Familial occurrence of psoriatic arthritis

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Although the association between psoriasis and arthritis has been known since the original description by Alibert (1818), it is only recently that the condition has become widely acknowledged as a disease *sui generis* (Vilanova and Piñol, 1951; Coste, Françon, Touraine, and Loyau, 1958; Wright, 1959).

The general acceptance of the disorder stems largely from epidemiological (Baker, 1965), clinical (Wright, 1956, 1961; Baker, Golding, and Thompson, 1963a), and radiological (Avila, Pugh, Slocumb, and Winkelmann, 1960) data reported over the last decade.

Despite this advance in our knowledge of psoriatic arthritis, the cause of the disorder remains unknown, but several recent studies have suggested that genetic factors may be important in aetiology (Tiedemann, 1951; Baker, Golding, and Thompson, 1963b; Theiss, Böni, Wagenhäuser, Schnyder, and Fehr, 1969a; Theiss, Schnyder, Böni, and Wagenhäuser, 1969b; Theiss, Schnyder, and Böni, 1970).

In order to examine further the importance of heredity in this disease, a large controlled family survey of probands with psoriatic arthritis has been undertaken at Leeds over a 2-year period. It is the purpose of this paper to report the major findings of this study.

Clinical material

The probands consisted of 88 patients with established psoriatic arthritis and twenty with psoriasis associated with other forms of arthritis. The composition of the proband sample is shown in Table I. Psoriatic arthritis was diagnosed according to the following criteria:

- (1) Unequivocal evidence of past or present psoriasis;
- (2) Unequivocal evidence of past or present inflammatory polyarthritis and/or sacroiliitis;
- (3) Persistently negative sheep-cell agglutination test.

Probands were ascertained from a hospital population, and sampling was consecutive and unselective. The 108 probands yielded 253 first-degree relatives, 48 second-degree relatives, and 83 spouse controls. The age distribution of probands, relatives, and spouses of both sexes showed a Gaussian (normal) pattern with the exception of a male preponderance of relatives in the 15 to 24 decade (Figs 1, 2, 3, overleaf).

The completion (response) rate was defined as:

$$\frac{\text{participant relatives or spouses}}{\text{relatives or spouses}} \times 100$$

Criteria for 'non-participation' and 'unavailability' used in the calculation of completion are shown in Fig. 4.

The overall completion rate (relatives and spouses) was 83 per cent. Individual completion rates for first- and second-degree relatives and spouses feature in Fig. 5.

Table I Composition of proband sample

Proband diagnosis		Sex		
		Male	Female	Total
True psoriatic arthritis	1. Distal pattern	19	26	45
	2. Rheumatoid arthritis	5	26	31
	3. Arthritis mutilans	1	5	6
	4. Spondylitis	5	1	6
	Total	30	58	88
Psoriasis + other arthritis	1. Psoriasis + Rheumatoid arthritis	2	10	12
	2. Psoriasis + Osteoarthritis	1	6	7
	3. Psoriasis + Gout	1	0	1
	Total	4	16	20

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FIG. 1 Age distribution of probands

FIG. 2 Age distribution of relatives

FIG. 3 Age distribution of spouses

FIG. 4 Derivation of survey population and reasons for non-participation and unavailability of family members

FIG. 5 Completion rate of relatives and spouses

Methods

Relatives and spouses were divided into inner and outer area groups. This division was based on a boundary of 20 miles radius from the study centre at Leeds (Fig. 6).

(1) CLINICAL METHOD

All inner-area subjects were examined clinically, radiologically, and serologically. The outer-area subjects were examined only radiologically at their local hospital. Thirty-five hospitals scattered throughout the United Kingdom participated in the outer-area survey.

The clinical examination was directed particularly to the integumentary and locomotor systems. The clinical conditions of particular interest to the present study were:

(i) Psoriasis

Baker's criteria (Baker, 1965) were applied to borderline cases. These criteria are shown in the Appendix. In the

FIG. 6 Map of inner survey area

event of remaining diagnostic uncertainty, the opinion of a consultant dermatologist was sought and Tfracuril testing (Holti, 1964) carried out when necessary.

(ii) *Inflammatory polyarthritis*

This was diagnosed according to the New York criteria for rheumatoid arthritis (Bennett and Wood, 1968) which were suitably modified to allow for important differences shown by psoriatic arthritis (see Appendix).

(iii) *Clinical evidence of ankylosing spondylitis*

Care was taken to correct chest and spinal measurements for both age and sex—factors which we have shown in separate studies to be important in modifying these movements (Moll and Wright, 1971, 1972). Chest expansion was measured by the conventional tape-measure method. Spinal mobility was measured in three directions (anterior flexion, lateral flexion, and extension) according to new objective clinical methods developed at Leeds (Macrae and Wright, 1969; Moll, Liyanage, and Wright, 1972a, b). The New York criteria (Bennett and Wood, 1968) for diagnosing ankylosing spondylitis were adopted (see Appendix).

(2) **RADIOLOGICAL METHOD**

The radiological examination included the following requirements for arthritis surveys laid down by the New York symposium (Bennett and Wood, 1968): postero-anterior (PA) view of the hands to include the wrist; antero-posterior (AP) view of the feet without weight bearing; antero-posterior (AP) view of the pelvis taken supine and to include the hips. The total number and type of x rays examined during the survey are shown in Table II.

Because of the radiation hazard, pelvic x rays were not taken in females under 45 years. Males under 15 years, who are also exempt from pelvic radiology by international agreement, were not included for study.

Table II Total (probands, relatives, and spouses) x rays examined during survey

X ray	View	Age (yrs)		No. of cases	
		M	F	M	F
Hands	PA	All	All	219	273
Feet	AP	All	All	219	273
Pelvis	AP	15+	45+	223	202

(3) **SEROLOGICAL METHOD**

For the estimation of rheumatoid factor each subject was asked to give a sample of blood. According to the New York recommendations (Bennett and Wood, 1968), the following details were observed:

- (i) Only serum was used because of insufficient information on the influence of anticoagulants.
- (ii) Every attempt was made to avoid bacterial contamination.
- (iii) Centrifugation of blood specimens was carried out without unnecessary delay (usually within 6 to 12 hours).
- (iv) Sera were stored without preservatives at -20°C .

The differential agglutination test (DAT) was carried out by a modification of the method originally described by Rose, Ragan, Pearce, and Lipman (1948), and later tested for the Association of Clinical Pathologists by Greenbury (1957). The test was performed by a senior laboratory technician as part of the routine hospital service. Previous experience at Leeds has led to the adoption of 1:32 or over as a positive titre, compared with a titre of 1:16 recognized by some centres.

(4) **STATISTICAL METHOD**

In assessing the significance of the difference between pairs of prevalences, three methods were used according to the numerator and denominator characteristics of the fractions involved.

When the expected cell frequency (*i.e.* expected on the null hypothesis in terms of row and column totals) was 6 or more than 6, the χ^2 test was used. In cases in which the lowest cell integer in the contingency table was less than 6, and the highest not greater than 999, computations were made using Fisher's exact test. When the highest cell frequency exceeded 999 and the lowest was less than 6, the binomial method was employed. (Fisher's exact test could not be undertaken when the largest figure exceeded 999 because common logarithms of factorials include only integers 1-999.)

Results

PEDIGREE STUDY

Of the probands with psoriatic arthritis (88 patients), ten (12.5 per cent.) had at least one relative with personally confirmed psoriatic arthritis (peripheral psoriatic arthritis, eight cases; psoriatic spondylitis, two cases; peripheral psoriatic arthritis and spondylitis, one case). By contrast, probands with psoriasis and other arthritis (twenty patients) had no relatives affected with psoriatic arthritis.

Table III Details of first-degree (10) and second-degree (1) relatives with confirmed psoriatic arthritis

Pedigree number	Proband diagnosis	Relationship to proband	Age (yrs)	Clinical grade of polyarthritis	Joints involved*	Nail psoriasis†
13/II-1	PAr	Mother	76	2	MTP, K	+
13/II-3	PAr	Brother	55	2	PIP, K, H	+
25/II-9	PAd	Sister	57	2	PIP	0
30/II-4	PAd	Brother	47	—	SI	+
43/III-3	PAd	Daughter	44	2	PIP	0
46/II-9	PAr	Father	60	2	PIP, W, K, SI	0
56/II-6	PAd	Sister	52	3	MCP	+
67/II-5	PAd	Brother	49	4	MCP, PIP	0
94/I-3	PAd	Mother	61	—	SI	0
107/I-4	PAd	Mother	49	3	MCP, PIP, W, K	0
111/III-9	PAs	Maternal aunt	55	2	PIP	+

* PIP = proximal interphalangeal joint; MCP = metacarpophalangeal joint; MTP = metatarsophalangeal joint; W = wrist; K = knee; H = hip; SI = sacroiliac joint.
† + = present; 0 = absent.

Details of affected relatives are shown in Table III. Further data on these subjects will be presented in the following pedigree reports. Because of the particular interest and rarity of these pedigrees they have been described in considerable detail. The pedigree charts and key are shown on pp. 188 and 189.

Family 13 (Fig. 7)

Proband

A man aged 50 years developed peripheral arthritis principally affecting the metatarsophalangeal (MTP) joints, knees, and hips at the age of 28 years. Fourteen years later, symptoms appeared in the cervical spine and lower back which have both remained painful and stiff. The main complaint at the time of examination was of pain in the right hip. Six months after the onset of arthritis he developed psoriasis. At first this was mild, but when he heard that his father had developed carcinoma the rash became very extensive. Examination revealed small patches of psoriasis on the scalp, elbows, and knees. The nails were normal. The only evidence of polyarthritis at the time of survey was swelling and tenderness of the proximal interphalangeal (PIP) joint of the right thumb. Chest expansion and spinal mobility were normal. The DAT was negative, and the erythrocyte sedimentation rate (ESR) was 36 mm./1st hr. Radiological examination of the hands and feet revealed no convincing abnormality, but the pelvic x ray showed bilateral grade 3 sacroiliitis.

Affected relatives

The brother (II-3), aged 55 years, was a known case of psoriasis. When examined for the survey, the rash involved extensive areas of the arms, legs, and back. The nails were pitted and ridged. The arthritis was of clinically similar

pattern to that of the proband. X rays of the hands were normal, but those of the feet showed grade 4 erosions of both 5th PIP joints. The spine was not involved either clinically or radiologically. The DAT was negative.

The mother (I-1), aged 76 years, also had psoriatic arthritis of mild degree. On examination, small patches of typical psoriasis were evident on the chest, and the left little finger-nail was involved. Although pain and swelling had been experienced recently in the knees and feet, at the time of survey examination the locomotor system was normal. X rays of the hands, feet, and pelvis showed no abnormality, and the DAT was negative.

The eldest son (III-1), aged 23 years, had had psoriatic patches on the extensor surface of the arms very similar to his father's rash, but no psoriasis was evident at the time of examination.

Comment

Two main points of interest are illustrated by this family.

(1) The aggravation of the proband's psoriasis on hearing that his father had developed carcinoma was just one of many examples in the study in which a strong link could be demonstrated between worsening of the rash and emotional trauma.

(2) Both the proband's mother and brother had a polyarthritis of very similar pattern to that of the proband. Moreover, this arthritis predominantly affected the feet. In our experience this is one of the characteristic patterns of presentation of psoriatic arthritis.

Family 25 (Fig. 8)

Proband

A man aged 49 years first had psoriasis at the age of 17 years and this was not complicated by arthritis until 12

years later. Throughout, the arthritis has been of typical DIP pattern. Examination revealed psoriasis of mild degree affecting the elbows, knees, natal cleft, groins, and scalp. The nails of the fingers showed typical pitting. Slight swelling and tenderness were evident in all DIP joints of both hands and feet, and similar involvement affected the PIP and MCP joints, knees, and shoulders. The DAT was negative and *x* rays of the hands, feet, and pelvis were normal.

Affected relatives

The eldest brother (II-3) and youngest sister (II-9) were found to have uncomplicated psoriasis, and a niece (III-2) and maternal uncle (I-2) were reported to have had the disorder.

A sister (II-6), aged 57 years, was found to have mild psoriatic arthritis. The psoriasis was distributed in small plaques over the elbows, knees, and posterior thighs. Pain, stiffness, and intermittent swelling had involved the PIP joints of the middle and ring fingers, but at the time of examination there was no definite abnormality. The DAT was negative and *x* rays of hands, feet, and pelvis were normal.

Comment

The distribution of psoriasis in this family (probable and definite cases) is consistent with autosomal dominant transmission. This is evidenced by the vertical pattern of inheritance and the 1:1 ratio between affected and unaffected sibs (proband included).

Family 30 (Fig. 9)

Proband

A man aged 47 years first noticed psoriasis in 1963. The rash appeared on the buttocks and later spread to the knees, scalp, and ears. Four years later acute arthritis developed in the right ankle, and since this time the left index finger, left ankle, fourth toe, and right shoulder have become involved. Recent examination revealed typical psoriasis on the right knee, natal cleft, and scalp. The right middle finger-nail was ridged and slight onycholysis was present at the left index finger-nail and thumb-nail. Although active arthritis had previously been confirmed at the ankles, left index finger (flexor tendon involvement), and DIP joint of the left 4th toe, no evidence of this could be found at the time of examination. The latex screen test and DAT have been persistently negative. Radiological examination of hands, feet, and pelvis revealed no abnormality.

Affected relatives

The father (I-12), who had died many years previously, was said to have been 'crippled with arthritis'. Apparently this had severely affected his hands (the fingers were 'knobbly' and deviated ulnar-wards), knees, and feet. His back was 'bent, painful, and stiff'. Psoriasis had been present on the buttocks.

The proband's mother (I-11), aged 86 years, although symptom-free, was found to have grade 3 bilateral sacroiliitis.

The proband's triplet brothers provided much interest. The identical brother (II-4) was found to have psoriasis

and definite ankylosing spondylitis, while the non-identical brother (II-5) was entirely normal.

Comment

As one of us has commented elsewhere (Wright, 1969), this family represents the first reported example of psoriatic arthritis in triplets. The proband had peripheral psoriatic arthritis and his identical brother psoriatic spondylitis.

Of further interest was the presence of pain-free sacroiliitis in the mother, and also the reliable information from the proband's sister (a qualified nurse) that the father had had severe arthritis of the hands and spine. It is possible that the illness of both parents represented conjugal spondylitis.

Family 43 (Fig. 10)

Proband

A woman aged 62 years first developed arthritis at the age of 55 years. The arthritis has been largely confined to the hands, wrists, and ankles. Having had arthritis for 2 years, she then noticed psoriatic patches of classical distribution. Examination confirmed these lesions, and the arthritis was found to be of DIP distribution. The left 5th and right 3rd DIP joints were the site of swelling and flexion deformity. The other joints which had been painful—the MCP joints of both hands, wrists and ankles—were normal in appearance. The DAT was negative and radiological examination revealed grade 4 erosions, narrowing and osteoporosis at the wrists, and soft tissue swelling of the left 2nd DIP joint. Grade 3 erosions, narrowing, osteoporosis and subluxation were evident at the 2nd, 3rd, and 5th MTP joints of both feet. The pelvic *x* ray was normal.

Affected relatives

The sister (III-3), aged 44 years, was found to have psoriatic arthritis. The psoriasis first appeared at the age of 34 years, and was followed 5 years later by an asymmetrical arthritis of the fingers and knees. Examination confirmed small areas of psoriasis on the knees and shins. The nails were not involved. The right 4th PIP joint was slightly swollen, but other joints at this time showed no abnormality. The DAT was negative. *X* rays of the hands and feet were normal. In view of the patient's age, the pelvis was not *x* rayed.

Comment

Two important points are illustrated here:

(1) The temporal relationship between the onset of psoriasis and arthritis. In the proband, arthritis preceded psoriasis; in the affected sister, psoriasis preceded arthritis. This variation of presentation was often seen in our series, in contrast to the simultaneous onset of psoriasis and arthritis which was only rarely encountered.

(2) The asymmetrical oligoarticular pattern of psoriatic arthritis in both proband and affected relatives, in contrast to the symmetry and multi-joint involvement of rheumatoid arthritis, was found to be a relatively common presentation. In fact, we now regard this to be a characteristic feature of psoriatic arthritis.

Family 46 (Fig. 11)*Proband*

A woman aged 31 years had had psoriasis for 6 years when arthritis developed in the hands, wrists, elbows, shoulders, left knee, ankles, and feet at the age of 19 years. Back pain appeared at the same time as the polyarthritis. This was experienced at night and was not relieved by rest. The pain often radiated to the left buttock. Examination confirmed the presence of psoriasis which at the time of survey was confined to the scalp and finger-nails. Previously it had been more extensive. No obvious joint swelling or tenderness was evident at this time, but the patient pointed to the 2nd MCP, 2nd PIP and 1st and 5th DIP joints of the right thumb, both wrists, ankles, and feet as being the most persistently painful areas. Chest expansion and spinal mobility were normal. The DAT was negative. Radiological examination revealed grade 2 erosions of both ulnar styloid processes. The feet and pelvic x rays were normal.

Affected relatives

The mother (II-4) and maternal aunt (II-2), now deceased, had had 'arthritis' of the feet and knees, and a paternal uncle (II-8) and the paternal grandmother (I-1) were thought to have had psoriasis.

The father (II-9), aged 60 years, had had psoriasis which recently had become replaced by a seronegative polyarthritis involving the right PIP joints, right wrist, and left knee. The affected finger joints were swollen and the site of a swan's neck deformity. In addition, he had had long-standing pain in the lumbar region. Examination revealed limitation of spinal extension and chest expansion of only 2.6 cm. Radiological examination showed grade 2 sclerosis and erosion of the sacroiliac joints. The patient was considered to be an example of psoriatic arthritis complicated by definite ankylosing spondylitis (New York criteria).

Comment

This pedigree provides an interesting example of familial linkage between psoriatic arthritis (proband) and ankylosing spondylitis (proband's father), and also further supports the concept of 'psoriatic spondylitis'.

Family 56 (Fig. 12)*Proband*

A man aged 49 years had had psoriasis of the skin and nails since the age of 16 years and developed inflammatory polyarthritis 29 years later. Examination revealed typical psoriasis of the scalp, elbows, knees, and natal cleft. The nails were normal. An asymmetrical arthritis affected the hands and feet. Swelling was evident at the MCP and DIP joints of the right thumb, and PIP and DIP joints of the index and little fingers respectively. The left ankle and PIP joints of the right foot were also involved. The DAT was negative. Radiological examination of the hands and pelvis were normal, and only borderline erosions and narrowing were evident at the DIP joints of the feet.

Affected relatives

The mother (I-7), eldest brother (II-1), and second sister

(II-3), all deceased, were thought to have had psoriasis.

A sister (II-6), aged 52 years, was found to have psoriasis associated with asymmetrical seronegative arthritis. The psoriasis, affecting both skin and nails, appeared at the age of 7 years. The arthritis presented much later when the patient was aged 48 years. Examination revealed swelling of the 3rd and 4th MCP joints of the right hand only. However, pain and stiffness had been experienced in the PIP joints of the hands and feet, and also in the wrists, left elbow, knees, and ankles. Despite a complaint of morning stiffness in the back, which appeared at the same time as the peripheral arthritis, spinal examination and chest expansion were entirely normal. The DAT was negative, and x ray examination of the hands, feet, and pelvis was normal.

Comment

The presentation of psoriatic arthritis in both the proband and her sister exemplifies the fact that in psoriatic arthritis the onset of psoriasis and the onset of arthritis may be separated by many years. In the proband, arthritis followed the rash after 29 years, and in the affected sister the interval was even longer (41 years).

Family 67 (Fig. 13)*Proband*

A woman aged 69 years developed psoriasis and arthritis simultaneously at the age of 54 years. Examination revealed typical psoriasis on the elbows and knees. Tenderness and swelling were present at the right MCP and PIP joints, and left 2nd and 3rd PIP joints. Although no changes were evident in these joints, she had had much pain in the DIP joints of the fingers and toes, and also in the wrists and elbows. The DAT was negative. Radiological examination revealed grade 3 erosions and narrowing of the right 2nd and 4th DIP joints and similar involvement of both wrists.

Affected relatives

Three brothers (II-2, 3, 5) had uncomplicated psoriasis and a fourth (II-7), aged 49 years, had psoriasis complicated by arthritis of similar pattern to that of the proband. For over 10 years pain and swelling had affected the MCP and PIP joints of the right hand, both wrists, elbows, shoulders, knees, ankles, and feet. On examination, an asymmetrical arthritis was evident which affected the 2nd right MCP and 3rd PIP joints, both of which were swollen and tender. Psoriasis was present on the elbows, groins, and genital area. The DAT was negative. Radiological examination revealed grade 3 erosions and soft tissue swelling of the right PIP joint and left 3rd and 5th MCP joints. The feet and sacroiliac joints were normal.

Comment

The intrafamilial clustering of relatives with psoriatic arthritis and relatives with psoriasis unassociated with arthritis is well illustrated in this pedigree. The co-existence of complicated and uncomplicated cases of psoriasis was frequently observed in pedigrees of the present series.

Family 94 (Fig. 14)

Proband

A 25-year-old woman developed psoriasis at the age of 14 years. The rash gradually cleared until at the age of 19 years skin lesions were entirely absent. At this time the nails became affected, and 2 months later arthritis developed in the DIP joint of the right hallux after surgical removal of the nail of this toe. Later, the DIP joints of the right thumb and 5th finger and the left 2nd finger became involved. Examination at this time revealed tenderness, erythema, and swelling of affected joints. A topographical relationship between arthritic joints and affected nails was observed. The nails were pitted and keratotic. The ESR was 18mm./1st hr, and the DAT was persistently negative. Radiological examination showed grade 3 erosions and narrowing of the right 5th DIP joint, and grade 2 erosions and narrowing of the left 2nd DIP joints. X rays of the feet and pelvis were normal.

Affected relatives

The mother (I-3), aged 61 years, developed psoriasis at the age of 56 years, and this was confirmed on examination; 4 years previously she had become troubled by attacks of lumbo-sacral pain radiating down the right leg. At about the same time pain had appeared in the ends of the fingers and bases of the thumbs. Chest expansion and spinal mobility were normal, although anterior flexion (Schober's modified method) was at the lower range of normality (4.2 cm.). Examination of the peripheral joints revealed typical Heberden's nodes and no evidence of inflammatory arthropathy. Radiological examination revealed normal hands and feet, except for osteoarthrotic change. However, bilateral grade 3 sclerosis and grade 2 erosions were clearly evident in the left sacroiliac joint.

Comment

The proband exhibits an uncommon but characteristic topographical relationship between psoriatic nails and arthritis of neighbouring DIP joints.

The family tree provides another example of familial linkage between peripheral psoriatic arthritis and psoriatic spondylitis.

Family 107 (Fig. 15)

Proband

A young woman aged 19 years was noticed to have psoriasis at the age of 3 years. This remained uncomplicated until the age 17 when she developed arthritis of the PIP and DIP joints of both hands, and also involvement of the knees. At no time has she had spinal symptoms. Examination confirmed typical psoriasis of the scalp and left elbow. The finger-nails were affected by psoriatic thickening and onycholysis. Swelling, tenderness, and flexion deformity were evident at the right 2nd and 5th, and left 4th PIP joints. A similar pattern was seen at the left 5th PIP joint. Although chest expansion was normal, anterior lumbar flexion was limited according to Schober's modified method. The DAT has been negative on several occasions, and radiological examination showed grade 3 erosions in the joints affected clinically. Bilateral grade 2 sacroiliitis was revealed on pelvic radiography.

Affected relatives

The father (I-2) and mother (I-4) were both found to have typical psoriasis. The mother, aged 49 years, had also had an inflammatory polyarthritis which had necessitated hospital treatment. At the time of examination, however, she had no evidence of arthritis either clinically or radiologically. The DAT was negative.

Comment

The interesting feature here was the entirely pain-free presentation of psoriatic spondylitis in the proband. We have also observed this in spondylitic relatives of patients with psoriatic arthritis. Symptomless spondylitis may also be seen in idiopathic ankylosing spondylitis, but in our experience this is less frequent in this condition (6.6 per cent. of ninety patients) compared with the frequency in psoriatic spondylitis (23 per cent. of seventeen patients).

Family 111 (Fig. 16)

Proband

A young man aged 25 years developed psoriasis at the age of 14 years, and 5 years later pain and stiffness appeared in the thoracolumbar spine and right buttock. The stiffness was worse in the morning. At no time has there been any evidence of peripheral arthritis. Examination revealed psoriasis of the scalp. The locomotor system was normal. The ESR was 9 mm./1st hr; the DAT was negative. The hands and feet were radiologically normal, but the pelvic x ray revealed bilateral grade 2 sclerosis.

Affected relatives

Uncomplicated psoriasis was apparently present in ten relatives who were not available for study (I-1; II-1, 3, 5; III-2, 6; IV-5, 9, 13, 21). In a further two, the rash was confirmed on examination (III-9, 10); one of these (III-9), a maternal aunt aged 55 years, in addition to psoriasis also had a seronegative polyarthritis. Pain, stiffness, and swelling of the PIP joints of the fingers had been present for over 2 years, and this was confirmed on examination. The psoriasis affected the elbows, knees, groins, natal cleft, breasts, and back. The toe-nails showed hyperkeratosis and lateral discolouration. The finger-nails were normal.

A second maternal aunt (III-8), aged 71 years, although free from psoriasis, had had a chronic childhood polyarthritis.

Two further maternal aunts (III-5, 7) suffered from uncomplicated monarticular arthritis—in one case affecting the right 3rd PIP, and in the other the left 1st PIP joint. All three relatives (III, 5, 7, 8,) were seronegative, and all had normal x rays of hands, feet, and pelvis.

Comment

This family provides further support for the contention that psoriatic spondylitis is likely to be an alternative clinico-radiological expression of psoriatic arthritis.

The intrafamilial co-existence of uncomplicated psoriasis (ten cases) with psoriatic arthritis is also well shown in this pedigree.

Epidemiological aspects

For the purpose of this analysis only the results obtained from first-degree relatives will be reported. The small number of second-degree relatives did not justify statistical evaluation.

(1) PREVALENCE OF PSORIATIC ARTHRITIS

Psoriatic arthritis as defined in the present survey included not only subjects with psoriasis and polyarthritis but also those with psoriasis and sacroiliitis (Wright and Moll, 1971). However, estimates of psoriatic arthritis in the general population are based on the definition of psoriatic arthritis as 'psoriasis associated with seronegative polyarthritis'. In order to compare our results with control data, the frequency for peripheral psoriatic arthritis will therefore be used.

Reference to Table IV and Fig. 17 shows that eight (4.4 per cent.) of 181 first-degree relatives of patients with psoriatic arthritis had peripheral psoriatic arthritis (two with psoriatic spondylitis were not

included in this group). Compared with spouse controls ($P = 0.04$) and population controls ($P < 10^{-8}$), the difference was statistically significant. The greater difference between the prevalence of psoriatic arthritis in relatives and population controls compared with spouse controls will be discussed later. By contrast, no cases of psoriatic arthritis were found in relatives of patients with psoriasis and other arthritis.

In view of the absence of epidemiological data on the frequency of psoriatic arthritis in the general population, it was necessary to use an estimated prevalence. This was calculated from:

- (1) The frequency of psoriasis in the general population. This is generally considered to be between 1-2 per cent. (Ingram, 1954; Baker, 1966). For the purpose of our calculation the intermediate prevalence, 1.5 per cent., was used:
- (2) The most reliable estimate of the frequency of inflammatory polyarthritis in a psoriatic population, 6.8 per cent. (Leczinsky, 1948);

Table IV Prevalence of peripheral psoriatic arthritis (present, grade 2-4) in (1) first-degree relatives of psoriatic arthritis (PA) probands, (2) first-degree relatives of probands with psoriasis and other arthritis (P + A), (3) spouse and population controls

Prevalence	In first-degree relatives of PA probands						In first-degree relatives of P + A probands						In controls			
			Total		Significance				Total		Significance		Spouse		Population	
	M	F	No.	Per cent.	Spouse P	Popn. P	M	F	No.	Per cent.	Spouse P	Popn. P	No.	Per cent.	No.	Per cent.
Peripheral psoriatic arthritis	3	5	8	4.4	0.04	<10 ⁻⁸	0	0	0	0	NS	NS	0	0	536,000	0.10
			181						33				79		52.6M	

NS = Not statistically significant ($P > 0.05$).

FIG. 17 Prevalence of peripheral psoriatic arthritis in first-degree relatives of psoriatic arthritis probands (PA) and first-degree relatives of probands with psoriasis and other arthritis (P + A) compared with prevalence in spouse (S) and population (P) controls. The statistical significance of the difference between the prevalence in relatives and controls is indicated above the appropriate control value. N.S. = not statistically significant

FIG. 18 Prevalence of psoriasis in first-degree relatives of psoriatic arthritis probands (PA) and first-degree relatives of probands with psoriasis and other arthritis (P + A) compared with the prevalence in spouse (S) and population (P) controls. The statistical significance of the difference between the prevalence in relatives and controls is indicated above the appropriate control value. N.S. = not statistically significant

FIG. 19 Prevalence of uncomplicated seronegative clinical seronegative arthritis in first-degree relatives of psoriatic arthritis probands (PA) and first-degree relatives of probands with psoriasis and other arthritis (P + A) compared with the prevalence in spouse (S) and population (P) controls. The statistical significance of the difference between the prevalence in relatives and controls is indicated above the appropriate control value. N.S. = not statistically significant

- (3) The current population of the United Kingdom, 52.6 million. Our calculated prevalence of 0.10 per cent. closely conforms to previous estimates of the population prevalence of psoriatic arthritis (Leader, *ARC*, 1967; Theiss and others, 1969b, 1970).

If relatives with psoriatic spondylitis without polyarthritis (two cases) are included as examples of psoriatic arthritis, the overall prevalence of psoriatic arthritis among first-degree relatives is 5.5 per cent. (Table V).

Table V Overall prevalence of psoriatic arthritis

Presentation of psoriatic arthritis	No.	Per cent.
Psoriasis + seronegative polyarthritis	7	3.8
Psoriasis + seronegative polyarthritis + sacroiliitis	1	0.5
Psoriasis + sacro-iliitis	2	1.1
Total	10	5.5

(2) PREVALENCE OF RELATED CONDITIONS

We felt that it would be interesting to report the individual prevalences of clinical and radiological conditions contributing to the psoriatic arthritis complex.

(i) Psoriasis

In view of the intermittent nature of psoriasis, both present and past evidence of the disease were included in order to provide a realistic frequency of the

condition. However, past episodes of psoriasis were included only if the diagnosis had been previously confirmed by a physician.

Table VI and Fig. 18 show that first-degree relatives of probands both with psoriatic arthritis and with psoriasis and other arthritis were affected with psoriasis significantly more often than either spouse or population controls. Of the 38 affected relatives of psoriatic arthritis probands, 31 had personally confirmed psoriasis, and seven, although affected in the past, were clear at the time of examination.

Similarly, of the six affected relatives of probands with psoriasis and other arthritis, five had a rash at the time of examination and one evidence of past psoriasis only.

The similarity between the prevalence of psoriasis in relatives of psoriatic arthritic probands (21 per cent.) and the prevalence in relatives of probands with psoriasis and other arthritis (18.1 per cent.) will be discussed later.

(ii) Uncomplicated seronegative clinical polyarthritis

The prevalence of seronegative polyarthritis without psoriasis is shown in Table VI and Fig. 19. In the first-degree relatives of psoriatic arthritis probands a significantly increased frequency of uncomplicated seronegative polyarthritis was found with regard to both spouse ($P=0.05$) and population ($P=0.03$) controls. By contrast, the prevalence (6 per cent.) in relatives of probands with psoriasis and other arthritis was not greater than would be expected in population controls.

Table VI Prevalence of

- (1) psoriasis (past 7; present 31);
- (2) uncomplicated (without psoriasis) seronegative clinical polyarthritis (present, grade 2-4);
- (3) erosive polyarthritis (grade 2-4);
- (4) sacroiliitis (grade 2-4) in first-degree relatives of psoriatic arthritis (PA) probands, first-degree relatives of probands with psoriasis and other arthritis (P + A) and controls

Feature	First-degree relatives of PA probands						First-degree relatives of P + A probands						Controls				Reference
			Total		Significance				Total		Significance		Spouse		Population		
	M	F	No.	Per cent.	Spouse P	Popn. P	M	F	No.	Per cent.	Spouse P	Popn. P	No.	Per cent.	No.	Per cent.	
Psoriasis	17	21	38	21.0	0.00002	<0.0005	3	3	6	18.1	0.008	<10 ⁻⁹	2	2.5	38	1.1	Lawrence (1967)
			181						33				79		3486		
Uncomplicated seronegative clinical polyarthritis	4	8	12	6.6	0.05	0.03	0	2	2	6.0	NS	NS	1	1.2	<4	<2.2	Lawrence and Ball (1958)
			181						33				79		183		
Erosive polyarthritis	4	0	4	1.8	NS	NS	0	2	2	5.0	NS	NS	0	0	48	3.3	Lawrence Behrend, Bennett, Bremner, Burch, Gofton, O'Brien, and Robinson (1966)
			221						40				84		1476		
Sacroiliitis	5	8	13	7.4	0.04	0.005	0	0	0	0	NS	NS	1	1.3	3	1.1	Macrae and Moll (1972)
			174						27				76		266		

NS = Not statistically significant ($P > 0.05$).

FIG. 20 Prevalence of erosive polyarthritis in first-degree relatives of psoriatic arthritis probands (PA) and first-degree relatives of probands with psoriasis and other arthritis (P + A) compared with the prevalence in spouse (S) and population (P) controls. The statistical significance of the difference between the prevalence in relatives and controls is indicated above the appropriate control value. N.S. = not statistically significant

FIG. 21 Prevalence of sacroiliitis in first-degree relatives of psoriatic arthritis probands (P) and first-degree relatives of probands with psoriasis and other arthritis (P + A) compared with the prevalence in spouse (S) and population (P) controls. The statistical significance of the difference between the prevalence in relatives and controls is indicated above the appropriate control value. N.S. = not statistically significant

(iii) Erosive polyarthritis

No significant increase in frequency of erosive polyarthritis was found either in relatives of psoriatic arthritis probands or in relatives of probands with psoriasis and other arthritis, compared with spouse and population controls (Table VI and Fig. 20). Of the four relatives of psoriatic arthritis probands with erosive arthritis, two had psoriatic arthritis. Patients with erosive peripheral psoriatic arthritis represent only 25 per cent. of the total (two of eight). The significance of this observation will be discussed later.

(iv) Sacroiliitis

The prevalence of grade 2-4 sacroiliitis (7.4 per cent.) was significantly greater in first-degree relatives of psoriatic arthritis probands than in spouse ($P = 0.04$) or population ($P = 0.005$) controls (Table VI and Fig. 21). No such difference was observed between relatives of probands with psoriasis and other arthritis, and controls.

Of the thirteen affected relatives, seven had uncomplicated sacroiliitis, three had sacroiliitis + clinical polyarthritis, two had sacroiliitis + psoriasis, and

FIG. 22 Clinical 'overlap' in first-degree relatives of probands with psoriatic arthritis

FIG. 23 Clinical 'overlap' in first-degree relatives of probands with psoriasis and other arthritis

FIG. 24 Clinical 'overlap' in spouse controls

one had the full complement of sacroiliitis + clinical polyarthritis + psoriasis.

Of the thirteen relatives with sacroiliitis, eleven (6.3 per cent.) had definite ankylosing spondylitis according to New York criteria.

(3) CLINICAL OVERLAP BETWEEN PSORIASIS, POLYARTHRITIS, AND SACROILIITIS

We were struck by the overlap between clinical and radiological conditions relevant to the psoriatic arthritis complex. Venn diagrams illustrate the degree of this overlap in first-degree relatives of psoriatic arthritis probands (Fig. 22), first-degree relatives of probands with psoriasis and other arthritis (Fig. 23), and spouse controls (Fig. 24). The spectrum of associations between clinical features in first-degree relatives of psoriatic arthritis probands is summarized in Table VII. The largest group of affected relatives

Table VII *Combinations of clinical features in affected first-degree relatives of patients with psoriatic arthritis*

No.	Per cent.	Combination of features in individuals
28	47.4	Psoriasis alone
9	15.2	Clinical arthritis alone
7	11.8	Sacroiliitis alone
2	5.3	Erosive arthritis alone
5	8.3	Psoriasis + clinical arthritis
3	5.0	Sacroiliitis + clinical arthritis
2	3.3	Psoriasis + sacroiliitis
2	3.3	Psoriasis + clinical + erosive arthritis
1	2.4	Psoriasis + clinical + sacro-iliitis

were those with uncomplicated psoriasis (47.4 per cent.). Of the eight relatives with peripheral psoriatic arthritis, only two had erosive arthritis and one sacroiliitis. Two relatives had psoriasis and sacroiliitis without peripheral arthritis. Some authors (Baker and others, 1963a) would term this 'psoriatic spondylitis' and would include these cases as examples of psoriatic arthritis. This point of definition remains debatable, but we agree that these individuals should be diagnosed 'psoriatic arthritis' despite the absence of peripheral arthritis.

Of particular note was the high proportion (15.2 per cent.) of relatives with uncomplicated seronegative clinical polyarthritis (grade 2-4). The possible significance of this type of arthritis will be discussed later.

In addition, there were also four relatives with grade 1 arthritis (two joints involved), three with monoarthritis, and three with a convincing history of prolonged arthritis in childhood. In subjects with only one or two affected joints the arthritis was usually confined to PIP joints.

Familial aggregation and heritability

(1) FAMILIAL AGGREGATION

A popular index for expressing the degree of familial aggregation is the K factor (Harris, 1962; Kellgren, 1964). This is defined as the ratio between the observed prevalence in relatives and the expected prevalence in spouse or population controls. K provides a convenient means by which hereditary comparisons can be made between diseases. Although the factor provides no indication of the mechanism of inheritance, it does indicate the importance of genetic factors if spouse controls are used in the calculation. Any K value exceeding 10 should be regarded as a significant index of genetic determination.

The degree of familial aggregation was calculated for peripheral psoriatic arthritis and related con-

Table VIII Degree of familial aggregation (*K*) calculated from population controls (*K_p*) and spouse controls (*K_s*) in first-degree relatives of psoriatic arthritis probands

Disease	Observed prevalence per cent.	Expected prevalence		Familial aggregation	
		Population	Spouse	<i>K_p</i>	<i>K_s</i>
Peripheral psoriatic arthritis	4.4	0.09	0.0	48.8	4.4
Psoriasis	21.0	1.10	2.5	19.0	8.4
Uncomplicated seronegative clinical arthritis (grade 2-4)	6.6	<2.20	1.2	3.0	5.5
Erosive arthritis (grade 2-4)	1.8	3.30	0.0	0.5	3.6
Sacroiliitis (grade 2-4)	7.4	1.10	1.3	6.7	5.6

Table IX Degree of familial aggregation (*K*) calculated from population controls (*K_p*) and spouse controls (*K_s*) in first-degree relatives of probands with psoriasis and other arthritis

Disease	Observed prevalence per cent.	Expected prevalence		Familial aggregation	
		Population	Spouse	<i>K_p</i>	<i>K_s</i>
Peripheral psoriatic arthritis	0.0	0.09	0.0	0.0	0.0
Psoriasis	18.1	1.10	2.5	16.4	7.2
Uncomplicated seronegative clinical arthritis (grade 2-4)	6.0	< 2.20	1.2	2.7	5.0
Erosive arthritis (grade 2-4)	5.0	3.30	0.0	1.5	5.0
Sacroiliitis (grade 2-4)	0.0	1.10	0.0	0.0	0.0

ditions by means of population controls (*K_p*) and spouse controls (*K_s*). The *K* values obtained from first-degree relatives of psoriatic arthritis probands and first-degree relatives of probands with psoriasis and other arthritis are shown in Tables VIII and IX respectively.

The feature of particular interest is the high *K* value for peripheral psoriatic arthritis (48.8) calculated from the prevalence among first-degree relatives of psoriatic arthritis probands and population controls. The figure represents a frequency of psoriatic arthritis in relatives 48.8 times that found in population controls. The *K* value falls markedly when calculated from spouse controls (4.4)—a difference which may signify the importance of environmental as well as genetic factors in the aetiology of psoriatic arthritis. By contrast, *K_p* and *K_s* values were zero when calculated from prevalence rates of psoriatic arthritis in first-degree relatives of probands with psoriasis and other arthritis.

Familial aggregation of sacroiliitis was also higher in relatives of psoriatic arthritis probands compared with relatives of probands with psoriasis and other arthritis (Tables VIII and IX). The *K_p*—*K_s* differential for this condition was small compared with the difference between these indices in psoriatic arthritis. This suggests that the familial aggregation of

sacro-iliitis in families of patients with psoriatic arthritis is likely to be predominantly genetic rather than environmental.

K_p for psoriasis was found to be equally high in both groups of relatives (Tables VIII and IX). This supports previous evidence provided by the present investigation that the genetic liability to psoriasis is independent of the liability to arthritis. The fact that *K_p* exceeded *K_s* in both groups of relatives suggests that environmental as well as genetic factors may be important in the aetiology of psoriasis.

(2) HERITABILITY

This estimation is applicable to disease not inherited in a simple (Mendelian) manner. The 'heritability' expresses the extent to which phenotypes exhibited by parents are transmitted to their offspring. Falconer (1965) defined heritability as the additive genetic variance (attributable to the average effects of genes considered singly—as transmitted in the gametes) as a proportion of the phenotypic variance. If the heritability is very high the degree of genetic determination must also be very high and environmental factors therefore relatively unimportant. Falconer devised a simple graph for estimating heritability from the prevalence in first-degree relatives and the prevalence in the general population. Using this graph

and the data obtained from the present investigation, heritability values for conditions thought unlikely to be transmitted in a Mendelian manner were determined. These results are presented in Tables X and XI. Reference to these Tables shows the striking differences between the heritability values for relatives of psoriatic arthritis probands (Table X) compared with relatives of probands with psoriasis and other arthritis (Table XI). Particularly striking are the heritability values for psoriatic arthritis (80-90 per cent.) and sacroiliitis (60-70 per cent.) in first-degree relatives of psoriatic arthritis probands. Values for uncomplicated seronegative clinical arthritis were found to be in the intermediate range

Table X *Heritability among first-degree relatives of psoriatic arthritis probands*

<i>Disease</i>	<i>Prevalence in first-degree relatives per cent.</i>	<i>Prevalence in general population per cent.</i>	<i>Heritability per cent.</i>
Peripheral psoriatic arthritis	4.4	0.09	80-90
Uncomplicated seronegative clinical arthritis (grade 2-4)	6.6	< 2.20	40-50
Erosive arthritis (grade 2-4)	1.8	3.30	0
Sacroiliitis (grade 2-4)	7.4	1.10	60-70

Table XI *Heritability among first-degree relatives of probands with psoriasis and other arthritis*

<i>Disease</i>	<i>Prevalence in first-degree relatives per cent.</i>	<i>Prevalence in general population per cent.</i>	<i>Heritability per cent.</i>
Peripheral psoriatic arthritis	0.0	0.09	0
Uncomplicated seronegative clinical arthritis (grade 2-4)	6.0	< 2.20	30-40
Erosive arthritis (grade 2-4)	5.0	3.30	10-20
Sacroiliitis (grade 2-4)	0.0	1.10	0

in both the relatives of probands with psoriatic arthritis and the relatives of probands with psoriasis and other arthritis. Heritability for erosive arthritis was zero in relatives of psoriatic arthritis probands and relatively small (10-20 per cent.) in relatives of probands with psoriasis and other arthritis. The significance of these findings will be discussed later. Heritability for psoriasis in both groups of relatives would have exceeded 100 per cent., but it was considered invalid to apply heritability analysis to this condition in view of the evidence favouring Mendelian inheritance in uncomplicated psoriasis.

Discussion

Surprisingly little previous work has been done on the hereditary aspects of psoriatic arthritis. Of the few studies that have been reported, most have been based on individual pedigree observations (Tiedemann, 1951; Baker and others, 1963b; Wright, 1969). A few family surveys of psoriatic arthritis have been reported recently, but most of these have been relatively small and uncontrolled.

Vilanova and Piñol (1951) took a family history from 100 patients with psoriatic arthritis and reported '12 per cent. with a rheumatic history, 13 per cent. with a history of psoriasis, 2 per cent. with psoriasis and rheumatism, and 4 per cent. in whom the family history showed arthropathic tendencies'. Such diagnostic vagueness makes it almost impossible to evaluate these results, but the authors' conclusion that heredity must be an important factor in the aetiology of psoriatic arthritis accords with the results of the present study.

Baker and others (1963b) studied the families of 53 patients with psoriatic arthritis. Only relatives with a history of 'rheumatism' were examined and the completion rate was only 54 per cent. Otherwise, however, this was a valuable study. Ten relatives were found to have a seronegative arthritis, which in three were complicated by psoriasis. However, in view of the fact that the total number of relatives was not reported, it was not possible to calculate the prevalence of psoriatic arthritis in this series. Nevertheless, considering the yield of psoriatic arthritis among relatives as a proportion of the total number of probands, no significant difference was found between the results of Baker's group (three affected relatives from 53 probands) and our results (nine affected relatives from 88 probands).

Recently, Lawrence (1967) reported a 12 per cent. prevalence of grade 2-4 clinical polyarthritis, and a 7 per cent. prevalence of psoriasis among 81 first-degree relatives of patients with psoriatic arthritis. The patients with polyarthritis represented a miscellaneous collection, including one case each of Reiter's disease, ankylosing spondylitis, and seropositive rheumatoid arthritis, and also seven cases of seronegative 'rheumatoid' arthritis. No mention was

made of any complicating psoriasis in these patients, but presumably this was absent. If the 12 per cent. prevalence for clinical polyarthritis is recalculated after excluding the single patient with seropositive rheumatoid arthritis, a frequency of eleven per cent. for seronegative polyarthritis is obtained. This prevalence precisely matches that obtained from the present investigation in which twenty of 181 (11 per cent.) first-degree relatives were found to be so affected. Incidentally, of our twenty arthritic relatives, eight also had psoriasis.

Világhy and Krebs (1970) have recently undertaken a study of twelve families of patients with psoriatic arthritis, but they could find no evidence of any hereditary basis for psoriatic arthritis. However, their survey was relatively small (129 relatives) and uncontrolled, and 'psoriatic arthritis' was not clearly defined. Seven (5.4 per cent.) relatives had uncomplicated skin psoriasis, four (3.1 per cent.) had nail psoriasis, and two (1.5 per cent.) 'primary chronic polyarthritis'. The serology (for rheumatoid factor) of probands and affected relatives was not reported.

A more extensive German study of 23 families of patients with psoriatic arthritis has been reported by Theiss and others (1969b; 1970). The prevalence of psoriatic arthritis among 145 relatives (125 first-degree relatives; and twenty 'other' relatives) was 2.4 per cent. The three affected individuals were first-degree relatives (mother, brother, and sister). A further five (3.4 per cent.) relatives (mother, two sisters, and two brothers) had uncomplicated seronegative arthritis. Seven of the eight 'secondary' cases of arthritis (three with and five without psoriasis) had 'bland asymmetrical mono or oligoarthritis'. The mildness of the clinical presentation of psoriatic arthritis in relatives, with regard to both number of joints affected and degree of involvement of individual joints, is consistent with our own findings. However, we did not include examples of monoarthritis in our calculation of psoriatic arthritis prevalence. Theiss and others (1970) have extended their family study to 31 probands (23 with 'psoriatic arthritis' and eight with 'psoriatic spondylarthritis'). The prevalences obtained from examination of 227 relatives are remarkably similar to those found in our own study. This applies particularly to the frequency of peripheral psoriatic arthritis which was 4.4 per cent. in both series (Table XII). Furthermore, if our relative classified as 'peripheral psoriatic arthritis' who also had sacroiliitis is added to the two relatives with psoriasis and sacroiliitis uncomplicated by peripheral arthritis, our 'psoriatic spondylitis' prevalence becomes 1.6 per cent. instead of 1.1 per cent., and therefore even more closely approximates to the figure of 2.2 per cent. observed by Theiss and others (1970).

A smaller family study of eight patients with psoriatic spondylitis from the same department

Table XII Comparison of prevalences obtained from present investigation with those reported by Theiss, Schnyder, and Böni (1970)

Disease	Personal series (per cent.)	Theiss and others (1970) (per cent.)
Uncomplicated psoriasis	15.4	7.4
Uncomplicated arthritis	6.6	4.4
Psoriatic spondylitis	1.1	2.2
Peripheral psoriatic arthritis	4.4	4.4

(Theiss and others, 1969a) yielded five relatives with seronegative arthritis and sacroiliitis uncomplicated by psoriasis. The authors concluded that genetic factors operate in psoriatic spondylitis, but they were unable to define the hereditary mechanism involved.

Although there can now be little doubt about the importance of Mendelian inheritance in uncomplicated psoriasis (Romanus, 1945; Steinberg, Becker, Fitzpatrick, and Kierland, 1951; Hoede, 1957; Lomholt, 1963), the question concerning the aetiology of psoriatic arthritis has hitherto remained obscure.

Our own observations, and also those derived from recent studies (Tiedemann, 1951; Baker, 1965; Baker and others 1963b; Theiss and others, 1969a, b, 1970), present reasonable grounds for believing that psoriatic arthritis, as well as uncomplicated psoriasis, is genetically determined. However, the mechanism involved in this disease is probably more complex than that operating in uncomplicated psoriasis.

Careful scrutiny of our psoriatic arthritis pedigrees has failed to reveal any obvious Mendelian pattern of inheritance. This suggests that transmission is likely to be polygenic. Theiss and others (1968) reached the same conclusion, and also suggested the likelihood of a 'stimulus threshold effect' in precipitating arthritis in genetically predisposed individuals. This implies multifactorial (genetic and environmental factors) rather than polygenic (genetic factors alone) inheritance. The distinction between multifactorial and polygenic inheritance has recently been outlined by Clarke (1972). The fact that environmental factors may be important in the aetiology of psoriatic arthritis is underlined by the fact that familial aggregation (K) of this disorder was much greater when compared with population controls (48.8) than spouse controls (4.4). This type of aetiology, involving both environmental and genetic factors, is known to occur in other rheumatoses (Kellgren, 1964).

The nature of the environmental 'trigger' in psoriatic arthritis remains unknown, but it is possible that this may be trauma. In this respect a paper by Buckley and Raleigh (1959) is of particular interest. These authors described acro-osteolysis following a blow to the finger in a previously non-arthritic subject with classical psoriasis. This observation prompted us to make a particularly careful search for further instances of this 'deep Koebner phenomenon'. It is interesting therefore that we did, in fact, encounter several additional examples of trauma-precipitated arthritis during our survey. Not only could patients clearly recall classical Koebner reactions affecting the skin but many examples, often freely volunteered by the patient, were given of trauma initiating chronic arthritis in a previously normal joint.

We propose therefore that psoriatic arthritis may be triggered by trauma in genetically predisposed individuals. Trauma might, in addition, partly explain the asymmetrical and peripheral localization of affected joints. Furthermore, the higher prevalence of nail involvement in psoriatic arthritis (Wright, 1969) than in uncomplicated psoriasis might also suggest an increased predisposition in arthritic subjects not only to the effect of trauma on the joints but also to its effect on the nails.

The significance of a knowledge of genetic factors in the causation of psoriatic arthritis is based on the generally accepted value of genetic counselling. Equally, concerning the idea of trauma as a possible arthritis-triggering factor, the obvious practical importance of this lies in the possibility of preventing arthritis in the predisposed, either by avoiding traumatic occupations, or, if this is not practicable, possibly by wearing protective gloves or footwear.

We were particularly interested in the relatively high proportion (6.6 per cent.) of relatives with seronegative clinical polyarthritis not associated with psoriasis. The clinical characteristics of this arthropathy were very similar to those observed in the arthritis associated with psoriasis. It is tempting to speculate, as Baker and others (1963b) have done, that these non-psoriatic relatives with arthritis represent 'psoriatic arthritis *sine* psoriasis'. Similarly, it could be argued that relatives with uncomplicated psoriasis (15.4 per cent.) might represent 'psoriatic arthritis *sine* arthritis'. The plausibility of this idea is supported by the frequent observation by us and other workers (Vilanova and Piñol, 1951; Wright, 1965; Baker and others, 1963a) that long intervals, sometimes extending over many years, may elapse before psoriasis is complicated by arthritis, and *vice versa*.

We therefore propose the concept that established cases of psoriatic arthritis simply reflect the tip of the clinical iceberg (Fig. 25). The submerged portion of the iceberg may be thought of as containing examples

of latent psoriatic arthritis. Some of these cases will be psoriatic patients destined to develop arthritis, and some will be arthritic patients destined to develop psoriasis.

FIG. 25 Schematic 'iceberg' illustrating possible distribution of latent and manifest psoriatic arthritis

The relatively low prevalence of erosive polyarthritis (1.8 per cent.) in our relatives is consistent with the general view that psoriatic arthritis, except for the rare arthritis mutilans, tends to be a milder affliction than rheumatoid arthritis (Wright and Moll, 1971). The relative freedom from erosive change in those with inflammatory arthritis paralleled the clinical mildness of the arthritis which, as has been observed by others (Serre, Simon, and Sany, 1969), tended to be a bland, asymmetrical, oligoarticular arthropathy. The prognostic importance of this observation is self-evident.

The high prevalence of sacroiliitis among probands (22.9 per cent.) and among first-degree relatives (7.4 per cent.) provides further evidence to strengthen the link which has been previously reported between psoriatic arthritis and ankylosing spondylitis (Wright, 1961; Reed, 1961; Hill, 1961). As we and others have expressed elsewhere (Baker and others, 1963a; Wright and Moll, 1971), it would seem reasonable, in view of the clinical and familial interrelationships between psoriatic arthritis and ankylosing spondylitis, to regard the latter as a frequent complication of the former. In fact, Baker and others (1963a) regard 'psoriatic spondylitis' as an alternative presentation of psoriatic arthritis. We entirely agree with this view and favour a broader definition of psoriatic arthritis to include not only cases of psoriasis associated with seronegative peripheral arthritis but also those in whom psoriasis is associated with sacroiliitis, whether or not there is an accompanying peripheral arthritis. However, to simplify comparison of our data with studies in which

the traditional definition of psoriatic arthritis (peripheral psoriatic arthritis) has been used, we have reported the prevalences of peripheral psoriatic arthritis and psoriatic spondylitis separately.

Other diagnostic difficulties stemmed from the wide clinical spectrum of psoriatic arthritis and the intermittent nature of its individual components, psoriasis and arthritis. The policy enumerated below appreciably simplified diagnosis in incomplete or borderline cases:

- (1) Patients with arthritis and nail involvement, without evidence of skin psoriasis, were diagnosed as cases of psoriatic arthritis only if the nails were pitted and free from fungal infection, or if there had been a convincing past history of skin involvement or a family history of psoriasis.
- (2) Patients with present arthritis and only past evidence of psoriasis were diagnosed as cases of psoriatic arthritis only if the rash had been confirmed by a dermatologist.
- (3) Patients presenting with the classical picture of psoriatic arthritis in the absence of present or past skin or nail involvement should be regarded as 'psoriatic arthritis *sine* psoriasis', particularly if there is a family history of psoriasis. However, patients with this incomplete diagnosis should not, in our present stage of knowledge, fulfil the criteria for psoriatic arthritis when selecting index cases for family surveys. On the other hand, it would seem reasonable, in these suspected cases, to avoid the use of antimalarial therapy or other medication which may aggravate latent psoriasis, and also in other ways, particularly prognostically, to treat such cases as being true examples of psoriatic arthritis.
- (4) Patients with psoriasis, particularly nail psoriasis, who have had transient pain and swelling of peripheral joints should be regarded as potential cases of chronic psoriatic arthritis, especially if the pattern of transient joint involvement has been asymmetrical and oligoarticular and has affected small peripheral joints.
- (5) Although this problem was not experienced in the present study, the difficulty in diagnosing seropositive patients with classical clinical and/or radiological features of psoriatic arthritis is occasionally encountered. In view of the 5 per cent. prevalence of positive sheep-cell tests in the normal population (Waller and Toone, 1968), we feel that such patients should be diagnosed as cases of psoriatic arthritis fortuitously associated with rheumatoid factor, rather than true rheumatoid arthritis.

Finally, that psoriatic arthritis is a disease *sui generis*, and not simply the coincidental occurrence of psoriasis and rheumatoid or other arthritis, is

supported by the different pattern of aggregation of psoriatic arthritis between families of psoriatic arthritis probands and families of probands with psoriasis and other arthritis. Whereas a highly significant excess of psoriatic arthritis cases compared with population and spouse controls was found in the families of patients with true psoriatic arthritis, not a single example of psoriatic arthritis could be found in the families of patients with psoriasis and other arthritis. In other words, the fact that a condition is capable of genetic transmission implies that it is itself a specific disease entity and not purely a syndrome resulting from the fortuitous association of two common diseases.

Summary

- (1) In order to study genetic factors in psoriatic arthritis, the families of 108 probands with psoriasis and arthritis were examined; 88 probands had true psoriatic arthritis and twenty had psoriasis associated with other arthritis. The families yielded 253 first-degree relatives, 48 second-degree relatives, and 83 spouse controls. The overall completion rate of relatives and spouses was 83 per cent.
- (2) Prevalences obtained from the first-degree relatives of probands with psoriatic arthritis were as follows: peripheral psoriatic arthritis, 4.4 per cent. (8 of 181); psoriatic spondylitis, 1.1 per cent. (2 of 181); total psoriatic arthritis, 5.5 per cent. (10 of 181); uncomplicated seronegative clinical polyarthritis, 6.6 per cent. (12 of 181); uncomplicated psoriasis, 15.4 per cent. (28 of 181); total psoriasis 21 per cent. (38 of 181); total seronegative clinical polyarthritis, 11.0 per cent. (20 of 181); erosive polyarthritis, 1.8 per cent. (4 of 221); sacroiliitis, 7.4 per cent. (13 of 174); ankylosing spondylitis, 6.3 per cent. (11 of 174).
- (3) The increased prevalences of psoriasis, uncomplicated and total seronegative clinical polyarthritis (but not erosive polyarthritis), peripheral and total psoriatic arthritis, and sacroiliitis were statistically significant compared with both spouse and population controls. By contrast, only the prevalence of psoriasis in first-degree relatives of probands with psoriasis and other arthritis was significantly increased. No examples of psoriatic arthritis were found in these relatives.
- (4) In first-degree relatives of psoriatic arthritis probands, the degree of familial aggregation (K) of psoriatic arthritis was 48.8 compared with population controls, and 4.4 compared with spouse controls. Falconer's heritability for psoriatic arthritis in these relatives was 80-90 per cent.

(5) The following conclusions were reached:

- (i) The clustering of psoriatic arthritis in families of patients with psoriatic arthritis, but not in families of patients with psoriasis and other arthritis, supports the concept that psoriatic arthritis is a disease *sui generis*;
- (ii) The high frequency of sacroiliitis in psoriatic arthritis families is consistent with previously reported linkages between psoriatic arthritis and ankylosing spondylitis.
- (iii) Genetic factors are involved in the aetiology of psoriatic arthritis;
- (iv) Inheritance is probably multifactorial;
- (v) Environmental factors, particularly trauma, could be important in precipitating arthritis in genetically predisposed subjects.

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Appendix

Criteria for borderline psoriasis (Baker, 1965)

- (1) Psoriasis in the scalp must be palpable.
- (2) Mild psoriasis of the scalp simulating dandruff must, in addition, show areas of completely uninvolved skin between the scaly patches.
- (3) In the presence of eczema, seborrhoea corporis, or seborrhoeic dermatitis anywhere on the body, lesions other than classical plaques on the scalp or elsewhere cannot be accepted as psoriasis.
- (4) Toe-nail lesions alone cannot be accepted as evidence of psoriasis.
- (5) Only classical finger-nail lesions of psoriasis, namely: pitting, onycholysis, and the characteristic discolouration of the lateral aspect of the free edge of the nail, can be accepted in the absence of unequivocal psoriasis elsewhere or a definite previous history of psoriasis. In these cases microscopy and culture of the nail should have excluded infection.
- (6) Flexural lesions in the absence of psoriasis elsewhere are rare and should only be accepted

in the presence of other lesions. However, flexural lesions alone may be accepted if they appear classical, *i.e.* have a sharply-defined margin around the whole circumference of all affected areas. Lesions confined to the flexures can only be accepted if microscopy of scrapings has excluded *Tinea* or *Candida* infection.

- (7) Pustular dermatosis of the palms and soles, whether or not conforming to the published descriptions of 'pustular psoriasis', cannot be accepted as psoriasis in the absence of unequivocal lesions of the skin elsewhere or unequivocal nail lesions.

Criteria for the inflammatory polyarthritis of psoriatic arthritis

These criteria are modified from the New York criteria for rheumatoid arthritis (Bennett and Wood, 1968).

- (1) A history, past or present, of an episode of joint pain involving three or more limb joints, but without stipulation as to duration. For joint-scoring purposes, the joints on either side should count separately, but joints that occur in groups,

such as the PIPs or MCPs, should count only as a single joint, even if more than one has been involved on the same side.

- (2) Involvement by swelling (soft tissue thickening or effusion, but not bony overgrowth alone), limitation of motion, subluxation, or ankylosis of at least three limb joints. To satisfy this criterion there must also be involvement of one hand, wrist, or foot, but arthritis limited to large joints such as elbows or knees does not qualify. The following joints are excluded: first carpometacarpals, hips, and first MTPs. Subluxation of the lateral MTPs must be irreducible.

Modifications

Criterion 2 has been modified in four respects:

- (i) Exclusion of DIP involvement (to avoid diagnostic confusion with osteoarthritis) in the original recommendation has been omitted in view of the common occurrence of involvement of this joint in psoriatic arthritis.
- (ii) The fifth PIPs were excluded in the original recommendation to avoid confusion with the relatively common congenital deformity (familial pyknodactyly) at this joint. In view of the not infrequent occurrence of isolated involvement of this joint in psoriatic arthritis, this exclusion has been omitted.
- (iii) The possibility of confusing DIP joint involvement by psoriatic arthritis with Heberden's nodes was anticipated by stipulating soft tissue and not bony thickening.
- (iv) Symmetry of two involved joints, as stipulated in the original recommendation, has been excluded in view of the common occurrence of asymmetry in psoriatic arthritis.

Clinical joint score

Grade 2: More than two but less than seven joints affected.

Grade 3: Seven to twelve joints affected

Grade 4: More than twelve joints affected

Diagnosis of ankylosing spondylitis from clinical and radiological criteria (Bennett and Wood, 1968)

Ankylosing spondylitis was defined as radiographic sacroiliitis accompanied by one or more clinical criteria. Spondylitis was graded as definite or probable according to the following scheme:

Definite

- (1) Grade 3-4 bilateral sacroiliitis with at least one clinical criterion
- (2) Grade 3-4 unilateral or grade 2 bilateral sacroiliitis with clinical criterion 1 or with both clinical criteria 2 and 3.

Probable

Grade 3-4 bilateral sacroiliitis without any clinical criteria.

Clinical criteria

- (1) Limitation of motion of the lumbar spine in all three planes (anterior flexion, lateral flexion, and extension).
- (2) A history or the presence of pain at the dorsolumbar junction or in the lumbar spine.
- (3) Limitation of chest expansion to 2.5 cm. or less measured at the fourth intercostal space.

Discussion

DR. J. S. LAWRENCE (*Manchester*)

Some years ago I carried out a survey of psoriatic families in which the probands were divided into patients with psoriatic arthritis and patients with psoriasis but no arthritis. The findings fit the proposed polygenic type of inheritance and give a heritability of 84 per cent. which corresponds very well with your findings. When the relatives of the two groups of probands were looked at separately it was found that psoriatic arthritis was just as likely to occur in the relatives of patients with psoriasis without arthritis as in the other group. Now this group of probands had more severe psoriasis, they were taken from the skin clinic and I am wondering whether possibly your probands with psoriatic arthritis had more severe psoriasis than those in the group with psoriasis without arthritis.

DR. MOLL

This was the case in a large proportion of our psoriatic arthritis probands, in respect of both skin complaint and arthritis. This was why we have suggested a multifactorial mode of inheritance because one criterion for this type is that there is heavier clustering in families or more severely affected probands (Carter, 1969).

DR. A. CATS (*Leiden*)

When you calculate from the numbers you found in your first-degree relatives with psoriasis and the number of relatives with arthritis, the number you can expect in such a population suffering from both diseases, and compare it with the number you actually found, did you find a statistically significant difference between the observed and expected numbers? Have you compared the psoriasis in the relatives of your seronegative and seropositive probands; do you find a difference in the prevalence of psoriasis in these relatives? Finally what are your criteria for psoriatic arthritis; because you showed us psoriasis with peripheral arthritis, psoriatic spondylitis, and terminal interphalangeal involvement with psoriasis.

DR. MOLL

The prevalence of uncomplicated psoriasis was the same in the relatives of probands with psoriasis and other arthritis as it was in families in which the proband had true psoriatic arthritis. We undertook statistical analysis of the difference between the prevalence of psoriasis and/or

polyarthritis in our relatives compared with both population and spouse controls. The statistical differences we found between these prevalences were estimated by one of three methods—Chi-squared, Fisher exact, or binomial. The criteria we used for epidemiological purposes defined psoriatic arthritis as the association of psoriasis with seronegative inflammatory polyarthritis and/or sacroiliitis.

PROF. W. W. BUCHANAN (*Glasgow*)

I am not at all happy with the authors' conclusions. Familial aggregation does not necessarily mean that the disease has a genetic basis. After all many conditions run in families, such as syphilis, tuberculosis, lice, and bad manners, which are clearly not genetic. At best the "first-degree relatives" method can only indicate a familial aggregation. Genetics rests on a firm mathematic basis, and genetic hypotheses are susceptible to mathematical testing, but only if the kinds and degrees of relationships are known. First-degree relatives do not, of course, have the same degree of relationship; parent-child and child-parent pairs are unilineal, whereas sib-sib pairs are bilineal. The paper is interesting and seminal, but I would suggest that the authors test their genetic hypothesis statistically.

DR. MOLL

The reason why we felt strongly about genetic factors was that there was a statistically significant difference between the prevalence of psoriatic arthritis in the first-degree relatives and spouse controls. The multifactorial element was further strengthened by the absence of any finding of a mendelian pattern of inheritance in our pedigrees. It was strengthened still further by data showing a very

sharp drop in prevalence from first to second-degree relatives.

DR. P. H. N. WOOD (*Manchester*)

I would disagree strongly with Professor Buchanan. For single-gene conditions you are usually required to demonstrate the mode of inheritance before claiming a genetic aetiology. However, it is almost impossible to comply with this requirement for multifactorial genetic aetiology, as we don't fully understand the operation of multifactorial models. Turning now to the paper, I want to emphasize the need for consistency in data when exploiting the precision of mathematical models in genetics. Working on the data in your abstract, I was unable to detect a significant difference in prevalence between spouses and first-degree relatives. You did not define your population controls, but relatives were more like spouses than the population. This would be consistent with non-genetic familial factors, the opposite of what you are trying to suggest. The remedy, unfortunately, is to study very much larger numbers of relatives than any of us have done so far. However, a comparison of second-degree and first-degree relatives might help to resolve the genetic element, providing the two heritability estimates were consistent.

DR. MOLL

We agree that the larger prevalence difference between relatives and population controls compared with relatives and spouse controls probably does suggest a large environmental rather than a large genetic factor in the aetiology of psoriatic arthritis.

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