yet. The occurrence of false positives in the latex test does not, we know, imply a greater degree of sensitivity—rather, it seems to be due to some random factor not yet identified. Goldin (1962) encountered two false positives in his 69 cases. The Ortho Research Foundation (1961) differ from us in their much bigger series. Their latex testing gave 2.09% false-negative and 0.14% false-positive reactions. Conversely, their frog tests gave values of 0.50% and 1.51% respectively.

It is clearly necessary for the clinicians who request tests for pregnancy to agree with the pathologists performing these tests about the limits of accuracy that should be acceptable.

So far as the laboratory is concerned there is much to recommend a tube test which is of approximately equal effectiveness to the more laborious biological tests. However, our limited experience shows that if the latex test is adopted, an appreciable number of false-positive results must be expected, a situation which hitherto has not had to be considered.

We are reluctantly unable to recommend the latex test to our clinical colleagues unless they are prepared to accept the possible consequences of the false-positive results.

There is one aspect of the latex test which may, however, be used to advantage, even though it is not used for pregnancy diagnosis. To confirm the diagnosis of chorion-epithelioma and other moles it is usual to carry out a quantitative biological test with urine dilutions. The quantitative Hogben test (Hobson, 1952) uses six toads and is therefore wasteful of animals and time. We believe that the latex test may be valuable here, but have not had the opportunity to try it.

Summary

Two methods of testing urine for pregnancy are compared. One is a recently introduced sensitized latex particle precipitation test, and this is compared with the widely used Hogben test—a biological test using *Xenopus laevis* female frogs.

Early-morning urine samples from 233 women were examined by the two methods. In 159 of these cases it was possible to determine whether or not the results obtained were correct.

The latex test was accurate in 144 (90.6%) cases and the Hogben test in 148 (93.1%) cases.

The Hogben test did not make any false-positive predictions, whereas the latex test did so in a third of the incorrectly predicted cases (5 out of 15).

The latex test was found to be sensitive to a minimum concentration of 20 units of H.C.G./ml. and the Hogben test to a concentration of approximately 2 units of H.C.G./ml.

It is suggested that the latex test may be of value for the quantitative determination of H.C.G. in urine.

Our thanks are due to Ortho Pharmaceuticals for allowing us to have some of their test kits free and subsequent kits at a reduced price. We are also grateful to the Portsmouth Group Hospital Management Committee, who made a grant to cover the expenses incurred.

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ANKYLOSING SPONDYLITIS AND CHRONIC INFLAMMATORY DISEASES OF THE INTESTINES

BY

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A number of reports have been published in the past few years which note an association between ankylosing spondylitis and inflammatory diseases of the bowel. Many of these reports are of patients who, in addition to ankylosing spondylitis, had either Crohn's disease or ulcerative colitis. In one series of 177 male patients Romanus (1953) found that three had ulcerative colitis, and Steinberg and Storey (1957) reported six cases, all with ankylosing spondylitis, of whom four had ulcerative colitis, one had Crohn's disease, and one had both Crohn's disease and ulcerative colitis. Among 220 cases of ankylosing spondylitis, Wilkinson and Bywaters (1958) described four with ulcerative colitis and one with Crohn's disease; and Fernandez-Herlihy (1959), in a review of 555 cases of ulcerative colitis, found 28 patients with ankylosing spondylitis. In a study of 13,352 patients who had received radiotherapy for ankylosing spondylitis an apparent excess of deaths ascribed to ulcerative colitis was found (Court Brown and Doll, 1957, and personal communication). Thus up to December, 1955, 13 deaths from ulcerative colitis had occurred where 0.65 might have been expected.

This paper reports further instances of the association of inflammatory diseases of the gastro-intestinal tract with ankylosing spondylitis. In addition, attention is drawn to a familial predisposition to the development of these diseases, alone or in combination.

Clinical Material

Two groups of hospital patients were investigated. The larger, group A, consisted of 870 patients who had been treated with radiotherapy for ankylosing spondylitis in Edinburgh between 1935 and 1960. The smaller group (B)

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comprised 170 patients who had attended the gastro-intestinal unit at the Western General Hospital between 1954 and 1960, and in whom a diagnosis of idiopathic ulcerative colitis or Crohn's disease had been established.

Of the 870 patients in group A, 560 were interviewed and questioned specifically about symptoms of gastro-intestinal disease in themselves or in their relatives. During the course of this investigation it was noted that in a number of families one member had ankylosing spondylitis while another had chronic inflammatory disease of the bowel. These coincidences led to a closer search for families in which both diseases occurred. The last consecutive 67 cases in this group had a barium-meal and follow-through examination carried out whether or not there were symptoms referable to the gastro-intestinal tract.

Diagnostic Criteria

The minimum requirements for a diagnosis of ankylosing spondylitis were bilateral loss of definition or irregularity of the sacro-iliac joint spaces with subchondral sclerosis. In most cases the intervertebral joints were also involved.

Diagnosis of the bowel lesion was based on history, radiological evidence, sigmoidoscopic examination, and, where possible, histological studies. The radiological changes included evidence of ulceration, shortening, and narrowing in disease of the colon; and of inflammation, ulceration, and fistula formation in small-bowel disease. In no case was chronic inflammatory bowel disease diagnosed without such radiological evidence or, alternatively, the finding of characteristic histological changes.

Results

Of the patients in group A presenting with ankylosing spondylitis, 20 gave a history of diarrhoea or of unexplained loss of weight. Five of these patients had already attended other hospitals, where an acceptable diagnosis of ulcerative colitis had been made. The remaining cases were investigated by us and nine were found to have chronic inflammatory bowel disease. In addition, the case-notes of four patients in this group who had died of ulcerative colitis were obtained and critically reviewed. In the small subgroup of 67 patients who were routinely subjected to a barium-meal and follow-through examination two new cases of small-bowel disease were discovered. Both these cases were remarkable in that they were completely asymptomatic.

The 170 patients in group B in whom a diagnosis of ulcerative colitis or of Crohn's disease had been made were recalled to a special clinic and questioned about rheumatic symptoms in themselves or in their families. The *x*-ray films of their previous barium follow-through examinations were re-examined for evidence of ankylosing spondylitis and, where necessary, further views of the sacro-iliac joints were obtained. Five patients were found who showed radiological changes in the sacro-iliac joints. Four of these had the typical bilateral changes of ankylosing spondylitis. In the fifth patient radiological changes were restricted to the left side, and, since a diagnosis of ankylosing spondylitis was uncertain, this patient was omitted from the present series.

Details of the 24 cases with both ankylosing spondylitis and chronic inflammatory bowel disease are summarized in Table I.

In the two groups of patients eight families were found where at least one member had ankylosing spondylitis, and a hospital diagnosis of ulcerative colitis or Crohn's disease had been made in another member. The data for these families are summarized in Table II.

TABLE I.—*Patients with Ankylosing Spondylitis and Ulcerative Colitis or Crohn's Disease*

No.	Sex	Year of Birth	Ankylosing Spondylitis Diagnosed	Radio-therapy	Bowel Lesion Diagnosed	Nature of Lesion
			Group A			
1	M	1906	1943	1943	1942	Ulcerative colitis
2	M	1914	1942	1942	1948	,, ,,
3	M	1915	1951	1951	1958	Crohn's disease
4	M	1931	1949	1949	1949	Ulcerative colitis
5	F	1919	1946	1949	1959	,, ,,
6	F	1911	1949	1949	1959	,, ,,
7	M	1916	1946	1946	1952	,, ,,
8	F	1888	1952	1952	1956	,, ,,
9	F	1929	1959	1959	1959	Crohn's disease
10	M	1933	1960	1960	1960	Ulcerative colitis
11	M	1908	1942	1943	1960	,, ,,
12	M	1915	1948	1948	1948	,, ,,
13	F	1927	1956	1956	1954	,, ,,
14	M	1909	1951	1951	1932	,, ,,
15	M	1911	1951	1951	1943	,, ,,
16	M	1914	1949	1949	1942	,, ,,
17	M	1916	1954	1954	1958	,, ,,
18	F	1931	1954	1954	1958	Crohn's disease
19	F	1915	1959	1960	1958	,, ,,
20	F	1926	1958	1958	1950	Ulcerative colitis
			Group B			
21	M	1935	1959	—	1949	Ulcerative colitis
22	F	1910	1959	—	1950	,, ,,
23	M	1906	1959	—	1943	Crohn's disease
24	F	1924	1958	1960	1948	Ulcerative colitis

TABLE II.—*Families in which both Ankylosing Spondylitis and Chronic Bowel Disease Occur*

	Sex of Propositus	Disease	Affected Relative	Disease
1	Male	Ankylosing spondylitis	Brother	Ulcerative colitis
2	Female	Ankylosing spondylitis	Sister	Ankylosing spondylitis
			Daughter	Ulcerative colitis
3	Male	Ankylosing spondylitis	Brother	Ulcerative colitis
4	Male	Ankylosing spondylitis	Brother	Ankylosing spondylitis
			Brother	Ulcerative colitis
5	Male	Ankylosing spondylitis	Mother	Ulcerative colitis
6	Female	Ankylosing spondylitis	Sister	Ulcerative colitis
7	Female	Ankylosing spondylitis	Sister	Ulcerative colitis
8	Male	Ankylosing spondylitis	Mother	Crohn's disease

Discussion

The occurrence of two relatively uncommon diseases in one patient may be due to chance or to some aetiological factor common to both diseases. The incidence of ankylosing spondylitis in the general population has been estimated by West (1949) as 0.5 per 1,000. Houghton and Naish (1958) estimated the frequency of ulcerative colitis as 0.85 per 1,000 and of Crohn's disease as 0.14 per 1,000. In contrast, of the 560 patients in group A who were interviewed, 16 were found to have ulcerative colitis and four Crohn's disease, an incidence of 18.38 and 4.58 per 1,000 respectively. Thus the total incidence of chronic inflammatory bowel disease in this group was at least 22.96 per 1,000. This is much greater than the expected rate should association with ankylosing spondylitis be due solely to chance.

In their study of 13,352 patients with ankylosing spondylitis, Court Brown and Doll (1957) noted that 13 deaths ascribed to ulcerative colitis had occurred up to the end of 1955, whereas the expected number was 0.65. By November, 1962, the number of deaths had risen to at least 22—a minimal figure, as the follow-up is as yet incomplete. This is probably 15 times the number which might have been expected in the general population and is much greater than could reasonably be attributed to chance. In addition, in the same group of patients ulcerative colitis is mentioned as an associated cause of death in eight more

cases. The limitation of the methods of the present study must be remembered. A number of mild cases of bowel disease might readily be missed and the true incidence of chronic inflammatory bowel disease in ankylosing spondylitis may be much greater than 23 per 1,000. In this respect it is worthy of note that seven of the patients with ankylosing spondylitis (group A) had had diarrhoea of such severity that they had been referred for specialist investigation. In all seven cases, however, the investigations, including radiological, sigmoidoscopic, and bacteriological studies, had proved negative. The episodes of diarrhoea in those patients have been quite unrelated to their ankylosing spondylitis, but, on the other hand, these may represent examples of a *forme fruste* of the complete syndrome or even one stage of its natural history.

Acheson (1960) has reviewed the records of a series of 2,320 male patients with ulcerative colitis or Crohn's disease who had been admitted to hospitals of the United States Veterans Administration. He found that 3% of the patients with Crohn's disease and 2.6% of those with ulcerative colitis also had ankylosing spondylitis. In group B of our series 4 of the 170 patients with ulcerative colitis or Crohn's disease also had ankylosing spondylitis, an incidence of 2.4%. Fernandez-Herlihy (1959) described 28 cases of ankylosing spondylitis among 555 cases of ulcerative colitis, an incidence of 5%, and Zvaifler and Martel (1960) reported 6 such cases in 100 patients with ulcerative colitis.

Ankylosing spondylitis is generally looked upon as a disease of young males. In recently reported series the sex ratio has varied between 9 to 1 and 5 to 1. It is interesting to note that among the relatively small number of 138 females in group A no fewer than five had ulcerative colitis while three had Crohn's disease, an overall incidence of 5.79%. In contrast, of the 732 male patients in group A only 12 were found to have either ulcerative colitis or Crohn's disease. This difference is in accord with the sex difference found in the patients whose certified causes of death were studied by Court Brown and Doll (1957). Of 11,827 males, 15 have been certified as dying of ulcerative colitis, while seven deaths from ulcerative colitis have been recorded among the 2,065 females studied. Thus females were certified as dying of this concomitant of ankylosing spondylitis more than twice as frequently as were males.

In this series only 9 of the 24 cases had been treated with radiotherapy for ankylosing spondylitis before an intestinal lesion was diagnosed. It does not seem likely, therefore, that radiation plays a part in the causation of the disease of the gastro-intestinal tract. The bowel disease was diagnosed before the ankylosing spondylitis in 11 patients, in the same year in four, and after the diagnosis of spondylitis in nine. The interval between the two diagnoses where these were not concurrent varied from 5 to 15 years. This is in agreement with the findings of Acheson (1960), who noted that in the 49 cases of chronic inflammatory bowel disease for which detailed records were available the symptoms of ankylosing spondylitis preceded the intestinal symptoms in 36 and a firm diagnosis of ankylosing spondylitis had already been made in 25 instances. Fernandez-Herlihy (1959) recorded that in 28 similar cases the diagnosis of ankylosing spondylitis had preceded that of ulcerative colitis in 13, while in a total of 21 cases reported by Steinberg and Storey (1957), Grainger (1959), and Zvaifler and Martel (1960) the intestinal lesion was diagnosed before the ankylosing spondylitis in 17. The difference in the order of recognition of these two conditions in the same patient may be influenced by the special interests of those reporting the series. It is reasonable to suggest that as this association becomes more widely known there will be an increase in the number of cases diagnosed.

The clinical manifestations of the intestinal disease associated with ankylosing spondylitis were usually mild. Nevertheless, surgical treatment was required by four patients (Cases 21, 22, 23, and 24). In the remaining 20 cases diarrhoea or loss of weight persisted for periods varying up to 24 months. Two patients were treated with corticosteroids. In one (Case 3) this resulted in the cessation of diarrhoea, which has not recurred one year after the withdrawal of steroid therapy. In the other (Case 18) diarrhoea was not troublesome but loss of weight was marked. Treatment with corticosteroids was followed by a gain in weight, but this was not maintained after treatment had been withdrawn. In each case the radiological appearances of the bowel were unaltered by treatment.

Both the clinical and the pathological features of all 24 cases in this series were reviewed carefully in a search for features which might differentiate them from cases of Crohn's disease or of ulcerative colitis unassociated with ankylosing spondylitis. In seven cases it was possible to examine part of the diseased bowel histologically. The appearances were typical in four cases of ulcerative colitis and in one case of Crohn's disease. In two cases of Crohn's disease, however, fibrosis and giant-cell formation were relatively inconspicuous.

Familial Incidence

In a study of ankylosing spondylitis among the relatives of patients with the disease Blécourt *et al.* (1961) found that the incidence was 22.6 times higher than among the relatives of normal control subjects. The occurrence of more than one case of ankylosing spondylitis in a family is thus not uncommon. Various authors have reported familial cases of ulcerative colitis and the incidence appears to be taken as between 0.5 and 7%, although Paulley (1950) described a series of 173 cases and found a familial incidence of 11.3%. Examples of familial Crohn's disease are much less common, but in his review of 298 cases Crohn (1949) described eight familial cases. In Table II we summarize the findings in eight families where one or more members had ankylosing spondylitis and another member had either ulcerative colitis or Crohn's disease. A number of cases have already been reported in which chronic inflammatory bowel disease has occurred with ankylosing spondylitis in the same individual, but this would appear to be the first occasion on which these diseases have been described in different members of the same family.

The occurrence of these relatively uncommon disorders in the same individual suggests the presence of related aetiological mechanisms, and the familial occurrence suggests either an inherited predisposition or the operation of an aetiological factor in the family environment. Although the influence of environmental factors cannot be excluded the importance of inherited predisposition appears to be established. The data at our disposal are incomplete and it is not possible to define the mode of inheritance. Hersh *et al.* (1950) have suggested that susceptibility to ankylosing spondylitis is determined by a single autosomal dominant gene which has a penetrance of 70% in males and 10% in females; our data are not incompatible with this hypothesis. Although ankylosing spondylitis and ulcerative colitis or Crohn's disease coexist more often than would be expected by chance, the exact nature of the relationship is not clear. It may be that ankylosing spondylitis and the intestinal lesion are different manifestations of a general disorder of connective tissue. An inherited

abnormality of connective-tissue metabolism or a disordered immune mechanism involving connective tissue may underlie both conditions.

The factors which determine whether a predisposed individual develops ankylosing spondylitis, Crohn's disease, or ulcerative colitis, or these diseases in association, are quite unknown; as are the factors which determine the order in which the associated diseases may appear.

Summary

The association of ankylosing spondylitis with ulcerative colitis and Crohn's disease is described. Of 870 patients with ankylosing spondylitis, 16 were found to have ulcerative colitis and four to have Crohn's disease. Four cases of ankylosing spondylitis were found among 170 patients with ulcerative colitis or Crohn's disease. The limitations of the methods of study make it likely that the real coincidence of ankylosing spondylitis with chronic inflammatory intestinal disease is even higher.

Attention is drawn to the relatively higher incidence of intestinal disease in females with ankylosing spondylitis. The occurrence of ankylosing spondylitis and intestinal disease in different members of the same family is described and discussed.

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SMOKING DETERRENT STUDY

A REPORT FROM THE RESEARCH COMMITTEE OF THE BRITISH TUBERCULOSIS ASSOCIATION*

Large doses of lobeline cause bradycardia, hypotension, and bronchoconstriction due to central vagal stimulation, and respiration is increased in rate and depth reflexly as a result of stimulation of the carotid-body chemoreceptors. These pharmacological actions are similar to those of nicotine, and for this reason lobeline preparations have been recommended as an aid to giving up smoking.

Some success has been claimed when large doses of the order of 8–10 mg. of lobeline sulphate are given orally (Dorsey, 1936; Wright and Littauer, 1937) or intramuscularly (Ejrup, 1956; Jost and Jochum, 1959). With these large doses tachycardia, epigastric pain, nausea, vomiting, and other unpleasant side-effects often occurred. These effects were not obtained when a smaller dose of lobeline sulphate (2 mg.) was given combined with antacids (Rapp and Olen, 1955).

The absence of side-effects might have been due to the smallness of the dose, but Rapp *et al.* (1959) claimed that when such a preparation was given three times daily, blood-levels of up to 180 μg. of lobeline per 100 ml. of blood were obtained. Unfortunately the exact details of the method of estimating the blood lobeline levels have not been published and this work has not to our knowledge been repeated.

The purpose of the present trial was to assess the value of such a preparation of lobeline as a deterrent of smoking. This preparation ("lobidan") contains, in each tablet, lobeline sulphate 2 mg., magnesium carbonate 125 mg., and tribasic calcium phosphate 180 mg.

Method

The trial was a co-operative one carried out at eleven chest clinics. The subjects selected were persons who regularly smoked 20 or more cigarettes a day and who wanted to give up smoking. Only those who smoked a registered brand of cigarettes—that is, no persons rolling their own cigarettes or pipe-smokers—were considered; they were not unduly coerced into joining the trial; they were normal subjects or patients suffering from chronic bronchitis and/or pulmonary fibrosis of tuberculous or other origin. The subjects were randomly allocated by the statistician to the lobidan or inert-tablet series; neither the subjects nor the clinic physicians were aware of the identity of the tablets.

The dose of either the lobidan or inert tablets was one tablet four times daily for six weeks. The inert tablets were identical to the lobidan in make-up and taste, but instead of 2 mg. of lobeline each tablet contained 15 mg. of quinine sulphate.

The subjects were asked to record on a form the number of cigarettes smoked in the week before the start of the trial and subsequently the number of cigarettes smoked and the number of tablets taken each week for the first six weeks of the trial, during which time they had been instructed to take one tablet four times daily. At the end of the six-week period the forms were returned to the co-ordinator, who decided whether or not the particular subject should be regarded as a success or failure. If

*The investigation was carried out by the Clinical Trials Sub-committee of the Research Committee of the British Tuberculosis Association at the request of Uni-Pharma Ltd., who supplied both the "lobidan" and inert tablets. The trial was co-ordinated by Dr. Peter Emerson, from Westminster Hospital. The report was prepared by Dr. Peter Emerson and Miss Ruth Tall (M.R.C. Statistical Research Unit).

The following physicians took part: Dr. D. ap Simon, Aldershot Chest Clinic; Dr. P. Baldry, Ashford Chest Clinic; Dr. N. Wynn-Williams, Bedford Chest Clinic; Dr. V. H. Springett, Birmingham Chest Clinic; Dr. P. Forgacs, Chislehurst Chest Clinic; Dr. D. Paradise, Croydon Chest Clinic; Dr. P. Stradling, Hammersmith Chest Clinic; Dr. P. A. Zorab, Paddington and Kensington Chest Clinic; Dr. P. Davies, St. Pancras Chest Clinic; Dr. B. Thompson, Windsor Chest Clinic; Dr. R. A. Chand, Wolverhampton Chest Clinic.

The report should be referred to as: British Tuberculosis Association (1963). Those who want reprints may obtain them from the Honorary Secretary of the Research Committee, British Tuberculosis Association, 59 Portland Place, London W.1.