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BEHÇET'S SYNDROME WITH ARTHRITIS

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Hulusi Behçet, formerly Professor of Dermatology at the University of Istanbul (Fig. 1), reported three cases of the syndrome which now bears his name, in 1937. He described a triple symptom complex (Behçet, 1940):

Fig. 1.—Prof. Hulusi Behçet.

"First transient aphthous changes in the mouth, secondly ulcerations on the genitalia, and thirdly attacks of iritis, although the latter symptom is not always present. Each of these three symptoms tends, according to its degree of severity at any one time, to simulate a number of better known diseases and this makes differential diagnosis somewhat complicated."

It has since been recognized that many other systems may be involved, including the skin, cardiovascular, central nervous and gastro-intestinal systems, and the joints, together with venous thrombosis. These manifestations have been well summarized by Strachan and Wigzell (1963).

Despite the many theories put forward the aetiology remains unknown. Behçet (1937), Sezer (1952, 1953, and 1956), and Evans, Pallis, and Spillane (1957) all proposed a viral aetiology, which was subsequently denied by Dudgeon (1961), and certainly the syndrome appears to lack infectivity.

Other theories of aetiology have included tuberculous or staphylococcal infections (Adamantiades, 1931; Urayama, 1960) and auto-immune disturbances (Jensen, 1941; Shimizu, Katsuta, and Oshima, 1965). Histological changes are not specific and no diagnostic test is available.

Thus, diagnosis depends on the Hippocratic method of grouping features together into a symptoms complex which makes it necessary to adopt arbitrary diagnostic criteria.

In some reports the "complete" syndrome has been diagnosed when cutaneous, oral, genital, and ocular lesions were present, an "incomplete" form being suspected if one or two of these features were absent (Curth, 1946; Phillips and Scott, 1955; Oshima, Shimizu, Yokohari, Matsumoto, Kano, Kagami, and Nagaya, 1963).

We, however, have taken the diagnosis as being definite when there have been at least three of the four principal symptoms—buccal ulceration, genital

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ulceration, eye and skin lesions—or two of these lesions with at least two of the more minor features described below.

Case Material

In the past 4 years 33 patients have attended The London Hospital in whom a definite diagnosis of Behçet's syndrome has been made, or in whom the diagnosis has been suspected. The cases are summarized in Table I.

Group A in this Table, nineteen patients, were considered to have definite Behçet's disease with arthritis.

Group B (Cases 20-24) comprised five relatives of patients from Group A. The diagnosis in Cases 21,

TABLE I
CASE MATERIAL: FOUR GROUPS OF PATIENTS

Group	Case No.	Sex	Buccal Ulceration	Genital Ulceration	Eye Lesions	Skin Lesions	Arthritis	Cardio-Vascular Involvement	Venous Thrombosis	Gastro-intestinal Involvement	Central Nervous System Involvement	Family History
(A) Definite Behçet's Disease with Arthritis	1	F	+	+	+	+	+		+	+		
	2	M	+	+	+	+	+			+		+
	3	F	+	+	+	+	+					+
	4	M	+	+	+	+	+		+			
	5	M	+	+	+	+	+					
	6	M	+	+	+	+	+					
	7	F	+	+	+	+	+					
	8	M	+	+	+	+	+					
	9	M	+	+	+	+	+					
	10	F	+	+		+	+			?		
	11	M	+	+		+	+		+			
	12	M	+	+		+	+					
	13	F	+	+	+		+					
	14	F	+		+	+	+			+		+
	15	M	+		+	+	+					
	16	M	+		+		+					+
	17	M	+		+		+					
	18	F	+			+	+		+			
	19	F	+	+			+					+
(B) Relatives of Patients in Group A	20	F	+	+				+				+
	21	F	+	+								+
	22	F	+	+								+
	23	M	+				+					+
	24	F	+							+		+
(C) Definite Behçet's Disease without Arthritis	25	M	+	+	+	+					+	
	26	M	+	+		+			+	+		
	27	M	+	+	+							
	28	M	+	+	?	+			+			
	29	M	+		+	+						
(D) Diagnosis Not Certain	30	M	+	+			+					
	31	F	+		+		+					
	32	M	+				+					
	33	F	+				+					

22, and 23 was not definite but included an episode of arthritis; in Case 24 the diagnosis was also doubtful and there was no history of arthritis.

In Group C (Cases 25-29) a diagnosis of definite Behçet's syndrome without arthritis was possible.

In Group D (Cases 30-33) the patients had arthritis with mouth ulceration but with insufficient criteria to make a definite diagnosis. Whilst this was consistent with an early phase of the disease the possibility of an inflammatory arthropathy with incidental aphthous ulceration could not be excluded.

Thus, of the 33 patients, 25 met our criteria for a definite diagnosis of Behçet's syndrome (Table I: Cases 1-19; 20; 25-29), nineteen of whom had arthritis. There were sixteen males and nine females; 21 were British, two West Indian, one Chinese, and one Indian.

Clinical Presentation (Table II)

In the 25 patients with definite Behçet's syndrome, the commonest initial symptom was mouth ulcers, which occurred in sixteen. The age at onset varied between 9 and 43 years (men 9 to 43 years, average 21: women 9 to 41 years, average 22). The initial symptoms did not necessarily cause the patient to attend hospital, so that thirteen attended for the first time on account of arthritis, seven on account of eye lesions, and three on account of skin lesions.

TABLE II
PRESENTATION OF DISEASE
IN CASES 1-19, 20, AND 25-29

Sympton	Initial	Presenting at Hospital
Mouth ulcers	14	1
Genital ulcers	2	
Mouth and genital ulcers	2	
Arthritis	2	11
Arthritis and Erythema nodosum	1	1
Arthritis and Erythema nodosum and Sore throat		1
Arthritis and Mouth and genital ulcers and Uveitis	1	
Uveitis	1	5
Uveitis and mouth ulcers	1	
Hypopyon		1
Retrobulbar neuritis	1	1
Skin ulceration/sepsis/rash		3
Pericarditis		1
Total	25	25

The duration from the first symptom to attendance at hospital was very variable (Table III). It seems that the timing depends on the development of a sufficiently serious manifestation of the condition, and that mouth ulceration in itself, while painful, is rarely sufficient to lead to hospital attendance.

Arthritis

Of these 25 patients, nineteen developed arthritis, of whom eleven were males and eight females. Thus the sex distribution in the arthritic group is approximately the same as in the entire group. The average age at onset of the arthritis was 28 years (range 15 to 45) in the men and 35·8 years (range 13 to 58) in the women.

TABLE III
DURATION FROM FIRST SYMPTOM TO
ATTENDANCE AT HOSPITAL IN CASES 1-19, 20, AND 25-29

Years	No. of Patients
0- 1	9
- 5	6
-10	2
-15	3
-20	4
-30	0
-40	0
>40	1
Total	25

The duration from the first symptom to the onset of arthritis was also variable (Table IV). It is worth noting that one patient had had symptoms of mouth ulcers for more than 40 years before an inflammatory arthropathy developed requiring his attendance at hospital.

TABLE IV
DURATION FROM FIRST SYMPTOM TO THE
CONDITION TO ONSET OF ARTHRITIS IN CASES 1-19

Years	No. of Patients
0- 1	6
- 5	5
-10	1
-15	2
-20	3
-30	1
-40	0
>40	1
Total	19

The arthritis was polyarticular with an average involvement of 5·5 sites per patient (Fig. 2). The knee was the most commonly affected joint—in fifteen of the nineteen patients.

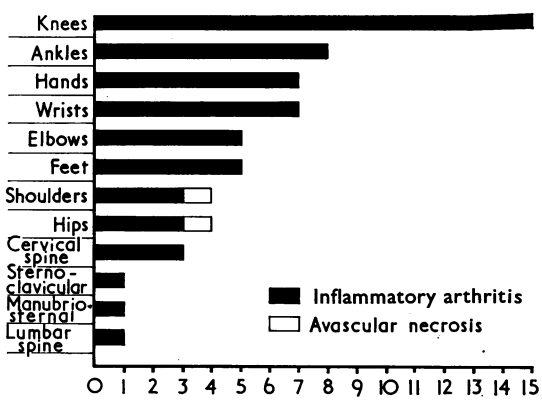

Fig. 2.—Joints affected (19 patients).

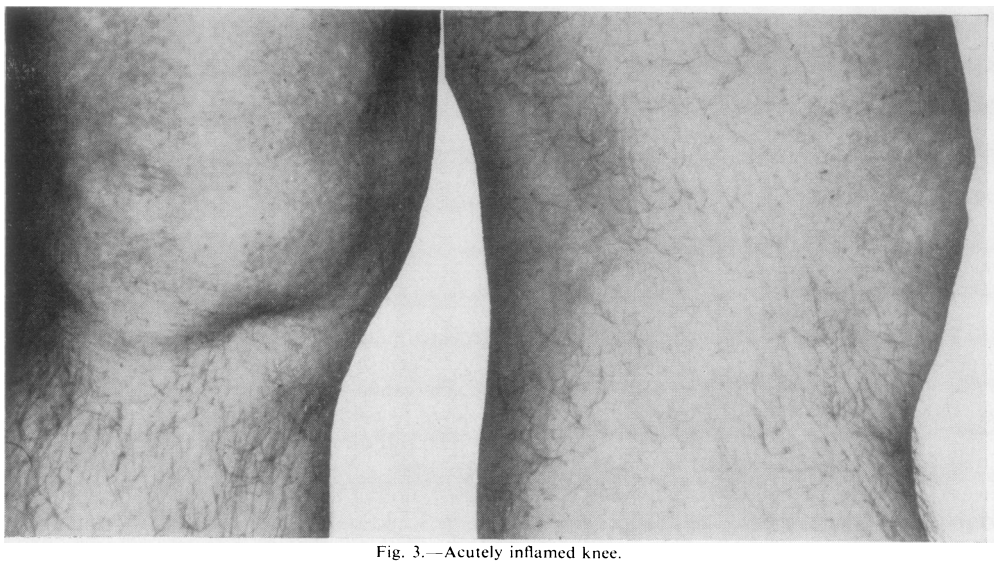

Fig. 3.—Acutely inflamed knee.

Pain on movement and joint swelling (Fig. 3) of insidious onset were the predominant symptoms. The arthritis was of inflammatory type, characterized by significant morning stiffness in 80 per cent. of cases; when the patients could be observed during active involvement, synovial thickening was present with warmth. Effusions were frequent.

The arthritis was not migratory, and was typically sub-acute or chronic. It was not episodic and in sex cases was self-limiting (Fig. 4). Permanent joint deformity was not seen even when the arthritis had been present for many years.

The erythrocyte sedimentation rate (Westergren: mm. Hg) was raised in thirteen of the nineteen cases (taking the upper limit of normal below age 50 years as men 15, women 25, and above 50 years as men 20, women 30: Böttiger and Svedberg, 1967). The elevation ranged between 24 and 114 mm./1 hr. The six patients with normal values were not receiving systemic corticosteroids. In all cases, either the latex test and/or the Waaler-Rose test was negative, and in only two was there a mild elevation of alpha$_2$ and gamma globulins. Radiographs of the affected joints, together with those of the hands and feet, were normal, showing no erosive or destructive change, except in two cases. Avascular necrosis of both femoral and humeral heads, which developed in Case 5 (Table I), was attributed to large doses of systemic corticosteroids given for severe uveitis. In Case 6 erosive changes developed in the manubriosternal joint with severe pain; surgical fusion of this joint was followed by complete relief (Currey, Elson, and Mason, 1968).

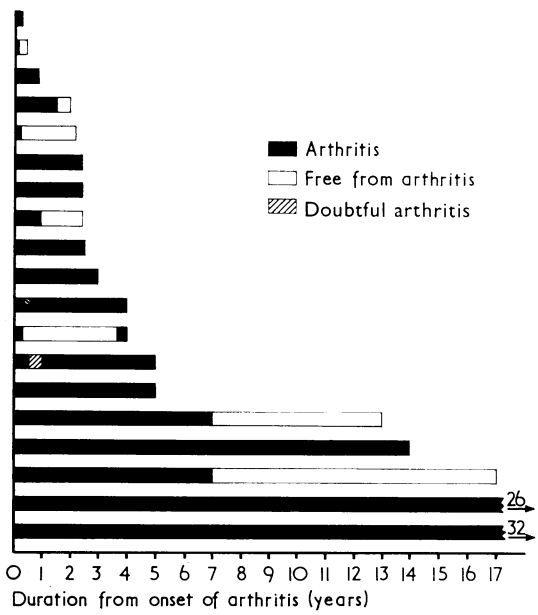

Fig. 4.—Course of the arthritis.

Extra-articular Manifestations (Table V)

In the 25 patients with definite Behçet's disease, enquiry was made for other manifestations.

Buccal Ulceration.—This was present in all cases (Fig. 5).

TABLE V
EXTRA-ARTICULAR MANIFESTATIONS IN 25 PATIENTS

Symptom	No.	Per cent.
Buccal ulceration	25	100
Genital ulceration	19	76
Skin lesions	19	76
Eye lesions	17	68
Gastrointestinal lesions	6	24
Thrombophlebitis	6	24
Cardiovascular involvement	1	—
Central nervous system involvement	1	—

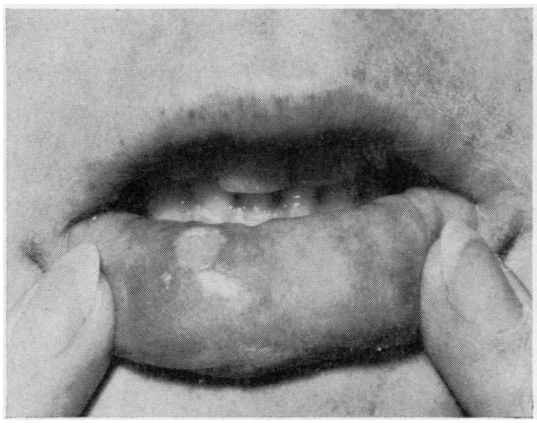

Fig. 5.—Typical buccal ulcer.

Cardiovascular Involvement.—Case 20 gave a past history of pericarditis.

Central Nervous System Involvement.—Case 25 developed mid-brain lesions with cranial nerve palsies, respiratory failure, and long-tract signs together with Addison's disease, from which he died. Similar lesions have been reported previously (Pallis and Fudge, 1956; Evans and others, 1957; McMenemey and Lawrence, 1957; Rubinstein and Urich, 1963; Pallis, 1966).

Eye and Skin Manifestations.—These are shown in Tables VI and VII.

Uveitis (Fig. 6) required treatment with corticosteroids, either systemic or in the form of ocular drops or sub-conjunctival depot injections.

Erythema nodosum, a well-recognized manifestation of the syndrome (France, Buchanan, Wilson, and Sheldon, 1951) occurred at some stage in one third of the cases.

Fig. 7 (overleaf) shows a typical pustule, and Fig. 8 (overleaf) residual scars after ulceration.

TABLE VI
EYE LESIONS IN 25 PATIENTS

Eye Lesion	No.	Per cent.
Uveitis (Hypopyon—3)	14	56
Corneal ulceration	4	16
Retrobulbar neuritis	2	8

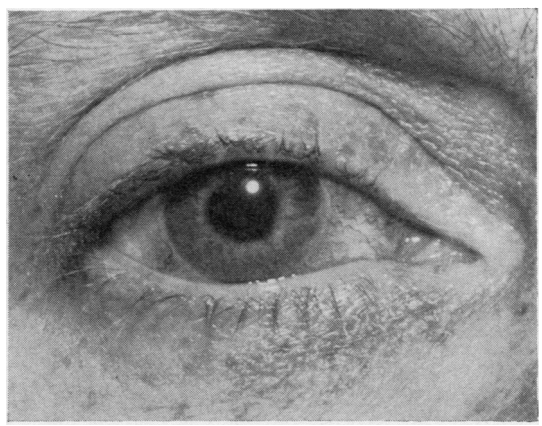

Fig. 6.—Uveitis.

TABLE VII
EXTRAGENITAL SKIN LESIONS IN 25 PATIENTS

Skin Lesions	No.	Per cent.
Sepsis	11	44
Ulceration	9	36
Erythema nodosum	8	32
Erythema multiforme	2	8
Other—maculopapular	1	2 8
psoriasis	1	

Gastrointestinal Lesions.—There was duodenal ulceration proven by barium meal studies in three patients, diarrhoea and vomiting in one, and dysenteric symptoms in a fifth patient. One of the patients with duodenal ulceration who developed symptoms while taking 10 mg. prednisone daily for a combination of arthritis and uveitis with hypopyon required an emergency partial gastrectomy.

Patient 24 (Table I) was found to be suffering from classical ulcerative colitis.

Thrombophlebitis.—This occurred in six patients (24 per cent.), as superficial thrombophlebitis or deep vein thrombosis of a limb vein. There was no evidence in any case of thrombosis of any of the inferior or superior venae cavae such as Mounsey (1966) described.

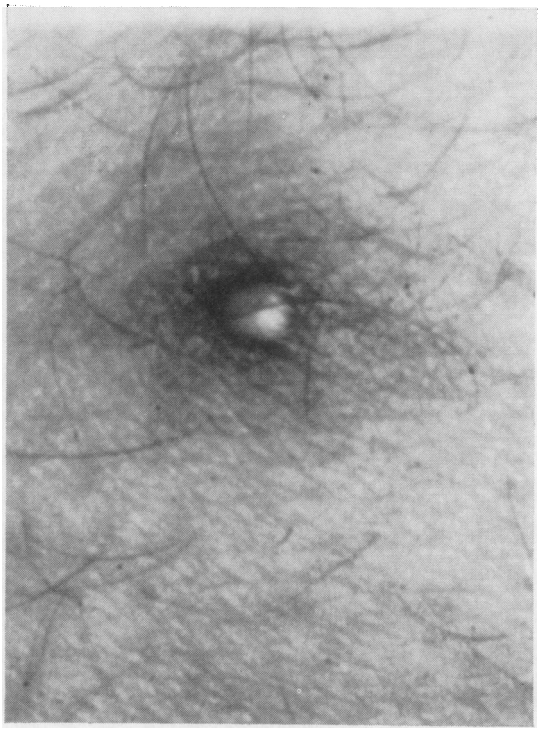

Fig. 7.—Skin sepsis in the form of a pustule.

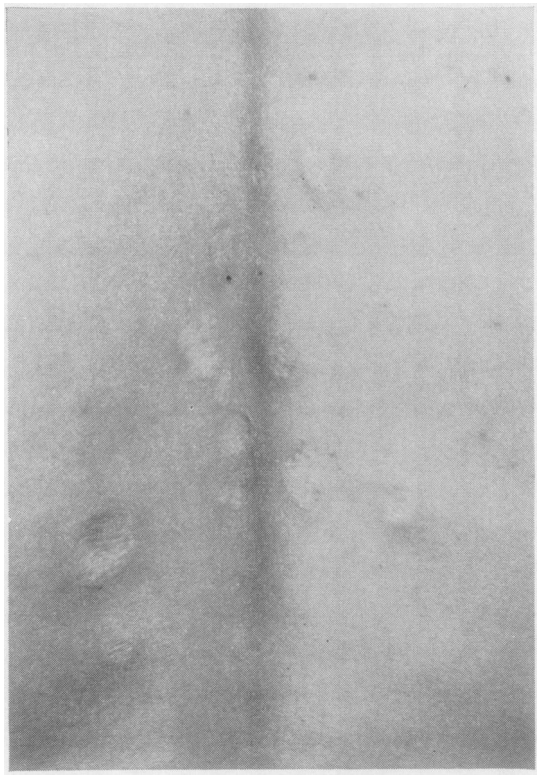

Fig. 8.—Scars of skin ulceration.

Family History

In four cases other members of the family were affected (Fig. 9).

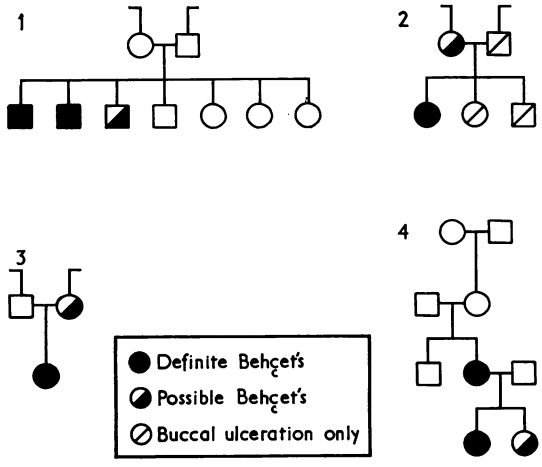

Fig. 9.—Family trees.

Few family aggregations of the disease have been described in the literature (Sezer, 1956, 1960; Fowler, Humpston, Nussey, and Small, 1968) but our experience suggests that this is not infrequent, so that a positive family history may assist the diagnosis.

Discussion

In this series, nineteen of 25 patients with Behçet's syndrome had an inflammatory polyarthritis, suggesting that this is a true component of the symptom complex. Unlike rheumatoid or psoriatic arthritis, the condition was self-limiting and non-destructive. It differed also from the arthritis associated with ulcerative colitis, which may also be associated with mouth ulceration (Wright and Watkinson, 1965), in that it did not appear to be characterized by relapses, and from Reiter's disease (apart from the absence of urethritis) in that the hands were more commonly affected than the feet. The knees were by far the most commonly affected joints.

It is not suggested that the incidence of symptoms shown by this survey is necessarily characteristic of the disease process as a whole, since our results may be biased by the selection of patients attending a Department of Rheumatology. We were impressed by the fact that buccal ulceration was present in all cases and consider that, in an uncertain case of inflammatory polyarthritis, it is often useful to enquire for this symptom as an aid to diagnosis.

Treatment is at present unsatisfactory. Of the nineteen cases with arthritis reviewed here, seven had been treated with systemic corticosteroids, and as far as their joints were concerned the result was never dramatic and usually unimpressive. Four patients had received courses of gold injections. Remission of the arthritis followed in two and there was no apparent effect in the third. In the fourth, there was a rapid exacerbation of mouth and skin ulcers before a likely therapeutic dose had been achieved.

On the incidence of the manifestations of the syndrome in this series, it is suggested that these may be grouped as follows:

Diagnostic Criteria

MAJOR	Buccal ulceration
	Genital ulceration
	Eye lesions
	Skin lesions
MINOR	Gastrointestinal lesions
	Thrombophlebitis
	Cardiovascular lesions
	Arthritis
	Central nervous system lesions
	Family history

On this basis it is suggested that to make a diagnosis of Behçet's syndrome a minimum of three major or two major and two minor criteria is required.

Summary

Of 33 patients with definite or possible Behçet's syndrome, 25 were considered to meet the diagnostic criteria and nineteen of these had an inflammatory polyarthropathy. The knees were most frequently affected, and the arthritis was not relapsing and tended to be self-limiting without permanent residua. The frequency of the manifestations of Behçet's syndrome in this series is described and arbitrary criteria for diagnosis are suggested.

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We also thank the Editor of the *Schweizerische Medizinische Wochenschrift* for permission to reproduce certain data (Mason and Barnes, 1968).

DISCUSSION

DR. J. A. BOYLE (*Glasgow*): I am not clear how you excluded the diagnosis of Reiter's disease in the male patient presenting with genital and buccal ulceration and arthritis.

DR. BARNES: Genital ulceration was always external and there was never any question of balanitis or urethral infection in any patient.

DR. M. WILKINSON (*Perth*): Did you do any histological studies of the joints?

DR. BARNES: We obtained histological material from two patients, one of whom had an avascular necrosis and had hip replacement performed, and another who had an excision and fusion of the manubriosternal joint which was the site of excruciating pain. The synovium showed chronic inflammatory change of a completely non-specific character.

DR. M. WILKINSON (*Perth*): Many of the complications of ulcerative colitis are very much like this. Did any patients have diarrhoea or a history of rectal bleeding?

DR. BARNES: One of the patients had diarrhoea with vomiting; another had true dysenteric symptoms, namely diarrhoea with mucus. One other patient, not in the eighteen I have reviewed since he did not have an arthritis, has developed classical ulcerative colitis. I cannot draw a definite dividing line between this syndrome and ulcerative colitis with the association of bowel manifestations, arthritis, mouth ulcers, etc.

DR. C. F. HAWKINS (*Birmingham*): Ulcers in the mouth are common in healthy people. Is there any difference between ulcers in Behçet's syndrome and those of aphthous stomatitis? Has anyone assessed the frequency of ulcers in the mouth in rheumatoid arthritis?

DR. BARNES: We have not made any specific survey of the incidence of mouth ulcers in rheumatoid arthritis. Since we became interested in Behçet's syndrome, most of our patients have been asked about mouth ulcers; we have not noticed any significant incidence in rheumatoid arthritics, but this is in no way a formal survey. The ulcers of Behçet's syndrome probably do not differ from ordinary aphthous stomatitis. The ulcers have no specific characteristics; they are extremely painful. We still take mouth ulceration alone as an incidental finding unless it is associated with the other criteria I have suggested.

DR. A. G. S. HILL (*Stoke Mandeville*): I presume this link with sacro-iliitis exists. In a personal series of two cases the sacro-iliac joints of one were *x*-rayed and there was unilateral involvement. I think this has been described elsewhere quite recently.

DR. BARNES: This was recently described by Professor Dilsen from Turkey at the Conference in Lisbon. He found a high incidence of sacro-iliitis in his cases of Behçet's syndrome. We have not. There was one patient in whom the sacro-iliac joints were a little doubtful but not definitely abnormal.

DR. A. G. S. HILL (*Stoke Mandeville*): Were they all examined?

DR. BARNES: About thirteen or fourteen of the eighteen patients.

DR. D. A. PITKEATHLY (*Wigan*): I would like to record an interesting family with Behçet's syndrome whom I have been looking after. A brother and sister in their teens are both affected with typical disease. The mother has an atypical arthritis with iritis but one couldn't make the diagnosis of Behçet's syndrome definitely; she however has unilateral sacro-iliitis.

DR. V. WRIGHT (*Leeds*): It is interesting to take, as you have done, the grouping of symptoms, but in ulcerative colitis patients have similar complications. They have skin lesions, mouth ulcers, arthritis, and eye lesions; and in one Scandinavian report of Behçet's syndrome, a patient at autopsy had ulcerative colitis. None of our patients with colitic arthritis has developed hypopyon or central nervous system involvement.

DR. BARNES: Central nervous system involvement was reported in 25 per cent. in a small series. In our series of 27 we have not yet observed any such involvement.

DR. R. E. PARTRIDGE (*Edinburgh*): I do not think this should be described as a separate disease until we get some criteria that everybody agrees on. I wonder if the disease you describe is the same as the disease seen in the Middle East?

DR. BARNES: We are describing not a disease but a syndrome.

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Le syndrome de Behçet compliqué d'arthrite

RÉSUMÉ

Des 33 malades avec le syndrome de Behçet défini ou possible, 25 étaient considérés comme ayant satisfait les critères diagnostiques et 19 d'entre eux avaient une polyarthropathie inflammatoire: Les genoux étaient le plus fréquemment affectés, sans rechute de l'arthrite qui avait tendance à se limiter d'elle-même sans laisser des séquelles permanentes. La fréquence des manifestations du syndrome de Behçet dans cette série est décrite et les critères diagnostiques arbitraires sont suggérés.

El síndrome de Behçet con poliartritis

SUMARIO

De 33 pacientes con síndrome de Behçet definitivo o posible se consideró que 25 correspondían a criterios diagnósticos y que 19 de ellos padecían poliartropatía inflamatoria. Las rodillas eran las más frecuentemente afectadas, y la poliartritis no era recidiva y tendía a ser autolimitante sin dejar residuo permanente. En esta serie se describe la frecuencia de las manifestaciones del síndrome de Behçet y se sugiere un criterio arbitrario para el diagnóstico.