that every patient should have at least two courses of injections, it is conceivable that if they had been able to do so the percentage of those showing improvement might have been higher, although a glance at table 4, which shows the relation of the results to the number of courses of gold, would not appear to bear this view out.

It is of interest to note that 28 (60 per cent.) of the 46 patients who received the inactive control substance, compared with 22 per cent. on

myocrisin, required two courses of injections, while others would probably have had further treatment had they been able to attend. From this it can be concluded that clinically the control substance was not so effective as the myocrisin.

I have already drawn attention to the fact that 72 per cent. of the patients who received the inactive control substance improved subjectively, although only 45 per cent. showed objective (clinical) improvement; and in the case of those receiving myocrisin a similar, though less marked discrepancy was obtained. This finding suggests that a psychological factor is present and must be borne in mind, more particularly when the patient's statements as to progress are used as one of the criteria in assessing results. That the "having an injection" mentality is in great part responsible for this subjective improvement is well known to medical men. Medicine, in any form, is always more to the patient's liking when given by injection. What magical and soothing powers can be extracted from 1 c.c. of sterile water when injected slowly into the buttock! There is, however, another factor in the production of this feeling of well-being, and that is the psychological effect of being one of many having the same treatment. On the whole, the larger the clinic the more apparent does this become, especially if one or two of the patients who have done well clinically are allowed to "show off" to their fellow-sufferers.

From my results it is fair to assume that the good results claimed for gold therapy in rheumatoid arthritis by the majority of observers are

unjustifiably high owing to lack of adequate controls. Likewise, the same criticism will apply to other forms of treatment in this condition, and, indeed, in all diseases. Great caution should therefore be observed in assessing the results of any form of therapy, and extravagant claims for any new drug should be avoided unless the investigation has been properly controlled.

In conclusion, in my view gold therapy is the best single form of treatment in rheumatoid arthritis that we have at our disposal at the present time, provided it is employed in properly selected cases, and that its results are enhanced when used in conjunction with general, physiotherapeutic and orthopaedic measures. It is by no means a panacea and its limitations should be kept in mind. It may well be that the relief obtained is only of a temporary nature, and a review of the cases after a period of at least five years is essential before any pronouncement is made on the lasting effects of gold therapy. Reports in the literature of follow-ups are conspicuous by their absence. Moreover, gold is a dangerous drug, and toxic reactions have been reported by some authorities in over 50 per cent. of their patients. For this reason I feel that gold salts should be given only by those who have had experience in their use and are fully aware of the dangers, and then only if improvement has not been obtained following the use of more conservative measures over a reasonable period of time - viz. three to four months - or if the course of the disease is rapidly progressive.

Summary

Part III opens with a discussion on the general principles of treatment in rheumatoid arthritis, and on the difficulties met with in trying to compare the results of the various investigations with one another. The main reasons for this state of affairs are given.

The theories concerning the mode of action of gold salts in rheumatoid arthritis and their fate in the body have been propounded.

An historical review of the literature on the subject of gold therapy has been carried out.

I have then dealt in detail with the clinical material used in the present study, the method and results of treatment, and the toxic reactions following on the use of gold salts in rheumatoid arthritis. Likewise, a detailed description of the results of treatment in a control series of patients with rheumatoid arthritis who received injections of an inactive substance has been given.

In order to control the investigation from the therapeutic aspect, the "blindfold" method of treatment, which had not previously been adopted in rheumatoid arthritis, was employed.

Of the 57 patients who received myocrisin, 82 per cent. improved clinically compared with 45 per cent. of the 46 patients on the control substance. The degree of improvement was more marked in the former group. The significance of the results has been discussed and the importance of the psychological aspect of treatment stressed.

Toxic reactions occurred in 75 per cent. of the patients who

received myocrisin, but most of these were of a mild nature. There were no deaths in this series, and only two patients, with exfoliative dermatitis, gave rise to some degree of anxiety.

Gold salts are considered of value in the treatment of rheumatoid arthritis, particularly when used in conjunction with general, physiotherapeutic and orthopaedic measures. On account of their toxicity, however, they should only be employed by those with experience in their use.

PART IV.

ON THE EFFECT OF JAUNDICE IN RHEUMATOID ARTHRITIS

It has been known for a number of years that many patients with rheumatoid arthritis and other rheumatic complaints have experienced complete remission of symptoms with the appearance of spontaneous jaundice. Isolated cases of this combination of diseases had been recorded in the literature from time to time, but little or no importance was attached to the therapeutic effect of the jaundice, the whole phenomenon having apparently been looked upon as a pure coincidence until Hench (1933) pointed out that it occurred too frequently to be entirely accidental.

The first reference to the analgesic effect of jaundice in rheumatoid arthritis was made by Still (1897), who reported that, "Curiously enough, some accidental complications have been followed by marked improvement; thus I have known measles, scarlet fever and catarrhal jaundice to be each followed by distinct improvement of the joint symptoms". A similar passing comment on the analgesia associated with

jaundice was made by Wishart (1903). Weir and Jordan (1930) reported the case of a woman with rheumatoid arthritis who developed a fatal acute yellow atrophy of the liver with jaundice three months after taking a few capsules of cinchophen. The pain rapidly disappeared and the swelling of the joints diminished with the onset of the jaundice. Beaver and Robertson (1931), Comfort (1932) and Weir and Comfort (1933) recorded similar experiences with jaundice following the use of cincophen, and all noticed that the alleviation of the pain and the diminution of joint swelling occurred either immediately before, at the onset or immediately after the onset of the jaundice. Parsons and Harding (1932) stated that a history of the taking of cinchophen, followed by the disappearance of pain associated with the onset of jaundice, is usually obtained. Other confirmatory evidence of the analgesic effect of jaundice has been given by Grigg and Jacobsen (1933), Sidel and Abrams (1934) and Borman (1936). It is of interest to note that this was not the experience of Hartfall and his colleagues (1937). In their report of 900 cases of arthritis treated with gold salts, of whom 85 (9.4 per cent.) developed a toxic jaundice, they stated that the results in those patients with toxic jaundice were worse than those having no jaundice, and they felt that their findings did not support the view that jaundice was a valuable therapeutic measure in rheumatoid arthritis.

It was Hench (1934), however, who first gave prominence in the literature to the beneficial effect of jaundice in rheumatoid arthritis and other rheumatic conditions. It was in 1929 that he noticed this

phenomenon for the first time. A patient came to him at the Mayo Clinic complaining of rheumatoid arthritis of four years' duration. He stated that a week previously, no medicine having been taken, a painless jaundice had suddenly developed, and that on the following day the pain and swelling in his joints began to diminish. When the patient was examined at the Clinic the joints were symptomless, and this complete symptomatic remission lasted for five and eight months in the case of the feet and hands respectively. This experience so impressed the patient that, when he returned to the Clinic two years later with moderately active rheumatoid arthritis, he reminded Hench that the only time his joints had ever been entirely free from pain was during and just after the jaundice.

In 1938, Hench reported further observations on the association of jaundice with rheumatoid arthritis and other forms of rheumatism. Nineteen of the patients who were suffering from rheumatoid arthritis had jaundice which lasted on an average for nine weeks, and a remission, complete in 12 and almost complete in 7, which lasted on an average for twice as long (eighteen and one-half weeks). The jaundice was associated with a variety of conditions:- cinchophen poisoning, "catarrhal" jaundice, hepatitis, cirrhosis and gall-stones. In addition, he found that coincident jaundice had brought about complete symptomatic relief in 9 cases of fibrositis, and partial relief in 2 cases of lumbo-sacral and sciatic pains and one case of osteoarthritis of the hips.

On the other hand, Hench found that 13 patients with a variety of

rheumatic complaints were unrelieved by jaundice. Four of these were patients with rheumatoid arthritis, but in each case the jaundice was mild. In 4 patients, however, with other forms of arthritis and with fairly intense jaundice there was no amelioration of symptoms. In the case of the four patients with rheumatoid arthritis he considered that the symptoms might not have been relieved on account of the mild degree of jaundice; that it was below the "zone of therapeutic effectiveness" which he suggested tentatively as beginning at a concentration of serum bilirubin of about 8 to 10 mg. per 100 ml. From his observations he concluded:-

(1) that the phenomenon was a quantitative one, and dependent on a certain intensity of jaundice;

(2) that it could apparently be precipitated by almost any type of obstructive or hepatogenous jaundice;

(3) that it might be relatively specific for rheumatoid arthritis and fibrositis;

(4) that the onset of relief was noted promptly with the appearance of visible jaundice; and

(5) that the amelioration of symptoms was only of a temporary nature, although the subsequent relapse of the joint symptoms was milder in 42 per cent. of the cases.

Hench then went on to speculate on the agent responsible for the phenomenon, and suggested that the responsible agent, "substance X", might be a normal or abnormal constituent of bile, or possibly a product of hepatic damage. After putting forward various possibilities, he came to the tentative conclusion that the jaundice brought about the phenomenon

as the result of:-

(1) the correction of some chemical deficiency,

(2) the correction of some chemical oversufficiency, or

(3) a process of bacteriolysis, bacteriostasis or detoxification.

Further than that he was unwilling to commit himself.

The therapeutic implications of nature's dramatic method of controlling the symptoms of rheumatoid arthritis seemed obvious to Hench, and he thereupon set out to try to reproduce the phenomenon by administering to volunteers with arthritis the different available constituents of bile, first alone and then in combination. Natural and synthetic bile salts (decholin) were given orally and parenterally, human bile was fed by stomach tube and transfusions of deeply jaundiced blood were tried. In only one instance did jaundice appear, and that in the case of a patient who received toluylenediamine orally. The jaundice was of the haemolytic type, but was ineffectual against the pain. The serum bilirubin reached a maximum level of 6.3 mg. per cent. (direct reaction), and so never entered the "zone of therapeutic effectiveness". Thus Hench was unable to reproduce this naturally occurring phenomenon of the analgesic effect of jaundice.

Concurrently with Hench's article another appeared in the medical press on attempts to reproduce the phenomenon artificially by the intravenous injection of bilirubin and bile salts by Thompson and Wyatt (1938). They found that the administration of bilirubin or bile salts alone was without beneficial effect on the symptoms of rheumatoid arthritis, but

that the combination of the two gave some amelioration. Their results, however, were not very convincing.

It will be seen, therefore, that jaundice is not easy to induce. However, with the Second World War an opportunity arose for trying out more daring methods of inducing jaundice artificially, some of which met with success. As is well known, in many campaigns in the late conflict the conduct of operations was hindered by the epidemic prevalence of acute infective hepatitis. Not the least of the difficult problems involved was ignorance of how the disease was spread, repeated attempts to transmit it to a wide variety of animals having failed. In 1942 Voegt claimed to have transmitted hepatitis to man by subcutaneous injections of serum and blood, and by oral administration of urine, duodenal juice and blood from patients with acute infective hepatitis. His results were interesting and important, but inadequate to form definite conclusions. Cameron (1943) gave intramuscular injections of serum and blood to seven volunteers. His subjects could not be observed throughout the incubation period, since they had to return to their units where they were exposed to ordinary infection, but six out of the seven developed acute infective hepatitis while on campaign, between thirty and one hundred days after inoculation. These experiments of Voegt and Cameron gave a clear indication that further experimental work was necessary and promising.

As animal experiments had failed, and as it was urgent and imperative to find out the method of transmission of the disease, it was felt that

the use of homo sapiens as a guinea-pig was justifiable. The next step was to find volunteers for the investigation and, with Hench's experiences with spontaneous jaundice in mind, it was decided to ask for these from patients with rheumatoid arthritis who had failed to benefit from the usual therapeutic measures. Before volunteers were accepted, however, care was taken to explain to them the experimental nature of the treatment and the risks involved. Emphasis was laid on the uncertainty of the benefit to be derived, and it is perhaps some indication of the present hopeless plight of the rheumatoid subject that many patients were anxious to participate in the experiment. The present work was a small part of a larger investigation under the auspices of the Medical Research Council designed to throw light on the epidemiology of acute infective hepatitis, and was initiated early in 1944.

Personal Observations

I shall first record cases of rheumatoid arthritis with spontaneous jaundice who came under my own observation while in hospital. Thereafter, I shall describe the experimental work done on the production of artificial jaundice in rheumatoid arthritis.

A. SPONTANEOUS JAUNDICE

I have personally observed four patients with rheumatoid arthritis who developed an intercurrent jaundice, and shall describe their cases in some detail.

Case 1. (previously reported - Fraser, 1934). The patient, a woman of 38, reported to her doctor at the beginning of April, 1934, with the complaint of pain and swelling in the joints of the fingers, wrists, knees and ankles. She was put on a salicylate mixture, and after a fortnight she returned to her work against her doctor's orders. The pain had diminished considerably, but there was still-swelling and stiffness in the joints.

About three weeks later, her joint condition having deteriorated, she again reported to her doctor, who prescribed a course of cinchophen. After five days he noticed that she was faintly jaundiced and stopped the drug; she had taken five tablets in all (37½ grs.). The day after the onset of the jaundice her pains had disappeared and the joint swelling rapidly subsided. She felt well enough to continue at her work for another twenty-five days, although the jaundice had slowly increased during that period. She was finally forced to take to bed on account of weakness, but her joints remained symptom-free. Four days later she became partially comatose, and was admitted to hospital on 30th May, 1934. On admission she was deeply comatose, and the skin and conjunctivae were intensely jaundiced. Serum bilirubin was 20 mg. per 100 ml. There was no evidence of any joint involvement. The patient never regained consciousness and died on the following day. Post-mortem examination revealed the presence of a subacute yellow atrophy of the liver.

This case illustrates the effect of spontaneous jaundice on rheumatoid arthritis. Alleviation of the joint symptoms was rapid and complete, and was noticed on the day following the onset of jaundice. It might be argued that the relief of symptoms was due to the taking of cinchophen, but this is highly improbable for the following reasons:-

(1) that the total amount of the drug taken was only 37½ grs., and

(2) that the analgesia and diminution of swelling remained complete until her death four weeks after the cessation of the cinchophen therapy.

Case 2. The patient, a woman of 55, was sent to my Rheumatic Clinic on 18th March, 1942, suffering from rheumatoid arthritis of 2½ years' duration. On examination, the proximal interphalangeal and metacarpo-phalangeal joints of the fingers of both hands were swollen, stiff and painful. The grip was very poor. Both wrists were swollen and painful, but there was

no limitation of movement. The elbows and knees were painful, but not swollen. The transverse arches of the feet had fallen. Erythrocyte sedimentation rate was 38 mm. in one hour (Westergren). The clinical picture was one of active rheumatoid arthritis.

It was decided that she was a suitable subject for chrysotherapy, and she was started on myocrisin injections. She was given four injections at weekly intervals - total = 0.1g. - during which time the joint condition remained unchanged. Two days after the last injection she developed pain in the right hypochondrium, and had several bouts of vomiting of greenish material. Two days later, on 19th April, 1942, she became jaundiced, and was admitted to hospital on 21st April, 1942.

On admission, patient was markedly jaundiced, with bile in the urine and clay-coloured stools. Blood serum gave a positive immediate van den Bergh reaction = 10 mg. per 100 ml. The joints were now free from swelling and pain, the latter having disappeared on the day of onset of the jaundice. The grip was good. Erythrocyte sedimentation rate was 10 mm. As the cholecystogram revealed the presence of a large single stone in a non-functioning gall-bladder, it was decided to operate. At operation a very thin-walled and distended gall-bladder was found containing one large pear-shaped cholesterol stone. The common bile duct was normal and patent. The liver was enlarged to about 1 inch below the right costal margin and presented a very fine diffuse granularity with a patch about 1 cm. in diameter of sharply circumscribed pale yellow tissue to the right of the ligamentum teres. A portion of this area was removed along with the gall-bladder and examined histologically. The pathologist reported the presence of a subacute necrosis of liver.

The jaundice slowly faded during the two weeks following the operation, and the patient was discharged from hospital on 21st May, 1942, feeling very fit and symptom-free. She remained so until the beginning of August, 1942, when she noticed a little pain and swelling in her finger joints. The erythrocyte sedimentation rate was 18 mm. Since then the arthritis of the hands has slowly relapsed, but when last seen it was not so marked as before the attack of jaundice. All the other joints remained symptom-free. The patient had put on one stone in weight.

As revealed by operation, this was a case of subacute necrosis of the liver presumably associated with chrysotherapy, which was being given for rheumatoid arthritis, the gall-stone being purely incidental. The therapeutic effect of the jaundice on the arthritis was well demonstrated. The remission started on the day of the onset of the jaundice, was complete

two days later, and remained so for 3½ months, when the arthritis insidiously returned. The relapse, however, was less severe than the original attack.

Case 3. The patient, a woman of 45, was admitted to hospital with the following story. In October, 1943, she noticed that her hands and wrists were painful and swollen. The condition was diagnosed as rheumatoid arthritis, and she was given out-patient treatment at an infirmary, but the arthritis slowly progressed. In August, 1944, she was admitted to the same infirmary with mild jaundice, and was discharged two months later, slightly jaundiced but feeling well apart from the joint symptoms which were still present, although less marked. The patient remained well apart from a mild icteric tinge of the skin and conjunctivae until August, 1945, when she had two severe haematemeses in the course of ten days. She was admitted to hospital on 7th September, 1945, when she first came under my notice.

On admission, she was pale and mildly jaundiced. There was a moderate degree of swelling of, and slight pain in the proximal interphalangeal joints of the fingers of both hands, which showed ulnar deviation. A trace of bile was detected in the urine, but the stools were normal in colour. Van den Bergh tests gave a positive biphasic reaction = 3 mg. per 100 ml. Erythrocyte sedimentation rate was 90 mm. Haemoglobin was 65 per cent. (Sahli). Patient was given a blood transfusion (2 pints), and put on physiotherapy. Her general condition improved and she was discharged on 26th October, 1945. The pains in the hands had disappeared, although the swelling remained the same. A mild degree of jaundice was still present.

Patient remained well until early in December, 1945, when the arthritis became active again and the jaundice increased. She was readmitted to hospital on 14th December, 1945, in a collapsed state having had another severe haematemesis. Haemoglobin = 30 per cent. Trace of bile in urine. Melaena present. Van den Bergh = 6.0 mg. per 100 ml. Finger joints were painful and swollen. Was given blood transfusions - 5 pints in all. She again made a rapid recovery and was discharged on 10th January, 1946. The jaundice had lessened, but was still apparent, and the finger joints were free from pain, but swollen.

After dismissal, patient remained well apart from some dyspnoea, and free from pain until 9th April, 1946, when she had another haematemesis, and was readmitted to hospital. She was in a very collapsed state. Haemoglobin = 30 per cent. The liver was enlarged to three finger breadths below the costal margin and the spleen was just palpable. A small quantity of free fluid was present in the abdomen. Mild jaundice

was present. Van den Bergh = 2 mg. per 100 ml. The swelling of the finger joints was a little more marked, but there was no pain. Interosseal wasting and flexion deformity of the thumbs were now present. A transfusion of 2 pints of blood was given. A week later she developed pains and stiffness in the finger joints. She made a fairly good recovery and was discharged on 20th May, 1946. The jaundice, though less, was still present, and the joint condition was still active.

After discharge the rheumatoid arthritis slowly advanced, but remained confined to the hands, while the jaundice became more marked. On 22nd June, 1946, patient had two large haematemeses, and was readmitted to hospital for the fourth and last time on the following day. She was pale, collapsed and moderately jaundiced. Haemoglobin = 45 per cent. Joints still painful and swollen. In spite of continuous intravenous drip-transfusion of blood and glucose saline she became comatose, and died four days later. The post-mortem examination revealed the presence of a subacute necrosis of the liver.

This was a patient with rheumatoid arthritis who developed an intercurrent jaundice due to subacute necrosis of the liver. Although in the early stages of the jaundice the pain was alleviated to some extent, it became more pronounced as the icterus increased, and was finally marked when the jaundice was at its height. Clinically and objectively the arthritis slowly progressed from the commencement of the jaundice until the patient's death. Although nature's phenomenon was not demonstrated by this case, it should be pointed out that the serum bilirubin only reached the level of 6 mg. per 100 ml., and thus did not enter Hench's "zone of therapeutic effectiveness".

Case 4. The patient, a woman of 57, was admitted to hospital on 3rd April, 1940, with a history of pain in the right hypochondrium, vomiting and jaundice of four weeks' duration. She had had rheumatoid arthritis for 26 years and had been more or less free from joint pains for a number of years, although she had never been able to walk during that time on account of the deformity of her knees. On admission, she was mildly jaundiced. In addition, she had an advanced and arrested rheumatoid arthritis of most of her joints with ankylosis of the wrists, elbows, knees and ankles, and marked flexion deformity of elbows

and knees. Four days after admission patient developed auricular fibrillation, and died five days later. Permission for a post-mortem examination was not granted and the cause of the jaundice was not ascertained.

This was a case of rheumatoid arthritis with intercurrent jaundice of unknown origin. I have only mentioned it very briefly as the arthritis had burnt itself out completely, and the joints had been free from pain for many years prior to the onset of jaundice. There was, therefore, no opportunity of observing the effect of the jaundice on the rheumatoid arthritis.

B. INDUCED JAUNDICE

Attempts were made during this investigation to induce jaundice in patients with rheumatoid arthritis by inoculation of serum, and by the oral administration and naso-pharangeal spraying of urine from patients suffering from acute infective hepatitis.

1. Inoculation with Serum. Ten patients with rheumatoid arthritis were inoculated with 0.5 or 1.0 c.c. of serum from two patients suffering from acute infective hepatitis, four receiving serum from donor X (Group a), and six from donor Y (Group b). Serum X had been stored at - 20°C. for four months, serum Y for seven days, and both sera were forty-eight hours in transit packed in a thermos flask in CO_2 snow.

Prior to inoculation with serum, records were made of joint measurements, severity of pain, mobility of joints and erythrocyte sedimentation rate. After inoculation the patients were questioned and examined weekly in the out-patient department. After three months the

time between the visits was lengthened to two weeks. Instructions were given to report at once should anorexia, nausea or vomiting develop.

Group a. The donor of the serum for this group was never jaundiced, but showed well-marked alimentary symptoms, and his plasma bilirubin was above normal when blood was withdrawn. He was an inmate of an institution in which there was at the time an epidemic of acute infective hepatitis.

Case 1. The patient, a man of 50, came to me originally in May, 1943, with the history of pain, swelling and stiffness of the proximal interphalangeal joints and 1st and 2nd metacarpo-phalangeal joints of the fingers of both hands, and of the left wrist,and of pain and stiffness in the elbows, shoulders, knees, ankles and feet of about 2 years' duration. He had been off work, as a caulker, for five weeks. Clinically, he had a moderately severe rheumatoid arthritis. Erythrocyte sedimentation rate was 22 mm. (Westergren). During 1943 he had two courses of myocrisin, and was given intensive physiotherapeutic treatment. By the end of this time his joint condition had greatly improved, and he was back at work. There was no complaint of pain in any of his joints, and apart from a little swelling, of a cystic nature, at both wrists the joints appeared normal. E.S.R. was 9 mm. Patient remained well for seven months when the arthritis became active again, and the joint condition slowly relapsed thereafter.

The patient was again seen on 17th August, 1944, when he presented the following picture. He complained of pain and swelling of the proximal interphalangeal joints of the 1st and 2nd fingers and of the metacarpo-phalangeal joints of both hands, and of both wrists (table 1). In addition, the feet and ankles were painful. The grip was poor. E.S.R. was 16 mm. Patient was given 1 c.c. of serum subcutaneously. During the following eight weeks the joints remained painful and swollen. Fifty-five days after the injection he developed nausea and a sense of fullness in his epigastrium. These symptoms persisted and by the sixty-first day anorexia was complete. He was thereupon admitted to hospital for closer observation. His plasma bilirubin was at that time 0.3 mg. per 100 ml., but on the sixty-second day it rose to 1.3 mg.,and reached a maximum of 17.0 mg. on the twenty-fifth day of illness. The liver and spleen were at no time palpable. Considerable subjective improvement in the joints was noted on the day the jaundice made its appearance, and one week later he stated that all his movements were painless and free. The swelling had completely subsided and the grip was good (table 1).

E.S.R. had dropped to 2 mm. The jaundice persisted for 2 months, but the joints remained symptomless for 4 months when a return of pain in the fingers was noted. E.S.R. was 14 mm. Thereafter, the arthritis slowly returned, and when seen in December, 1946, it was more advanced than before the investigation began. In addition to the involvement of the fingers and wrists, the left elbow and both knees were now painful and greatly swollen. E:S.R. was 25 mm. The course of the jaundice, its effect on the arthritis and the liver function tests are indicated in table 2.

The following liver function tests were employed:-

Plasma bilirubin was estimated by the method of Thannhauser and Andersen (1921), using the Lovibond Comparator. To measure the capacity of the liver to synthesize glycine the oral hippuric acid test of Quick (1936) was used, as modified by Probstein and Londe (1940). The cephalin-cholesterol test (Hanger, 1939) was read at twenty-four hours. Observations were made on the albumin, globulin and fibrinogen of the plasma, using the method of Howe (1921), as modified by Hawke and Bergeim (1938). A laevulose tolerance test (Rennie, 1943) was also carried out.

This case demonstrated clearly the therapeutic effect of jaundice on rheumatoid arthritis. At the time the jaundice was induced the patient was suffering from a moderately active arthritis, with marked pain and swelling of the finger joints and wrists. In common with the usual experience in the naturally occurring disease, it was found that the analgesia commenced on the day the jaundice made its appearance, and was complete on the following day. The swelling rapidly subsided, and by the end of a week there was neither subjective nor clinical evidence of arthritis. The jaundice persisted for two months, during which time, and for a further period of two months, the joints remained symptom-free. Thereafter, the arthritis slowly relapsed, until finally the condition was worse than in the pre-icteric stage.

The changes in the erythrocyte sedimentation rate are of interest.

Table 1.

Condition of affected joints before and one week after onset of jaundice

Joints	Right Hand								Left Hand							
	Before				After				Before				After			
	Swelling		Pain	Movement	Swelling		Pain	Movement	Swelling		Pain	Movement	Swelling		Pain	Movement
		cms.				cms.				cms.				cms.		
1st P.I.P.	+	6.7	+	Stiff	-	6.2	-	Free	+	6.9	+	Stiff	-	6.1	-	Free
2nd P.I.P.	+	6.5	+	"	-	6.2	-	"	+	6.8	+	"	-	6.2	-	"
M.C.P.	+	20.7	+	"	-	19.8	-	"	+	21.3	+	"	-	19.8	-	"
Wrist	+	17.8	++	"	-	16.8	-	"	+	18.0	++	"	-	16.7	-	"

Swelling = Circumference in cms.

Table 2.

Course of jaundice, effect on arthritis and E.S.R., and liver function tests (Case 1).

Date	Per 100 ml. of plasma					Van den Bergh	Urine benzoic ac. g. in 4 hr.	Cephalin-cholesterol flocculation	E.S.R. mm.	Remarks
	g.			mg.						
	Alb.	Glob.	Fib.	Laevulose	Bilirubin					
17.8.44.	..	..	..	..	0.4	Ind.	3.86	-ve	16	Inoculation 1 c.c. of serum.
24.8.44.	..	..	..	..	Nil	..	3.75	-ve	..	Joints active.
31.8.44.	..	..	..	..	0.3	Ind.	3.77	-ve	..	Joints active.
11.9.44.	..	..	..	..	0.2	Ind.	3.56	-ve	..	Joints active.
2.10.44.	..	..	..	..	0.4	Ind.	3.47	-ve	..	Joints active.
9.10.44.	..	..	..	..	0.3	Ind.	3.57	-ve	..	Joints active.
11.10.44.	..	..	..	..	0.2	Ind.	..	-ve	..	Nausea. Epigastric discomfort. Joints active.
12.10.44.	..	..	..	..	0.3	Ind.	..	-ve	..	Unchanged.
16.10.44.	..	..	..	..	0.3	Ind.	3.63	-ve	..	Unchanged.
17.10.44.	..	..	..	..	0.3	Ind.	..	-ve	..	Complete anorexia for 2 days. Joints unchanged.
18.10.44.	3.80	2.59	0.50	16.2	1.3	D.D.	..	++++	..	Fever. Bilirubin in urine. Joints less painful.

Table 2. (Continued)

Date	Per 100 ml. of plasma					Van den Bergh	Urine benzoic ac. g. in 4 hr.	Cephalin-cholesterol flocculation	E.S.R. mm.	Remarks
	g.			mg.						
	Alb.	Glob.	Fib.	Laevulose	Bilirubin					
19.10.44.	..	..	..	..	2.7	D.D.	1.60	..	..	Joints free from pain.
20.10.44.	..	..	..	..	4.2	Bi.	..	++++	..	Joints free from pain.
21.10.44.	..	..	..	..	4.8	Bi.	..	..	..	Joints free from pain.
22.10.44.	..	..	..	..	5.3	Bi.	..	..	..	Joints free from pain.
23.10.44.	..	..	..	..	6.4	Bi.	..	..	..	Joints free from pain.
24.10.44.	..	..	..	..	6.0	Bi.	..	..	..	Joints free from pain.
25.10.44.	2.93	2.95	0.50	23.2	9.0	Bi.	vom.	++++	2	Joints normal.
26.10.44.	..	..	..	..	7.2	Bi.	..	..	..	Joints normal.
27.10.44.	..	..	..	..	8.0	Bi.	..	..	..	Joints normal.
28.10.44.	..	..	..	..	9.0	Bi.	..	..	..	Joints normal.
30.10.44.	..	..	..	..	12.5	Bi.	..	..	..	Joints normal.
31.10.44.	..	..	..	..	13.0	Bi.	..	..	..	Joints normal.
2.11.44.	3.61	2.81	0.39	26.0	12.5	Bi.	vom.	++++	..	Joints normal.
4.11.44.	..	..	..	..	17.0	Bi.	..	..	..	Joints normal.

Table 2. (Continued)

Date	Per 100 ml. of plasma					Van den Bergh	Urine benzoic ac. g. in 4 hr.	Cephalin-cholesterol flocculation	E.S.R. mm.	Remarks
	g.			mg.						
	Alb.	Glob.	Fib.	Laevulose	Bilirubin					
6.11.44.	..	..	..	..	15.0	Bi.	..	..	..	Joints normal.
8.11.44.	..	..	..	..	15.0	Bi.	..	+++	..	Joints normal.
10.11.44.	..	..	..	..	11.0	Bi.	..	++	..	Joints normal.
13.11.44.	..	..	..	..	5.0	Bi.	..	..	..	Joints normal.
15.11.44.	4.13	4.28	0.58	13.6	4.8	D.D.	2.84	+	..	Joints normal.
17.11.44.	..	..	..	..	3.5	D.D.	..	..	..	Joints normal.
20.11.44.	..	..	..	..	2.7	D.D.	..	..	..	Joints normal.
23.11.44.	4.10	3.68	0.58	19.6	2.4	D.D.	..	-ve	..	Joints normal.
27.11.44.	..	..	..	..	1.6	D.D.	3.19	-ve	..	Joints normal.
4.12.44.	..	..	..	..	1.3	D.D.	2.89	-ve	..	Joints normal.
18.12.44.	4.32	2.92	0.43	..	0.7	D.D.	2.21	-ve	..	Joints normal.
8.1.45.	..	..	..	..	0.2	Ind.	3.59	-ve	..	Joints normal.
27.1.45.	4.05	2.69	0.37	13.3	0.2	Ind.	..	-ve	..	Joints normal.
19.2.45.	..	..	..	..	0.2	Ind.	..	..	14	Fingers painful.
25.6.45.	3.94	3.59	0.44	14.5	0.2	Ind.	3.41	-ve	..	Joints as before hepatitis.

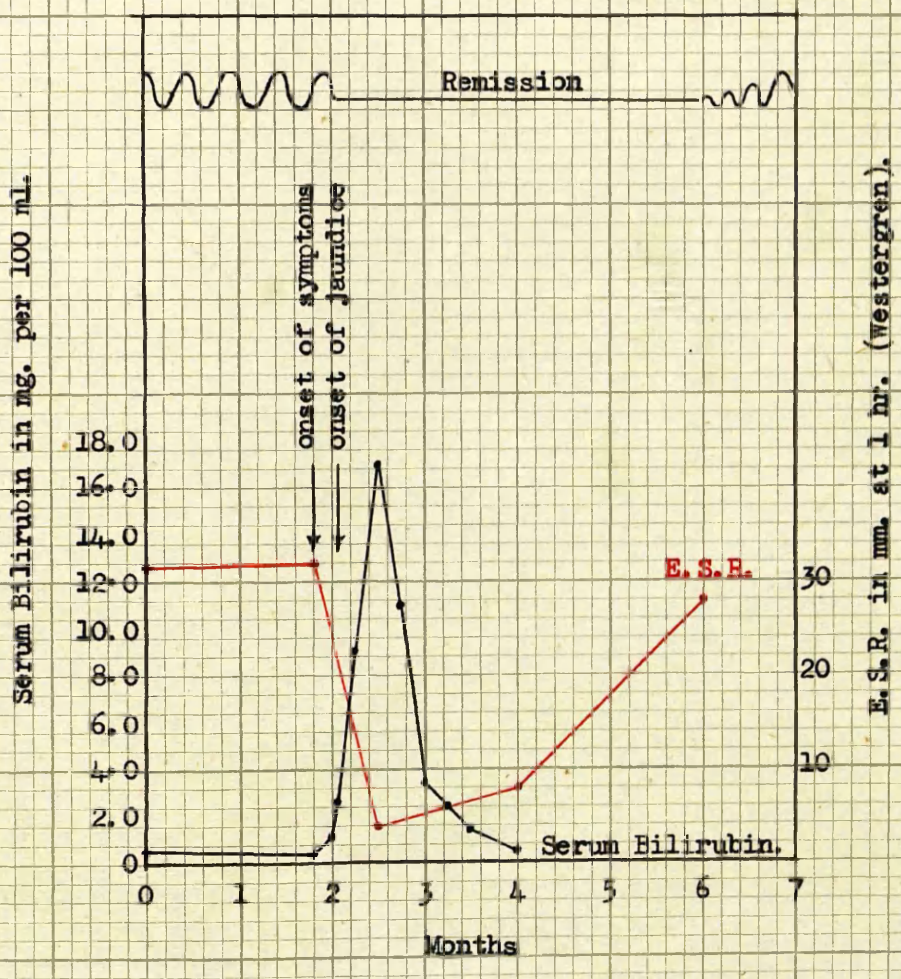
During the pre-icteric stage the E.S.R. was 16 mm., in the first week of jaundice there was an abrupt fall to 2 mm., and two months after recovery it had risen again to 14 mm.

In rheumatoid arthritis the E.S.R. generally provides an index of the activity of the disease process. In infective hepatitis, however, it has been shown that the E.S.R. is higher in the pre- and post-icteric stages of the disease than it is when jaundice is present (Wood, 1945; Miles, 1945). It is therefore quite probable that, when a patient with rheumatoid arthritis develops infective hepatitis, the E.S.R. no longer reflects the joint condition alone. Gardner et al. (1945) observed that in some of their cases of induced infective hepatitis in rheumatoid arthritis, the fall in the E.S.R. was not apparently related to changes in the clinical status of the rheumatoid arthritis. The early fall occurred in patients who failed to benefit from the intercurrent jaundice, as well as in those who obtained relief. Somewhat similar changes in the E.S.R. have been observed in tuberculous patients who develop infective hepatitis. Penman (1943) noticed a remarkable fall in the E.S.R. in patients in a sanatorium in which there was an epidemic of infective hepatitis.

In the case of the patient recorded above it would appear that the changes in the E.S.R. and the clinical activity of the rheumatoid arthritis were definitely related to one another. Figure 1 shows the relation between the E.S.R., serum bilirubin and the temporary remission of the rheumatoid arthritis.

Fig. 1.

To Show the Relation Between E.S.R., Serum Bilirubin and the Temporary Remission of the Rheumatoid Arthritis.



Case 1.

Case 2. The patient, a woman of 42, came under my care in September, 1943, with the history of pain, swelling and stiffness of the proximal interphalangeal joints of the fingers of both hands, and of both knees, and of pain in the wrists, elbows, shoulders and feet of 2 years' duration. She was able to do light housework. Clinically, she had a mild rheumatoid arthritis. Erythrocyte sedimentation rate was 12 mm. (Westergren). Patient was given two courses of myocrisin and intensive physiotherapy, but the arthritis remained unchanged. E.S.R. was still 12 mm.

The patient was again seen on 17th August, 1944, when she presented the following picture. There was some pain, stiffness and a little swelling of the finger joints, wrists and knees, and some fibrositic pain in the back (table 3). E.S.R. was 10 mm. Patient was given 0.5 c.c. of serum subcutaneously. During the following two months the joint condition remained unchanged. Sixty days after the injection she developed nausea and epigastric discomfort. These symptoms became progressively more marked and there was frequent vomiting. On the seventieth day the liver was tender and palpable one and a half finger-breadths below the costal margin, and she was admitted to hospital. The plasma bilirubin was 1.0 mg. per 100 ml. Next day the liver was larger, and there was jaundice, the plasma bilirubin reaching a maximum of 14.0 mg. per 100 ml. on the twenty-sixth day of illness. Considerable subjective improvement in the joints coincided with the development of jaundice. Thirteen days from the onset of the symptoms of hepatitis diminution in pain and stiffness was said to be considerable, and swelling had greatly lessened, being confined to the right middle finger, metacarpo-phalangeal joints of right hand and right knee (table 3). E.S.R. was 9 mm. The jaundice persisted for $2\frac{1}{2}$ months, and during this period, apart from occasional twinges of pain, analgesia was complete, although the above-mentioned joints continued to show a slight degree of swelling. Two months later, however, the arthritis became active again and six months after the onset of jaundice the joints were back to the pre-icteric state. E.S.R. was 11 mm. The course of the jaundice, its effect on the arthritis and the liver function tests are indicated in table 4.

As in case 1, the analgesic effect of jaundice on rheumatoid arthritis was demonstrated, though less completely, in this instance. Before the induction of jaundice the patient was suffering from a mild degree of arthritis with pain, swelling and stiffness of the finger joints, wrists and knees. Analgesia commenced on the day the jaundice made its appearance, and after two weeks it was complete, although later in the

Table 3.

Condition of affected joints before and two weeks after onset of jaundice

Joints	Right								Left							
	Before				After				Before				After			
	Swelling		Pain	Movement	Swelling		Pain	Movement	Swelling		Pain	Movement	Swelling		Pain	Movement
		cms.				cms.				cms.				cms.		
Thumb I.P.	+	6.6	+	Stiff	-	6.5	-	Free	+	6.6	+	Stiff	-	6.5	-	Free
1st P.I.P.	+	6.5	+	"	-	6.4	-	"	+	6.4	+	"	-	6.3	-	"
2nd P.I.P.	+	6.7	+	"	±	6.6	-	"	+	6.6	+	"	-	6.5	-	"
3rd P.I.P.	+	6.1	+	"	-	6.0	-	"	+	6.0	+	"	-	5.9	-	"
4th P.I.P.	+	5.5	+	"	-	5.3	-	"	+	5.4	+	"	-	5.3	-	"
M.C.P.	+	19.9	+	"	±	19.6	-	"	+	19.6	+	"	-	19.4	-	"
Wrist	+	16.7	+	"	-	16.5	-	"	+	16.5	+	"	-	16.4	-	"
Knee	+	38.5	+	"	∓	37.0	-	"	+	37.0	+	"	-	36.2	-	"

Swelling = circumference in cms.

Table 4.

Course of jaundice, effect on arthritis and E.S.R., and liver function tests (Case 2).

Date	Per 100 ml. of plasma					Van den Bergh	Urine benzoic ac. g. in 4 hr.	Cephalin-cholesterol flocculation	E.S.R. mm.	Remarks
	g.			mg.						
	Alb.	Glob.	Fib.	Laevulose	Bilirubin					
17.8.44.	..	..	..	..	0.2	Ind.	3.26	-ve	10	Inoculation 0.5 c.c. of serum.
28.8.44.	..	..	..	..	..	..	3.03	..	..	Joints active.
11.9.44.	..	..	..	..	0.3	Ind.	3.32	-ve	..	Joints active.
18.9.44.	..	..	..	..	0.3	Ind.	..	-ve	..	Joints active.
2.10.44.	..	..	..	..	0.4	Ind.	3.00	-ve	..	Joints active.
9.10.44.	..	..	..	..	0.4	Ind.	..	-ve	..	Joints active.
16.10.44.	..	..	..	..	0.2	Ind.	2.87	+++	..	Squeamish for three days. Joints active.
23.10.44.	..	..	..	..	1.4	D.D.	..	+++	..	Anorexia - epigastric discomfort.
24.10.44.	..	..	..	..	2.3	D.D.	..	+++	..	Joints improved.
25.10.44.	3.79	2.37	0.32	vom.	1.4	D.D.	vom.	++++	..	Joints improved.
26.10.44.	..	..	..	..	1.8	D.D.	..	..	9	Joints much improved.
27.10.44.	..	..	..	..	3.0	D.D.	..	..	..	Joints much improved.
28.10.44.	..	..	..	..	3.5	D.D.	..	..	..	Joints much improved.

Table 4. (Continued)

Date	Per 100 ml. of plasma					Van den Bergh	Urine benzoic ac. g. in 4 hr.	Cephalin-cholesterol flocculation	E.S.R. mm.	Remarks
	g.			mg.						
	Alb.	Glob.	Fib.	Laevulose	Bilirubin					
30.10.44.	..	..	..	..	6.0	Bi.	..	..	..	Joints much improved.
31.10.44.	..	..	..	..	7.0	Bi.	..	..	..	Joints much improved.
2.11.44.	3.14	3.84	0.52	vom.	12.5	Bi.	vom.	++++	..	Joints much improved.
4.11.44.	..	..	..	..	13.5	Bi.	..	..	..	Joints much improved.
6.11.44.	..	..	..	..	13.0	Bi.	..	..	..	Joints much improved.
8.11.44.	..	..	..	..	14.0	Bi.	..	++++	..	Joints much improved.
10.11.44.	..	..	..	..	12.0	Bi.	..	++++	..	Joints much improved.
13.11.44.	..	..	..	..	11.0	Bi.	..	..	..	Joints much improved.
16.11.44.	..	..	..	..	12.5	Bi.	..	++++	..	Joints much improved.
20.11.44.	..	..	..	..	8.0	D.D.	..	++++	..	Joints much improved.
22.11.44.	..	..	..	..	5.0	D.D.	..	++++	..	Joints much improved.
24.11.44.	..	..	..	..	3.5	D.D.	..	..	..	Joints much improved.
27.11.44.	..	..	..	..	3.0	D.D.	..	++++	..	Joints much improved.
30.11.44.	4.51	2.42	0.58	vom.	3.0	D.D.	vom.	..	..	Joints much improved.
2.12.44.	..	..	..	..	2.0	D.D.	..	++++	..	Joints much improved.
4.12.44.	..	..	..	..	4.5	Bi.	2.42	+++	..	Joints much improved.
5.12.44.	..	..	..	..	1.3	D.D.	..	+++	..	Joints much improved.
6.12.44.	..	..	..	..	1.8	D.D.	..	..	..	Joints much improved.
18.12.44.	3.92	2.08	0.29	..	0.8	..	..	+++	..	Joints much improved.
8.1.45.	..	..	..	..	0.4	Ind.	3.24	+++	..	Joints much improved.
25.6.45.	3.69	3.76	0.16	10.7	0.2	..	3.02	+++	11	Joints as before hepatitis.

course of the jaundice occasional twinges of pain were felt in the right hand and knee. The swelling rapidly subsided, but never entirely disappeared, the right middle finger and metacarpo-phalangeal joints, and the right knee remaining a little puffy throughout the illness. The jaundice persisted for two and a half months, during which time, and for a further period of two months, the improvement in the joints was maintained. Thereafter, the arthritis slowly relapsed, and six months after the onset of jaundice the joint involvement was as marked as in the pre-icteric stage.

Cases 3 and 4 of this group, a man of 40 and a woman of 39, received 1.0 and 0.5 c.c. serum subcutaneously, respectively. They were observed over a period of two years, and did not show any clinical evidence of hepatitis, rise in plasma bilirubin or alteration in the tests of hepatic function. During this time the course of the rheumatoid arthritis was unaffected.

Group b. Six patients in this group received 0.5 or 1.0 c.c. of serum subcutaneously from a patient with acute infective hepatitis in the first day of jaundice. They also were observed for a period of two years, and did not show any evidence of hepatitis or relief of joint symptoms.

11. Inoculation with Urine. Nineteen volunteers with rheumatoid arthritis were inoculated with urine obtained from six male patients with acute infective hepatitis on the first day of jaundice. The pooled urine was used after standing for seven days at - 20°C., and after forty-eight hours transit in a thermos flask. Five c.c. of the urine were swallowed, and four c.c. were sprayed into the nares and pharynx of each patient. The same plan of observation was followed as in the patients who received serum - i.e., the patients were questioned and examined

weekly for three months, thereafter on every alternate week, and were told to report at once should anorexia, nausea or vomiting develop. Two of the nineteen patients reported with epigastric pain and vomiting, but on admission to hospital they were found to have gastritis which cleared up rapidly. Otherwise, none of this group showed any evidence of hepatitis, clinical or biochemical, up to two years from the time of inoculation; nor was there any appreciable change in the rheumatoid arthritis during the period of observation.

Discussion

The natural course of rheumatoid arthritis is so variable that the assessment of the value of any remedy which produces only temporary relief is a difficult task. The fact remains, however, that of the twenty-nine patients in this investigation, who received either serum or urine from cases of infective hepatitis, only two had a remission of the arthritis, complete in one and marked in the other, and that these were the two patients who were successfully inoculated. This was also the experience of MacCallum and Bradley (1944), and Gardner and her co-workers (1945), both of whose investigations ran concurrently with the present one, under the auspices of the Medical Research Council. In addition, further evidence of the temporary benefit of jaundice in rheumatoid arthritis was obtained from my experience with two of the three patients with active arthritis who developed spontaneous jaundice.

It is obvious, therefore, both in the spontaneous and artificially produced disease, that some change which occurs during the course of

infective hepatitis must exert a beneficial effect on the arthritis, but as to its nature we are as yet unaware. Hench (1938), who observed the phenomenon in many of his own patients, tentatively suggested that the improvement obtained might be related to the intensity of the jaundice, and that below the "zone of therapeutic effectiveness", the lower limit of which he took as 8 mg. of serum bilirubin per 100 ml., little improvement was to be expected. My own results tend to support this view, but naturally are too few in number to be of any significance in this connection. Gardner and her colleagues (1945), on the other hand, did not find any connection between the depth of jaundice and the degree of remission of joint symptoms, and concluded that the jaundice owed its effect to something more than the mere accumulation of bile in the blood.

The view has been expressed by Thompson and Wyatt (1938) that the phenomenon may be due to an increase in bile salts in the blood during the icteric stage. Recent work (Sherlock and Walshe, 1945), however, has shown that the blood level of free and conjugated cholic acid in infective hepatitis is very little raised.

As previously mentioned, the changes in the E.S.R. which occur in infective hepatitis have attracted much attention (Penman, 1943; Wood, 1945; Miles, 1945). It has been shown that the E.S.R. is higher in the pre- and post-icteric stages than it is when jaundice is present. Miles (1945) suggested that an increase in bile salts might cause an inhibition of the E.S.R. in the acute phase of the disease,

and was able to demonstrate the change by adding various dilutions of a bile-salt solution to samples of oxalated blood. Sherlock and Walshe (1945), however, did not support this view, as they found that the bile-salts in infective hepatitis never approached the levels required to produce the retardation obtained in the in vitro experiments of Miles. It is known, too, that the E.S.R. is affected by small changes in the plasma proteins (Fraser and Rennie, 1941). As shown in tables 2 and 4 there is a considerable, though temporary, disturbance of the plasma proteins during the icteric stage of infective hepatitis. It may be that this upset of the proteins is able in some way to exert a beneficial effect on the affected joints. Another possibility is that some, as yet unknown, substance liberated from the damaged liver is responsible for the phenomenon. These are at present matters for conjecture, but it is hoped that further research will reveal nature's secret.

In conclusion, one can say that the remissions in rheumatoid arthritis brought about by an attack of jaundice are striking, and show that reversible changes in this disease can be expected, especially in the early stages. It is not a form of treatment, however, which can be recommended for rheumatoid arthritis, as the relief obtained is only short-lived and does not justify the use of such a drastic measure.

It may be permissible to mention, as a foot-note, that an opportunity was afforded in this investigation of studying liver function tests before, at the very onset and during the course of the hepatitis.

The tests were carried out at frequent intervals, on all cases, and marked temporary departure from the normal was observed in the two patients who developed jaundice (tables 2 and 4).

Summary

Part IV opens with a review of the literature on the beneficial effect of spontaneous jaundice on rheumatoid arthritis, and on the various unsuccessful attempts to reproduce nature's phenomenon by artificial means.

This is followed by my personal observations on the effect of spontaneous and induced jaundice in rheumatoid arthritis.

Case reports have been given of four patients who developed spontaneous jaundice. Complete remission of the joint symptoms was observed in two of the patients, but a relapse occurred $3\frac{1}{2}$ months later in one case. In the other, the joints remained symptom-free until the patient's death one month after the onset of jaundice.

Case reports of two patients with rheumatoid arthritis in whom jaundice was induced by the subcutaneous injection of serum from a case of acute infective hepatitis have been recorded. Temporary relief of the joint symptoms, complete in one and partial in the other, was obtained.

A brief discussion then follows on the various theories that have been put forward to explain the phenomenon, and the conclusion is reached that, while most observers agree that jaundice has a beneficial effect on rheumatoid arthritis, the mechanism by which it brings this about is still unknown.

REFERENCES

PART 1.

ON THE INFECTIVE NATURE OF RHEUMATOID ARTHRITIS

Angevine, D.M., Rothbard, S., and Cecil, R.L. (1940): Proc. Amer. Rheumatism Ass., J. Amer. med. Ass., 115, 2111.

Ashworth, O.O. (1932): Virg. med. Month., 59, 452.

Bannatyne, G.A. (1896): Rheumatoid Arthritis: Its Pathology, Morbid Anatomy and Treatment, London.

Bannatyne, G.A., and Lindsay, J. (1911): Brit. med. J., 1, 192.

Bannatyne, G.A., Wohlman, A.S., and Blaxall, F.R. (1896): Lancet, 1, 1120.

Bernhardt, H., and Hench, P.S. (1931): J. infect. Dis., 49, 489.

Bouchard, C. (1891): Semaine Méd., 11, 387.

Callow, B.R. (1933): J. infect. Dis., 52, 279.

Cecil, R.L. (1933): J. Amer. med. Ass., 100, 1220.

Cecil, R.L. (1940): ibid., 115, 2111.

Cecil, R.L., Nicholls, E.E., and Stainsby, W.J. (1929): Arch. intern. Med., 43, 571.

Cecil, R.L., Nicholls, E.E., and Stainsby, W.J. (1931): Amer. J. med. Sci., 181, 12.

Clawson, B.J. (1925): J. infect. Dis., 36, 444.

Clawson, B.J., Wetherby, M., Hilbert, E.H., and Hilliboe, H.E. (1932): Amer. J. med. Sci., 184, 758.

Coburn, A.F. (1936): Int. Clinics, 4, 49.

Coburn, A.F., and Pauli, R.H. (1935): J. exp. Med., 62, 129.

Crowe, H.W. (1913): Brit. med. J., 2, 1435.

Crowe, H.W. (1930): J. Lab. clin. Med., 15, 1072.

Dawson, M.H., Olmstead, M., and Boots, R.H. (1932): Arch. intern. Med., 49, 173.

Gray, J.W. (1940): Proc. Amer. Rheumatism Ass., J. Amer. med. Ass., 115, 2111.

Gray, J.W., and Gowen, C.H. (1931): Amer. J. med. Sci., 182, 682.

Greene, H.M. (1912): New York med. J., 2, 421.

Hadjopoulos, L.G., and Burbank, R. (1927): J. Bone and Joint Surg., 25, 278.

Jones, D.W.C. (1913): Brit. med. J., 1, 1047.

Jordon, E.P., and Boland, J.P. (1930): J. infect. Dis., 46, 148.

Key, A.J. (1935): J. Amer. med. Ass., 105, 1378.

Klugh, G.F. (1931): South. med. J., 24, 706.

Kracke, R.R. (1931): ibid., 24, 708.

Lichtman, S.S., and Gross, L. (1932): Arch. intern. Med., 49, 1078.

McCrae, T. (1904): J. Amer. med. Ass., 42, 1.

McEwen, C., Alexander, R.C., and Bunim, J.J. (1936): J. Lab. clin. Med., 21, 453.

Margolis, H.M., and Dorsey, A.H.E. (1930): J. infect. Dis., 46, 442.

Moon, V.H., and Edwards, S.R. (1917): J. infect. Dis., 21, 154.

Munro, J.M.H. (1922): Lancet, 1, 938.

Munro, J.M.H. (1925): Brit. med. J., 2, 598.

Nye, R.N., and Waxelbaum, E.A. (1930): J. exp. Med., 52, 885.

Okell, C.C., and Elliott, S.D. (1935): Lancet, 2, 869.

Richards, J.H. (1920): J. Bact., 5, 511.

Rosenow, E.C. (1914): J. Amer. med. Ass., 63, 903.

Rosenow, E.C., quoted by Margolis and Dorsey (1930): J. infect. Dis., 46, 442.

Rowlands, M.J. (1916): Lancet, 1, 133.

Rowlands, M.J. (1927): Proc. R. Soc. Med., 20, 1711.

Schüller, M. (1893): Berl. klin. Wchnschr., 30, 865.

Shands, A.R., Jr. (1930): South. med. J., 23, 818.

Steinfeld, F. (1932): (orig.) Zbl. Bakt., 123, 414.

Strauss, A. (1932): Virg. med. Month., 58, 801.

Surányi, L., and Forró, E. (1928): Klin. Wschr., 7, 453.

Topley, W.W.C., and Wilson, G.S. (1946): Principles of Bacteriology and Immunity, 2, 1002.

Traut, E.F. (1933): J. infect. Dis., 52, 230.

Wainwright, C.W. (1934): J. Amer. med. Ass., 103, 1357.

Wetherby, M., and Clawson, B.J. (1932): Arch. intern. Med., 49, 303.

PART II.

ON THE BLOOD CHEMISTRY IN RHEUMATOID ARTHRITIS

Aldred-Brown, G.R.P., and Munro, J.M.R. (1935): Quart. J. Med., 28, 269.

Baggenstoss, A.H., and Rosenberg, E.F. (1943): Arch. Path., 35, 503.

Carter, A.B., and Maclagan, N.F. (1946): Brit. med. J., 2, 80.

Davis, J.S., Jr. (1935): J. Lab. clin. Med., 21, 478.

Dick, A. (1945): Brit. med. J., 1, 182.

Enders, J.F. (1944): J. clin. Invest., 23, 510.

Fahraeus, R. (1921): Acta. med. Scand., 55, 1.

Fraser, T.N., and Rennie, J.B. (1941): Brit. J. exp. Path., 22, 81.

Gray, S.J. (1942): Proc. Soc. exper. Biol., 51, 400.

Hanger, F.M. (1939): J. clin. Invest., 18, 261.

Hawke, P.B., and Bergeim, O. (1938): Practical Physiological Chemistry, London.

Howe, P.E. (1921): J. biol. Chem., 49, 109.

Kabat, E.A., Hanger, F.M., Moore, D.H., and Landow, H. (1943): J. clin. Invest., 22, 563.

Lange, C. (1912): Berl. klin. Wschr., 49, 897.

Lister's Tables (1926): Finlayson's Clinical Manual.

Maclagan, N.F. (1944): Brit. J. exp. Path., 25, 15.

Maizels, M. (1946): Lancet, 2, 451.

Mateer, J.G., Baltz, J.I., Marion, D.F., and Hollands, R.A. (1942): Amer. J. digest. Dis., 9, 13.

Pohle, F.J., and Stewart, J.K. (1941): J. clin. Invest., 20, 241.

Rawls, W.B., Weiss, S., and Collins, V.L. (1937): Ann. intern. Med., 10, 1021.

Schull, C.W., Bach, T.F., and Pemberton, R. (1939): ibid., 12, 1463.

Sherlock, S.P.V. (1946): J. Path. Bact., 58, 523.

Swedin, B., and Bengtsson, G. (1944): Acta med. Scand., 119, 426.

Sweet, W.H., Gray, S.J., and Allen, J.G. (1941): J. Amer. med. Ass., 117, 1613.

Thannhauser, J.E., and Andersen, E. (1921): Dtsch. Arch. klin. Med., 137, 179.

Westergren, A. (1920): Acta med. Scand., 54, 247.

Westergren, A., Theorell, H., and Widestrom, G. (1931): Z. ges. exp. Med., 78, 668.

Zsigmondy, R. (1901): Ztschr. f. anal. Chem., 40, 697, quoted by Gray, S.J. (1942): Proc. Soc. exper. Biol., 51, 400.

PART III.

ON GOLD THERAPY IN RHEUMATOID ARTHRITIS

Bach, F. (1936): St. Bart's Hosp. J., 43, 206.

Bagenstoss, A.H., and Rosenberg, E.F. (1941): Arch. int. Med., 67, 241.

Baylis, T.B., and Hall, M.G. (1943): New England J. Med., 228, 418.

Benedict, S.R. (1922): J. biol. Chem., 51, 187.

Benedict, S.R. (1922): ibid., 54, 233.

Block, W.D., and Buchanan, O.H. (1940): J. biol. Chem., 136, 379.

Buckley, C.W. (1934): Brit. med. J., 1, 469.

Cecil, R.L., Kammerer, W.H., and De Prume, F.J. (1941): Trans. Ass. Am. Phys., 56, 339.

Cecil, R.L., Kammerer, W.H., and De Prume, F.J. (1942): Ann. intern. Med., 16, 811.

Comroe, B.I. (1945): Arthritis and Allied Conditions, London.

Copeman, W.S.C., and Tegner, W. (1937): Lancet, 1, 554.

Crawford, J.C.C. (1937): Ulster med. J., 6, 29.

Crosby, G.J.V. (1936): Lancet, 1, 1463.

Dawson, M.H., Boots, R.H., and Tyson, T.L. (1941): Trans. Ass. Amer. Phys., 56, 330.

Ellman, P., and Lawrence, J.S. (1935): Brit. med. J., 2, 622.

Ellman, P., Lawrence, J.S., and Thorold, G.P. (1940): Brit. med. J., 2, 314.

Feldt, A. (1917): Berl. klin. Wschr., 54, 1111.

Feldt, A. (1927): Klin. Wschr., 6, 1136.

Feldt, A. (1930): Med. Welt., 4, 437.

Forestier, J. (1929): Bull. Soc. méd. Hôp. Paris, 45, 323.

Forestier, J. (1935): J. Lab. clin. Med., 20, 827.

Freyberg, R.H., Block, W.D., and Wells, G.S. (1942): Clinics, 1, 537.

Gold, H. (1941): New York State med. J., 41, 688.

Graham, J.W., and Fletcher, A.A. (1943): Canad. med. Ass. J., 49, 483.

Hartfall, S.J., and Garland, H.G. (1935): Lancet, 2, 8.

Hartfall, S.J., and Garland, H.G. (1936): ibid., 1, 1459.

Hartfall, S.J., Garland, H.G., and Goldie, W. (1937): ibid., 2, 784 and 838.

Hartung, E.F., and Cotter, J. (1941): J. Lab. clin. Med., 26, 1274.

Hedenius, I. (1926): Acta med. Scand. Suppt. No 16, 313.

Junker (1913): Munch. med. Wschr., 60, 1376.

Key, J.A., Rosenfeld, H., and Tjoflat, O.E. (1939): J. Bone and Joint Surg., 21, 339.

Kling, D.H., Sashin, D., and Spancock, J. (1939): J. Lab. clin. Med., 24, 1241.

Koch, R. (1890): Dtsch. med. Wschr., 16, 756.

Landé, K. (1927): Munch. med. Wschr., 74, 1132.

Leiper, E.J.R. (1946): Brit. med. J., 2, 119.

Lewy, F.H., and Freund, R. (1926): Dtsch. med. Wschr., 52, 1857.

Lintz, R.M. (1941): J. Lab. clin. Med., 26, 1629.

McIntosh, J.F., Möller, E., and Van Slyke, D.D. (1928): J. clin. Invest., 6, 427 and 467.

Möllgaard, H. (1924): Chemotherapy of Tuberculosis, Kjobenhavn.

Oren, H. (1936): quoted by Rosenberg, E.F. (1942): Pro. Mayo Clin., 17, 264.

Parr, L.J.A., and Shipton, E.A. (1937): Med. J. Aust., 1, 864.

Pemberton, H.S. (1935): Lancet, 1, 1037.

Philips, R.T. (1936): New England J. Med., 214, 114.

Pick, E. (1927): Wien. klin. Wschr., 40, 1175.

Price, A.E., and Leichentritt, B. (1945): Ann. int. Med., 19, 70.

Rosenberg, E.F. (1942): Proc. Staff. Meet. Mayo Clin., 17, 264.

Rothbard, S., Angevine, D.M., and Cecil, R.L. (1941): J. Pharm. exp. Therap., 72, 164.

Sashin, D., Spanbock, J., and Kling, D.H. (1939): J. Bone and Joint Surg., 21, 723.

Schmidt, L. (1944): Brit. med. J., 1, 433.

Secher, K., and Gudiksen, E. (1935): Acta med. Scand., 86, 370.

Slot, G., and Deville, P.M. (1934): Lancet, 1, 73.

Snyder, R.G., and Traeger, C. (1943): New York State J. Med., 43, 245.

Snyder, R.G., Traeger, C., and Kelly, L. (1939): Ann. intern. Med., 12, 1672.

Sundelin, F. (1941): Acta med. Scand. Suppt., 117, 1.

Taylor, D. (1937): Canad. med. Ass. J., 36, 608.

Tegner, W. (1939): Proc. Staff. Meet. Mayo Clin., 14, 117.

Umber, F. (1929): Med. Welt., 3, 593 and 633.

Weiss, E., and English, O.S. (1943): Psychosomatic Medicine, Philadelphia.

Zimmer, A. (1930): Die Behandlung der rheumatischen Kraukheiten, Leipzig.

PART IV.

ON THE EFFECT OF JAUNDICE IN RHEUMATOID ARTHRITIS

Beaver, D.C., and Robertson, H.E. (1931): Amer. J. Path., 7, 237.

Borman, M.C. (1936): Wisconsin med. J., 35, 890.

Cameron, J.D.S. (1943): Quart. J. Med., 36, 139.

Comfort, M.W. (1932): Proc. Staff Meet. Mayo Clin., 7, 419.

Fraser, T.N. (1934): Brit. med. J., 2, 1195.

Fraser, T.N., and Rennie, J.B. (1941): Brit. J. exp. Path., 22, 81.

Gardner, F., Stewart, A. and McCallum, F.O. (1945): Brit. med. J., 2, 677.

Grigg, W.K., and Jacobsen, V.C. (1933): Ann. intern. Med., 6, 1280.

Hanger, F.M. (1939): J. clin. Invest., 18, 261.

Hartfall, S.J., Garland, H.G., and Goldie, W. (1937): Lancet, 2, 784 and 838.

Hawke, P.B., and Bergeim, O. (1938): Practical Physiological Chemistry, London.

Hench, P.S. (1933): J. Amer. med. Ass., 101, 1265.

Hench, P.S. (1934): Ann. intern. Med., 7, 1278.

Hench, P.S. (1938): Arch. intern. Med., 61, 451.

Howe, P.E. (1921): J. biol. Chem., 49, 109.

McCallum, F.O., and Bradley, W.H. (1944): Lancet, 2, 228.

Miles, J.A.R. (1945): Brit. med. J., 1, 767.

Parsons, L., and Harding, W.G., Jr. (1932): Ann. intern. Med., 6, 514.

Penman, A.C. (1943): Brit. med. J., 2, 760.

Probstein, J.G., and Londe, S. (1940): Ann. Surg., 111, 230.

Quick, A.J. (1936): Arch. intern. Med., 57, 544.

Rennie, J.B. (1943): Brit. J. exp. Path., 24, 26.

Rennie, J.B. (1945): Amer. J. med. Sci., 210, 18.

Sherlock, S.P.V., and Walshe, F. (1945), quoted by Gardner, F., Stewart, A., and McCallum, F.O. (1945): Brit. med. J., 2, 677.

Sidel, N., and Abrams, M.I. (1934): New England J. Med., 210, 181.

Still, G.F. (1897): Trans. Roy. med-chir. Soc., 80, 52.

Thannhauser, J.E., and Andersen, E. (1921): Dtsch. Arch. klin. Med., 137, 179.

Thompson, H.E., and Wyatt, B.L. (1938): Arch. int. Med., 61, 481.

Voegt, H. (1942): Münch. med. Wschr., 89, 76.

Voegt, H. (1942): Abst. Bull. Hyg., 17, 331.

Weir, J.F., and Jordan, F.M. (1930): Med. Clin. N. Amer., 13, 1439.

Weir, J.F., and Comfort, M.W. (1933): Arch. int. Med., 52, 685.

Wishart, J. (1903): Brit. med. J., 1, 252.

Wood, P. (1945): ibid, 1, 9.