THERAPEUTIC EFFECT OF INDUCED JAUNDICE IN RHEUMATOID ARTHRITIS

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It is an old observation that when patients suffering from rheumatoid arthritis develop jaundice there may be a remarkable improvement in the condition of the joints (Still, 1897; Wishart, 1903; Hench, 1938), but until jaundice could be induced without undue risk to life it was difficult to study this phenomenon systematically. Attempts to imitate the condition by the intravenous injection of bile salts and bilirubin (Thompson and Wyatt, 1938) failed to reproduce the effects observed in the naturally occurring disease, but in 1944 MacCallum and Bradley reported remissions in 6 patients who had been successfully inoculated with material from cases of infective hepatitis. Since then we have induced infective hepatitis and homologous serum jaundice in 29 patients. The present paper contains a report of the results obtained in these patients and in three of the patients referred to by MacCallum and Bradley who were under our care in Oxford.

Jaundice is not easy to induce and is not entirely without risk. Before accepting volunteers 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 courage and the present hopeless state of the rheumatoid subject that large numbers of patients were anxious to take part in the experiment. The work was carried out at several different centres, and, as it was impossible to foretell which patients would develop jaundice, only the simplest type of pilot investigation was undertaken. Our intention was to discover whether remissions in the joint condition occurred often enough to justify a more detailed study of the phenomenon at a later date.

From time to time batches of dried serum have produced jaundice when used for transfusion purposes. A small amount of such serum injected subcutaneously will produce jaundice in a high percentage of cases (Bradley, Loutit, and Maunsell, 1944). This method of inducing jaundice could have been used for all cases, but when planning the experiment it appeared to have two disadvantages. The first was the long incubation period, averaging nearly 100 days. The second was the fact that jaundice is sometimes unduly severe when the disease is induced in this way. At first, therefore, we attempted to transmit the disease with material from cases of infective hepatitis and, in order to discover the route with the shortest incubation period, we inoculated patients by the nasopharyngeal route as well as by parenteral injection. Unfortunately many of these attempts proved unsuccessful and only a small percentage of the patients developed jaundice. Later in the experiment we used icterogenic serum and induced jaundice in a high proportion of cases. The severity of the hepatitis produced in this way was no greater than in the previous cases, and the effect on the rheumatoid arthritis was essentially similar. Details of these experiments, in so far as they concern the transmissibility of infective hepatitis and homologous serum jaundice, will be discussed elsewhere.

All the patients had received other forms of treatment in the past. Several had responded to gold but had lately either become insensitive to this or had developed toxic reactions. Others had had spa treatment, vaccines, salicylates, or physiotherapy. So far as was possible only patients who had recently failed to obtain benefit from these treatments were included in the present investigation. At first no patient who had received gold injections during the previous six months was allowed to take part, but later this period was reduced to three months. After inoculation patients continued to have physiotherapy and aspirin, but no other treatment was allowed.

Details of the Investigation

The patients were all suffering from polyarticular arthritis of the rheumatoid type. They were arranged in four groups according to the classification of rheumatoid arthritis suggested by Sclater in 1943:—Group I: Periarticular swelling and stiffness, but only slight limitation of movement. Group II: Periarticular swelling and more marked limitation of movement than in Group I, but no evidence of ankylosis; still capable of employment. Group III: Fixation of joints and flexion deformities; either inability or great difficulty in continuing employment. Group IV: Gross deformities and severely crippled; usually bedridden and unable to walk.

Only 32 of the 312 patients inoculated developed jaundice. Ten were in Group I, five in Group II, eleven in Group III, and six in Group IV. Their ages ranged from 22 to 61 years, and there were 24 females and 7 males. The severity of the hepatitis induced was variable. In the mildest cases jaundice lasted only one week, and in the most severe it persisted for 45 days. The disease ran its usual course, and in most cases a few days of anorexia, vomiting, and low-grade pyrexia preceded the appearance of jaundice and biliuria. The liver became enlarged and tender in most cases, and in two the spleen was palpable. Persistent vomiting was a troublesome complication in some of the severely ill patients; fleeting erythematous rashes were seen and petechial haemorrhages occasionally occurred. Maximum serum bilirubin values ranged from 2 to 19 mg. per 100 c.cm. One patient had a recurrence of jaundice two months after her first attack; otherwise convalescence was uneventful.

All the patients who were inoculated were kept under observation for at least six months. During this time occasional minor fluctuations in the arthritis occurred among the subjects who failed to develop jaundice, and two patients had a genuine remission. This was ascribed by the patients to the inoculation they had received, but there was in fact no evidence to support this view. One remission may have been due to a recent course of gold injections. The other patient began to improve immediately after she received her inoculation.

In the cases successfully inoculated an interval which varied from 27 to 131 days elapsed between the day the inoculation was given and the day jaundice appeared. During the incubation period there was no radical change in the rheumatic

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condition, but with the appearance of jaundice dramatic improvement was noticed in many of the patients. In one instance this improvement began three days before jaundice was detected, in 8 it started on the first day, in 13 within the first ten days of jaundice, and in 3 after the first two weeks. One patient was exceptional in that all the affected joints became more painful during the attack of hepatitis, but immediately after recovery all pain and stiffness disappeared. She has remained free from symptoms since—a period of over three months.

The remissions, which were temporary, have been classified as follows:

A. Complete.—Ten patients became completely free from pain in all joints. Periarticular swelling disappeared and free movement was restored except where this was limited by permanent deformity.

B. Marked Improvement.—Eight patients became free from pain in many but not all affected joints. Periarticular swelling diminished and there was greatly increased mobility.

C. Slight Improvement.—Seven patients obtained some relief of pain and swelling with increased movement, but this was less marked than in Group B.

D. No Change.—In 7 patients the joint condition was unaltered.

In Groups A and B the amelioration in the joint condition was remarkable. Disappearance of pain and swelling was quickly followed by increase of power and range of movement in the affected joints. These changes were observed in both the larger and the smaller joints, but they were perhaps most pronounced in the fingers. One patient whose fingers had been locked for two years was able to move them on the third day of jaundice. Thereafter the swelling rapidly subsided, and by the sixth day she had full and painless movement of her fingers. Three other patients were able to wear their wedding-rings for the first time for several years. In Group C the joint changes were less obvious, but there was considerable subjective improvement. Two patients who had had constant pain and were unable to turn over in bed found that within a week of the onset of jaundice they could move freely and painlessly, and thereafter their general condition improved considerably. Details of the 32 cases are given in the accompanying Table.

The Results of Induced Jaundice in 32 Patients with Rheumatoid Arthritis. For Clue to the Roman Numerals recording the Rheumatic Status, see Text

Age and Sex	Duration of Rheumatoid Arthritis (years)	Rheumatoid Status (Sclater's Classification)	Period of Optimal Improvement (days)	Maximum Serum Bilirubin (mg. per 100 c.cm.)	Duration of Jaundice (days)	E.S.R. (mm. per hour)		
						Pre-icteric	During Jaundice	After Recovery
(A) Complete remission:								
41 F	14	I	7	14	25	36	38	21
48 F	1	II	20	10	24	27	13	40
47 F	4-5	III	28	18	21	49	11	64
23 F	9	I	28	6	28	26	18	—
30 F	0.5	I	30	4.2	26	7	4	7
50 F	1	III	34	6.4	27	20	15	42
35 F	3.5	I	39	6.4	16	6	16	6
42 F	2.5	II	71	—	14	25	—	34
42 F	8	II	93	18	46	12	10	15
41 F	6	III	93+	2	21	18	—	24
(B) Considerable improvement:								
54 F	4	IV	20	6	16	32	19	77
32 F	0.6	I	23	10	23	60	8	25
22 F	3	I	30	5	7	8	—	—
56 M	12	IV	31	8	33	31	4	37
52 M	7	II	37	10	38	7	17	30
48 F	7	III	40	13	54	35	6	45
57 F	10	III	58	10	32	30	15	20
52 M	13	I	78	3	10	10	7	9
(C) Slight improvement:								
46 F	10	III	7	4	14	8	14	9
43 M	6	IV	25	12	18	42	8	25
58 F	7	IV	32	10	30	45	12	40
29 F	10	III	35	6	21	20	10	38
52 F	2	I	56	4.5	30	5	—	10
39 M	12	III	85	4	35	6	—	35
61 M	8	IV	154+	4.5	40	34	34	63
(D) No improvement:								
58 F	0.8	III	0	19	46	95	42	14
23 F	0.5	I	0	4	21	2	5	4
50 M	5-6	IV	0	15	40	25	10	38
29 F	7	I	0	8	14	13	10	10
38 F	8	II	0	4	12 and 7	23	35	—
58 F	10	III	0	6	30	20	—	—
43 F	10	I	0	3	7	—	42	37

The following case histories illustrate the changes observed.

Case I (Sclater Group II; Type A Remission)

Housewife aged 42. 1936:—Pain and swelling in ankles and shoulders. 1940:—All joints affected. Unable to work. Course of bee venom injections without improvement. 1943-4:—Gold therapy, with gradual improvement. Able to do light housework.

Dec. 20, 1944.—All joints painful. Swollen interphalangeal joints. Grip weak. Extension of elbows limited by 50°. Knees swollen. Flexion to 45° only. Ankles swollen; only 5-10° of movement. E.S.R., 12 mm. Serum bilirubin, 0.25 mg. per 100 c.cm. Inoculation with nasal washings from case of homologous serum jaundice.

March 30, 1945.—Anorexia, vomiting, icteric sclera. Joint condition unchanged.

April 8.—Appetite improved. Joints less painful. No swelling of fingers; grip. Elbows—full extension. Knees still painful; flexion to 80°. Ankles—no swelling; full range of movement. E.S.R., 10 mm. Serum bilirubin, 18 mg. per 100 c.cm.

April 12.—All joints free from pain and swelling. Knee flexion to 90°. Other joints—full range of movement.

June 18.—Well. Able to do all her own housework. Full painless movement of all joints.

July 16.—Recurrence of pain, with swelling and limitation of movement in one finger of left hand; otherwise all joints remain satisfactory. E.S.R., 15 mm.

Case II (Sclater Group III; Type A Remission)

Housewife aged 47. 1940:—Pain and swelling in feet and hands. 1942:—Exacerbation, with involvement of all joints. Temporary remission following gold. Two further courses of gold, with no improvement. Unable to work for three years.

Case II. Diagram to show the relation between the E.S.R., serum bilirubin, and the temporary remission of the rheumatoid arthritis.

Nov. 7, 1944.—Ambulance case. Walks a few steps with difficulty. Gross flexion deformity of hands; swollen wrists, minimal movement of these joints. Feet swollen and painful. Moderate limitation of movement at shoulders, elbows, and knees. Right knee swollen. E.S.R., 49 mm. in 1 hour. Plasma bilirubin, 0.2 mg. per 100 c.cm. 0.5 c.cm. icterogenic serum given by subcutaneous injection.

Dec. 28.—Severe backache. Nausea. Non-irritating rash on arms and legs. Joint condition unchanged. E.S.R., 35 mm. Bilirubin, 0.5 mg. per 100 c.cm.

Jan. 2, 1945.—Vomiting, giddiness, and abdominal pain. Rash fading. Jaundiced sclera. Liver palpable and tender. Movements in right hand improved. Onset of pain in temporo-mandibular joints. Other joints i.s.q. E.S.R., 11 mm. Bilirubin, 6 mg. per 100 c.cm.

Jan. 5.—Lying comfortably in bed. No nausea. Appetite good. Jaundiced. Considerable relief of pain in all joints except right knee and jaw. Increased range of movement in fingers. No improvement of wrist movements. Bilirubin, 16 mg. per 100 c.cm.

Jan. 16.—Feels well. Still jaundiced. No pain except in right knee. Moves easily in bed. Full range of movement in hands and wrists. No visible swelling in any joint. E.S.R., 50 mm. Bilirubin, 18 mg. per 100 c.cm.

Jan. 23.—No symptoms. Jaundice almost faded. Complete relief of pain. Walking freely and using hands. Full range of movement in all joints. E.S.R., 52 mm. Bilirubin, 3 mg. per 100 c.cm.

Feb. 23.—Home doing housework for 5 weeks. Slight recurrence of pain in finger-joints 3 weeks ago. Since then pains in neck and left arm. Still free from pain in legs and shoulders. E.S.R., 52 mm.

April 25.—Steady deterioration in joint condition during last 2 months. Now no better than before jaundice. E.S.R., 64 mm.

Case III (Sclater Group IV; Type C Remission)

Ex-coalminer aged 56. 1932:—Pain and stiffness in the hands, 1940:—All joints affected; had to give up employment. 1943:—Gold therapy; discontinued because of generalized oedema.

Nov. 7, 1944.—Constant pain, unable to move in bed. Wrists ankylosed and painful. Wasting of interosseous muscles; swelling and limitation of flexion of finger-joints. Knees and ankles painful; full range of movement but great loss of power. E.S.R., 30 mm. Serum bilirubin, 0.2 mg. per 100 c.cm. Inoculation with 0.5 c.cm. icterogenic serum.

Jan. 13, 1945.—Nausea, vomiting. Jan. 18.—Jaundiced; joints less painful.

Jan. 22.—Anorexia. Deeply jaundiced. Liver enlarged. Moving freely in bed. All joints except feet free from pain. Range of movement and swelling of joints unaltered.

Feb. 8.—Up and about. Eating well. Wrists painless. Occasional pain in feet.

April 28.—Subjectively very well. Joint pain and swelling gradually returning. E.S.R., 37 mm.

The degree of improvement seemed to be influenced more by the duration of the rheumatoid arthritis than by the severity of the jaundice, but the number of cases is small and the difference is not statistically significant. Twelve patients had had the disease for less than 5 years. Of these, 6 had complete remissions, 4 had some relief, and only 2 failed to improve. Twenty patients had suffered from rheumatoid arthritis for over 5 years. Of these only 4 had complete remissions, 11 had some improvement, and 5 obtained no relief.

Twelve patients developed a maximum serum bilirubin of over 9 mg. per 100 c.cm. Of these, 4 had complete and 6 partial remissions, while 2 failed to improve. Twenty patients never had more than 8 mg. per 100 c.cm. serum bilirubin. Of these, 6 had complete and 9 had partial remissions, while 5 obtained no relief. There is no statistical difference between these results.

In most cases the period of optimal improvement was short, but it was often several months before the joints reverted to their pre-icteric condition. In Group A (complete remission) the average period of complete freedom from pain was 44 days, the longest time being 93 and the shortest only 7 days. In the cases with an incomplete remission the period of greatest relief averaged 41 days, the longest period being 154 and the shortest 7 days.

The Erythrocyte Sedimentation Rate

In rheumatoid arthritis the E.S.R. provides an index of the activity or quiescence of the disease process. In infective hepatitis 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. It is therefore probable that when a patient with rheumatoid arthritis develops infective hepatitis the E.S.R. no longer reflects the joint condition alone.

Changes in E.S.R. were observed in some of our cases. In 14 there was an abrupt fall shortly after the appearance of jaundice, in 7 there was no change, and in 4 the E.S.R. was raised. Two or more months after the recovery the E.S.R. had fallen below the pre-icteric level in 5 cases, in 7 it was unchanged, and in 15 it was well above its original value. These alterations were 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. At the time of the late rise in sedimentation rate only a few of the patients had relapsed; in 6 cases the joints were still much better than they had been before jaundice was induced, in 5 they were essentially unchanged, and in 4 they were worse than they had been before inoculation.

Somewhat similar changes in E.S.R. have been observed in tuberculous patients who develop infective hepatitis. Penman (1943) recorded an epidemic in a sanatorium in which all the patients showed a remarkable fall in E.S.R. while jaundiced. In his cases the E.S.R. had returned to its pre-icteric value within a month of recovery from the intercurrent infection.

Discussion

The natural course of rheumatoid arthritis is so variable that it is difficult to assess the value of any remedy which produces only temporary benefit. But the fact that only two of the patients who failed to develop jaundice had a spontaneous remission during the period of observation, whereas 10 of the 32 who were successfully inoculated became completely free from pain and 15 showed some improvement, suggests that the two events are related. Some change which occurs during the course of infective hepatitis must exert a favourable effect on the joint condition, but as to the nature of this change we have as yet no clue.

Hench (1938), who analysed all the cases in the literature and observed this phenomenon in many of his own patients, came to the conclusion that the improvement obtained was related to the intensity of the jaundice, and that below a threshold value of 8 mg. per 100 c.cm. serum bilirubin little improvement was to be expected. Our results do not confirm this view, and the fact that Thompson and Wyatt (1938) failed to produce remissions by artificial hyperbilirubinaemia suggests that the jaundice owes its effect to something more than the mere accumulation of bile in the blood stream.

The changes in the E.S.R. which occur in infective hepatitis have already attracted considerable attention. The view has been expressed that the inhibitory effect which is present while the patient is jaundiced may be due to an increase of bile salts in the blood (Miles, 1945). Recent work, however, has shown that the blood level of free and conjugated cholic acid in infective hepatitis is very little raised. In the 22 cases studied by Sherlock and Walshe (personal communication) it never approached the levels required to produce the retardation obtained in the *in vitro* experiments of Miles. The E.S.R. is known to be affected by minute changes in the protein composition of the fluid in which the red cells are suspended (Gordon and Wardley, 1943), and a temporary rearrangement of the blood proteins undoubtedly occurs in the early weeks of infective hepatitis (Gray and Barron, 1943). Whether such a change is capable of exerting a favourable effect on arthritic conditions is still unknown, but further investigations might reveal some relation between these changes and the temporary improvement in the joints.

The remissions which are induced in rheumatoid arthritis by an attack of jaundice are striking, and show that the disease is capable of undergoing considerable regression. They are unfortunately temporary, and treatment of rheumatoid arthritis by jaundice cannot be recommended for general use. Though the immediate improvement is more dramatic the long-term results are inferior to those of gold. Only in the field of research is the induction of jaundice in patients with rheumatoid arthritis justifiable. Here it provides an opportunity of producing a remission under controlled conditions and the possibility of analysing the mechanism by which it is produced.

Summary

Jaundice was induced in 32 patients with rheumatoid arthritis, and temporary improvement in the latter condition was obtained in 25 cases.

The remissions were unequal in degree and of short duration. Ten patients became completely free from pain and swelling, and 15 showed some improvement. The average period during which optimal improvement was observed was 42 days, but a longer time elapsed before the joints reverted to their pre-icteric condition.

Complete freedom from pain and swelling was obtained more often in patients who had had rheumatoid arthritis for less than 5 years than in those who had had it for more than 5 years.

There was no definite relationship between the intensity of the jaundice and the type of remission evoked.

In many cases a fall in the E.S.R. was noticed during the icteric phase. This was followed by a rise to a level above that recorded before jaundice was induced. These changes did not necessarily correspond to changes in the joint condition. A similar phenomenon has been observed when patients with active tuberculosis develop infective hepatitis.

The suggestion is put forward that improvement in the joint condition and the changes in the E.S.R. may be related to changes in the plasma proteins, but no evidence is available to support this view.

The induction of jaundice in rheumatoid arthritis is justifiable only as a research measure. Its aim is to identify the substance or mechanism responsible for the remission of the joint condition and ultimately to reproduce this mechanism by other less dangerous methods.

This therapeutic trial was carried out with the support of the Jaundice Committee of the Medical Research Council. Many of the investigations were made at centres other than Oxford, and we are indebted to the staff and management of the Royal Sheffield Infirmary and Hospital, the City General Hospital, Sheffield, the Montagu Hospital, Mexborough, and the Liverpool Royal Infirmary, for providing unique facilities and help. It would have been impossible to carry out the work unaided, and we wish particularly to acknowledge the friendly co-operation and help of Prof. Barnes and Prof. Wayne, Dr. Abercrombie, Dr. Imrie, Dr. Barrie, and Dr. Brodie, of the Royal Sheffield Infirmary and Hospital; Dr. Clark and Dr. Milne, of the City General Hospital, Sheffield; and Prof. Henry Cohen and Dr. Simonds of the Royal Infirmary, Liverpool.

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ACUTE NON-SPECIFIC MESENTERIC LYMPHADENITIS

BY

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Although often described in British, American, and other medical literature, acute non-specific mesenteric lymphadenitis has found no general acceptance as one of the commonest causes of acute abdominal pain in children and as an occasional puzzling affection of adults. As a rule the term is omitted from the index and text not only of surgical manuals but even of encyclopaedic reference works, and there are hospitals in which all inflammatory enlargements of abdominal lymphatic glands are presumed to be tuberculous. If the condition is mistaken for acute appendicitis, as it frequently is, no great harm is done; it may be wise to sacrifice accuracy for safety. Material injustice may be caused, however, if the disease is wrongly labelled tuberculosis: the patient's medical record is distorted, relatives are subjected to unnecessary anxiety, and later the premium for a life insurance policy may be loaded. Acute non-specific mesenteric adenitis is commoner in this country now than is acute abdominal tuberculosis; during last year the incidence of the disease has increased, and in my charge in the children's hospital there have been admitted during the year 37 patients suffering from non-specific adenitis, as compared with 83 suffering from acute appendicitis and four suffering from abdominal tuberculosis. These figures are only very roughly approximate; they underestimate the incidence of non-specific adenitis in children: a considerable number of children in whom a diagnosis of non-specific adenitis has been made in the out-patient department have not been admitted, but have confidently been allowed to go home.

Pathological Features

To the previous description of Wilensky (1920), Foster (1938), Klein (1938), and others there is little to add. The mesenteric glands—*juxta-intestinal* along the mesenteric attachment of the lowest few feet of ileum, *intermediate* along the ileal arteries, and *terminal* on the main superior mesenteric trunk—are discretely enlarged. The first or the last of these groups may be involved alone, or all three groups may suffer together. The anterior and posterior caecal and the ileo-colic glands may or may not be simultaneously affected. The *juxta-intestinal* glands are predominantly involved in early stages of the disease;

early in an attack they may be pink in colour, but usually they are found to be white. The intermediate and terminal glands are predominantly affected in later stages of the disease; they seem always to be white in colour. The enlarged glands are soft and juicy at first, elastic later, and finally quite hard; it is uncertain whether calcification ever occurs in non-tuberculous adenitis. Suppuration has been recorded in the mesenteric glands, but usually as a result of specific bacterial infection.

The leaves of the mesentery, and, if the terminal superior mesenteric glands are involved, the adjacent peritoneum of the posterior abdominal wall, may be congested. The peritoneum of the anterior abdominal wall is nearly always unaltered; I have found it slightly inflamed only once, in an adult. The ileum, and sometimes the caecum and appendix as well, may show serous hyperaemia, and sometimes a palpable oedema of the whole thickness of the bowel wall. This inflammatory appearance of the intestine is commonly found only during earlier attacks of the disease. Seldom of more than slight degree, it may be absent even in a first attack; it may affect a considerable length of lower ileum, or several discrete stretches of bowel, or only one short segment; or it may be restricted merely to palpable thickening of Peyer's patches. Frequently, with or without an inflammatory appearance of the bowel, there is a small quantity of clear fluid free within the peritoneal cavity.

Histologically the glands present a non-specific hyperaemia and cellular hyperplasia. In my experience, glands removed at operation, and free fluid from the peritoneal cavity, prove sterile on culture and on animal inoculation.

Symptoms

The history is not particularly characteristic. The patients, more often male than female, are usually children beyond the years of infancy, but the condition has been recorded at 10 months and at 70 years of age; the extremes in my own series have been 3 and 39 years. The pain is essentially a general abdominal colic, often of extreme severity, and more intense and alarming than the initial colic of appendicitis in childhood. Between spasms of colic there is entire freedom from pain, and the patient is happier and livelier between spasms than is any patient who harbours an inflamed appendix. Even during the actual attack of pain the patient moves freely always, and violently sometimes, with a constant changing of position which would be unusual in acute appendicitis. As in appendicitis, when the patient who has given a history of generalized abdominal pain is asked to indicate the site of most intense pain, he points to the right lower quadrant. In contrast to the patient with acute obstructive appendicitis, however, he cannot locate the site of maximum pain precisely, but indicates an ill-defined area on the right side. When first seen by a doctor, four out of five patients tell of a previous attack, and most have had more than one previous attack of an almost precisely similar character. Nausea, usually with vomiting, accompanies one at least of the initial attacks. Diarrhoea is exceptional. There has quite often been a recent sore throat or other upper respiratory infection.

Signs

Clinical examination provides no more specific evidence than does the history. The patient may seem little affected, except by pain, or may be flushed and obviously fevered, or pale; he is seldom or never prostrated or ominously motionless, and during the examination limb and body movements occur normally. If taken early in an attack, the temperature is elevated to 101° or even substantially higher, and on the first day also there is an almost invariable leucocytosis of 15,000 to 20,000, with 80% or more of granular cells. As a rule the white count falls again on the second day—its elevation is quicker, higher, and shorter-lived than in acute appendicitis. A bright-red pharyngitis is a not unusual concomitant of non-specific mesenteric adenitis, but neither its presence nor its absence is highly significant, for in more than 70% of my cases pharyngitis has not been detected, and acute pharyngitis sometimes closely precedes acute appendicitis.

On abdominal examination, tenderness is elicited in the right iliac fossa, higher and more medial than the usual tenderness of acute appendicitis. The lowest limit of tenderness is just below and to the right of the umbilicus. When the terminal