mental animals by Denny-Brown and Meyer (1957). An explanation of this type would account for the relationship observed between transient ischaemic attacks and polycythaemia by Millikan, Siekert, and Whisnant (1960) and probably also for the impressive results obtained by Fisher (1958b) and Millikan, Siekert, and Whisnant (1958) in the treatment of ischaemic attacks with coumarol derivatives, though it is still not clear whether coumarol and indanedione drugs prevent the formation of platelet thrombi *in vivo* in therapeutic dosage (Fulton *et al.*, 1953; Murphy and Mustard, 1961).

Some patients, mainly those with very brief basilar ischaemic attacks, relate their attacks to neck movements and it seems likely that in such cases brain-stem ischaemia might be produced by occlusion of one or other vertebral artery at the atlanto-axial junction (Biernond, 1951). There is evidence that internal carotid occlusion may also occasionally be produced in this way, the artery being compressed by the lateral process of the atlas (Boldrey *et al.*, 1956; Toole and Tucker, 1960).

It is probable that previous widespread acceptance of the "haemodynamic crisis" hypothesis is one of the main reasons for the reluctance of many physicians to treat hypertension in patients with cerebrovascular disease and indeed had led some physicians to endeavour to raise the blood-pressure with pressor agents. The results presented indicate that hypotension is not an important causal factor in the genesis of transient cerebral ischaemic attacks and that hypotension is remarkably well tolerated, even in patients with widespread ischaemic damage (Case 7—see Chart). Hypertension is known to affect prognosis adversely in cerebrovascular disease (Marshall and Kaeser, 1961). Although caution should be observed in patients known to have an occlusion of a major vessel, efficient hypotensive therapy seems unlikely to precipitate transient ischaemic episodes and may well lead to a reduction in the high mortality from cerebral haemorrhage and cardiac disease; this is particularly the case now that there is available in methyl dopa a powerful hypotensive drug that does not cause severe postural hypotension. The present study provides no brief for the use of pressor agents in the management of transient ischaemic episodes.

Summary and Conclusions

Hypotension was induced in 37 patients with transient focal cerebral ischaemic attacks, using intravenous hexamethonium and a pivoted bed. Systolic blood-pressure was reduced to a mean value of 42% of the initial pressure. In only one patient was an ischaemic attack reproduced; the remainder developed no evidence of focal cerebral ischaemia before the point at which they developed severe generalized ischaemia. It is concluded that hypotension is not normally a causal factor in the genesis of transient cerebral ischaemic attacks. There is therefore no rationale for the treatment of these patients with pressor drugs and no bar to the treatment of coincident hypertension.

We would like to thank those physicians who allowed us to include patients in this study, and the Trustees of the Nuffield Foundation for generous financial support.

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ATYPICAL POLYARTHRITIS IN PSORIATIC FAMILIES

BY

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There is good statistical evidence that psoriasis and polyarthritis occur together more often than can be explained by coincidence of two common diseases (Dawson and Tyson, 1938; Bauer *et al.*, 1941; Wassmann, 1949). In addition, tests for rheumatoid factors are negative in the vast majority of subjects with psoriasis and arthritis (Ball, 1952; de Forest *et al.*, 1956; Wright, 1959), whereas they are positive in 80% or more of patients with rheumatoid arthritis (Kellgren and Ball, 1959).

Differentiation of the arthritis occurring with psoriasis from classical rheumatoid arthritis on the basis of clinical and radiological features is less secure. Most recent authors have accepted the picture of erosive arthritis predominantly or exclusively affecting the terminal interphalangeal articulations as being peculiar to psoriatic arthritis, and rare, if seen at all, in rheumatoid arthritis. Other features that have been claimed to be characteristic of psoriatic arthritis are more controversial, and are shown in Table I.

TABLE I.—Previously Reported Features of Psoriatic Arthritis

Absence of subcutaneous nodules (Wright, 1959; Baker <i>et al.</i> , 1963)
Predominant involvement of terminal interphalangeal joints (Bauer <i>et al.</i> , 1941; Avila <i>et al.</i> , 1960; Wright, 1961)
Severe osteolysis; arthritis mutilans (Fawcitt, 1950; Sherman, 1952; Wright, 1959)
Resorption of tufts of terminal phalanges ("whittling") (Wright, 1959; Avila <i>et al.</i> , 1960)
Asymmetrical involvement of metatarsophalangeal joints (Wright, 1961)
Frequent bony ankylosis (Avila <i>et al.</i> , 1960)
"Mushrooming": impaction of the tapered distal end of a phalanx into the splayed opposed articular surface (Gibson, 1948; Fawcitt, 1950)
Involvement of interphalangeal joint of hallux with proliferation of base of distal phalanx (Avila <i>et al.</i> , 1960)
Sacro-iliac involvement, especially with ankylosis (Dixon and Lience, 1961; Wright, 1961)
"Sausage digits": red swollen toes or fingers due to involvement of both interphalangeal joints and tendon sheaths (Weissenbach, 1938; Dixon, 1960)

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Both psoriasis and rheumatoid arthritis are diseases of unknown aetiology. It has been established that there is a hereditary component in the aetiology of psoriasis (Romanus, 1945; Steinberg *et al.*, 1951; Hoede, 1957). Genetic factors certainly also bear on rheumatoid arthritis (Lawrence and Ball, 1958), and there is some evidence that cases of sero-negative arthritis may be familial (Lawrence and Ball, 1958; Bremner *et al.*, 1959; Lawrence *et al.*, 1961). In view of the above facts it is possible that genetic factors determine the association of psoriasis and sero-negative polyarthritis.

We therefore studied the relatives of patients with psoriasis or psoriatic arthritis to see whether arthritis occurring in these families tends to differ in any material way from rheumatoid arthritis or more specifically to resemble psoriatic arthritis.

Methods

A detailed family history was taken from 53 patients with psoriasis and sero-negative polyarthritis. Only children, siblings, parents, and parents' siblings were considered, and 86 relatives alleged to have "rheumatism" were asked to attend. Forty-seven did so and were subjected to full clinical examination. Radiographs were taken of the hands, feet, and sacro-iliac joints, and other joints were x-rayed if clinically involved. Blood was taken for cell counts, estimation of erythrocyte sedimentation rate (E.S.R.) by the method of Westergren, Wassermann reaction (W.R.), and uric acid estimation. The Rose-Waaler test was done by a modification of the method described by Gibson and Ling (1956) using pooled group O human red cells; agglutination at a titre of 1:32 or above was considered to indicate a positive result.

On the basis of these investigations the 47 relatives were divided into four groups as follows:

Group 1: Having classical features of psoriatic arthritis—that is, predominant terminal interphalangeal-joint involvement—1 patient.

Group 2: Having features suggestive of psoriatic arthritis—1 patient.

Group 3: Having an arthritis clinically and radiologically indistinguishable from rheumatoid arthritis—8 patients.

Group 4: Having miscellaneous "rheumatic" conditions other than inflammatory polyarthritis—for example, osteoarthritis—or no significant abnormality—37 patients.

The subjects in group 4 were not further considered, and the remaining 10 subjects were kept under observation.

In addition to these 10 patients we have studied six further patients with sero-negative polyarthritis without psoriasis, all of whom had one or more close relatives with psoriasis. Three of these fell into group 2 and three into group 3.

This report thus concerns 16 patients with proved polyarthritis and a family history of psoriasis. All were studied continuously for two years and the Rose-Waaler test was repeated at intervals.

Results

Incidence of Rheumatoid Factor.—The 10 patients with polyarthritis found as a result of the study of 53 psoriatic families all initially had negative Rose-Waaler tests. In five of these the test was repeated thrice or more, and in four twice over the period of study. One patient was available for testing only once. None of these patients became sero-positive during this two-year period. The six patients with sero-negative polyarthritis and a family history of psoriasis were repeatedly tested. One (Case 16) developed a positive test (1:64) after 18 months. The other five all had at least three further negative results.

Incidence of Subcutaneous Nodules.—None of these 16 patients showed subcutaneous nodules of rheumatoid type at any time.

Incidence of Psoriasis.—Three of the 10 patients obtained from the family study were found on examination to have psoriasis as well as arthritis. Two had long-standing and troublesome psoriasis; the third had typical lesions previously undiagnosed (Case 7 below) and did not know she had the disease. None of the remaining 13 patients studied had had psoriasis or developed it during the period of observation.

Group 1—Definite Psoriatic Arthritis

Only one patient fell into this category, but her case is so striking that it merits full description.

Case 1

A married woman aged 57 had suffered from generalized musculo-skeletal pains since adolescence. During the past six years she had complained of low back pain, intermittent swelling of the hands and feet, morning stiffness lasting for at least 30 minutes, and lassitude. On initial examination (February, 1960) there was tenderness of all the terminal interphalangeal joints, some of the proximal interphalangeal joints and the second and third metacarpophalangeal joints of the right hand, and also swelling of all terminal interphalangeal joints. The right knee-joint was swollen and there was some tenderness and swelling of the metatarsal joints. Subcutaneous nodules

FIG. 1.—Radiograph (Case 1) showing erosive arthritis confined to terminal interphalangeal joints.

were absent and no psoriasis was found in skin or nails. The E.S.R. was 17 mm./hr., and on another occasion 33 mm./hr.; white-cell count 6,700/c.mm., with a normal differential count; serum proteins and electrophoresis were normal. The Rose-Waaler test was negative on three occasions over 18 months. Radiographs of the hands showed erosions and narrowing of most terminal interphalangeal joints with proliferation of the bases of the distal phalanges. The proximal interphalangeal and metacarpophalangeal joints appeared normal (Fig. 1). The spinal and sacroiliac joints were also normal.

Her 61-year-old sister had had psoriasis for 33 years, and four years ago developed an erosive arthritis involving predominantly the terminal interphalangeal joints of both hands with "whittling" of the tufts of the distal phalanges. The Rose-Waaler test was negative on four occasions over two years. Two other sisters and her 29-year-old son were said to have "rheumatism" but were not available for examination. Her daughter, aged 28, recently developed psoriasis in the puerperium which lasted about a month before clearing completely; she had never previously had psoriasis.

This patient had classical features of psoriatic arthritis in the absence of past or present psoriasis, a daughter with psoriasis, and a sister with radiologically almost identical arthritis and psoriasis.

Group 2—Probable Psoriatic Arthritis

Four patients are included in this category. In addition to being sero-negative all had clinical and radiological features satisfying two or more of the criteria mentioned in Table I. Only one had psoriasis—the sister of a patient who herself had psoriatic arthritis. The details of these four patients are shown in Table II and a typical case-history is briefly described below.

TABLE II.—Features in Four Patients with "Probable" Psoriatic Arthritis (Group 2)

Case No.	Age	Sex	Psoriasis	Duration of Arthritis in Years	Predominant Terminal Interphalangeal Joint Involvement	Osteolysis	"Whittling" of Terminal Phalanges	Asymmetrical Arthritis	Bony Ankylosis	Mushrooming	Involvement of Interphalangeal Joint of Hallux	Sacro-iliitis	"Sausage Digits"
2	75	F	+	40	+	—	—	—	—	—	—	—	—
3	65	F	—	18	—	—	—	—	—	—	—	—	—
4	47	F	—	3	—	—	—	—	—	—	—	—	—
5	29	F	—	4	—	—	—	—	—	—	—	—	—

Case 3

A married woman aged 65 had suffered from joint pains for 18 years. She was thought to have rheumatoid arthritis, was treated with gold injections, and enjoyed a long remission except for occasional pain in the knuckles of the right hand. She also complained of frequent episodes of photophobia associated with epiphora. On examination (March, 1960) she had mild asymmetrical arthritis involving principally the right wrist, second metacarpophalangeal and the metatarsophalangeal joints. There were no subcutaneous nodules or tendon lesions and the only other finding was slight circumcorneal injection in the left eye. There was no evidence of psoriasis. The E.S.R. was 20 mm./hr.; white-cell count 8,100/c.mm., differential count normal; serum proteins and electrophoresis normal. The Rose-Waaler test was negative.

There was bony ankylosis of the right second metacarpophalangeal joint (Fig. 2) and expansion of the base of the proximal phalanx; no other joint in the hand was ankylosed. In the feet there was osteolysis with considerable asymmetrical destruction of metatarsal heads, bony ankylosis of some metatarsophalangeal joints and subluxation of others. The sacroiliac joints were normal.

Her son had mild psoriasis of elbows and scalp which had been present many years, and her granddaughter was recently under our care for treatment of the same condition, which began at the age of 7 years. Neither her parents, her late

husband, nor her husband's family were known to have psoriasis.

The isolated bony ankylosis and asymmetrical arthritis in this patient are features which have been reported in psoriatic arthritis. Although she has never had psoriasis, the presence of the disease in her son and granddaughter

FIG. 2.—Radiograph of right hand (Case 3) showing isolated bony ankylosis of second metacarpophalangeal joint.

FIG. 3.—Radiograph of left hand (Case 4) showing "mushrooming" of second metacarpophalangeal joint, and involvement of wrist and carpal joints.

is strong presumptive evidence that she or her husband had transmitted a psoriatic genetic factor.

In Case 4 of this group "mushrooming" of the second metacarpophalangeal joint and involvement of wrist and carpal joints occurred in the left hand (Fig. 3, Table II).

Group 3—Arthritis Indistinguishable from Rheumatoid Arthritis

Eleven patients fell into this category (Table III). There was absence of subcutaneous nodules in all and a negative Rose-Waaler test in 10, but their arthritis was indistinguish-

able from rheumatoid. Only two had psoriasis. One case is described below.

TABLE III.—Features in 11 Patients with "Indistinguishable" Arthritis (Group 3)

Case No.	Age	Sex	Duration of Arthritis in Years	Presence of Psoriasis	Rose-Waaler Test
6	68	M	25	—	—
7	72	F	11	+	—
8	63	F	14	—	—
9	46	F	15	+	—
10	46	F	5	—	—
11	59	F	4	—	—
12	51	F	11	—	—
13	46	F	7	—	—
14	61	F	8	—	—
15	63	M	14	—	—
16	60	F	21	—	+

Case 7

A married woman aged 72 was seen on August 3, 1961. She had complained of "rheumatism" and stiffness for 11 years. On examination she had severe symmetrical arthritis of fingers and toes affecting mainly the interphalangeal and metacarpophalangeal joints with slight ulnar deviation. Examination of the skin revealed one isolated plaque of psoriasis adjacent to the umbilicus which she said had been present for five years. In addition several toenails showed distal thickening of psoriatic type. An E.S.R. was 22 mm./hr. Her niece had psoriatic arthritis and five of her six siblings and two other nieces had psoriasis (Fig. 4).

FIG. 4.—Family tree (Case 7).

This case illustrates the importance of making a full and careful search for psoriasis in any patient with a sero-negative arthritis of undetermined aetiology.

Discussion

When psoriasis and arthritis occur together the skin and joint manifestations may vary greatly in both their individual and relative severities. Although the psoriasis usually begins before the arthritis, there may be a coincident onset, or the arthritis may even precede the skin lesions, sometimes by many years. Wright (1956) suggested that some patients with seronegative erosive arthritis are destined to develop psoriasis, and Dixon (1960) reported two patients with sero-negative arthritis which he considered might be of the psoriatic variety, despite the absence of skin lesions. We report similar cases and suggest that genetic evidence afforded by a family history of psoriasis supports the contention that the presence of skin lesions is not an essential prerequisite for the diagnosis of psoriatic arthritis. If this view is correct these patients would be liable to develop psoriasis in the future, but since this disease can appear for the first time late in life—even in the eighth decade (Ingram, 1954)—it is conceivable that psoriatic arthritis may run its entire course without the development of skin lesions.

On the basis of these considerations it is suggested that the following criteria should be satisfied if psoriatic arthritis is to be diagnosed in the absence of psoriasis: (1) all other causes of polyarthritis should be excluded; (2) there should

be clinical and radiological features suggestive of psoriatic arthritis (see Table I); (3) rheumatoid factor should be consistently absent from the serum; and (4) one or more close relatives should have psoriasis.

Case 1 completely satisfies these criteria, and, in our opinion, is an example of psoriatic arthritis occurring in the absence of psoriasis.

The justification for this diagnosis is less secure in the four patients in the second group. All satisfy two or more of the criteria advocated in the past by various authors (Table I), but these have sometimes been advanced on the basis of uncontrolled observations. It is conceded that the features in question may be found occasionally in rheumatoid arthritis, but they occur much more frequently in psoriatic arthritis.

Of the 11 patients in group 3, one (Case 16) clearly has sero-positive rheumatoid arthritis. The fact that the remaining 10 patients are sero-negative appears to be significant, and, in view of their family histories, it is tempting to relate this to the same absence of rheumatoid factor which is found in the majority of patients with overt psoriasis and erosive polyarthritis indistinguishable from rheumatoid arthritis (Wright, 1959).

Had all our 16 patients been suffering from rheumatoid arthritis, a few might have been expected to show subcutaneous nodules and the majority to be sero-positive. It could be argued that psoriasis might modify the serological reactions of rheumatoid arthritis, but against this hypothesis is the fact that many patients have been reported with coincident psoriasis and sero-positive rheumatoid arthritis (Wright, 1959). We ourselves have seen seven such patients, and we have had under observation a patient with rheumatoid arthritis, nodules, and a positive Rose-Waaler test who later developed psoriasis and remained strongly sero-positive (Baker *et al.*, 1963).

Of our 15 sero-negative patients two have had arthritis for less than four years, and it would be premature to suggest that all will remain sero-negative in the future, especially as it has been shown that the Rose-Waaler test can become positive up to 15 years after the onset of arthritis (Dixon, 1960). Nevertheless, six have had their joint disease for more than 10 years.

Whatever diagnostic conclusion is reached these observations have certain practical implications. The first is the necessity for careful and comprehensive examination of the skin, scalp, and nails of patients with sero-negative arthritis of undetermined aetiology. Psoriasis may lurk for years unrecognized in the scalp or it may be restricted to the perineum, natal cleft, or other flexures, especially in post-menopausal women. The second is the importance of seeking a family history of psoriasis in these patients: history alone may be inadequate for this purpose and examination of relatives is always worth while.

The recognition of trivial localized psoriasis has assumed added importance since the introduction of chloroquine and related compounds in the treatment of rheumatoid arthritis. It is not perhaps widely known that this and other antimalarials commonly aggravate psoriasis (Ziprowski *et al.*, 1954; Cornbleet, 1956). Exacerbation of the skin disease usually begins during the third week of chloroquine therapy (Baer and Witten, 1962), and, if the drug is not stopped, generalized erythrodermia may ensue and persist for many weeks.

Summary

The cases of 16 patients with polyarthritis, all of whom had one or more close relatives with psoriasis, are

described. Fifteen had consistently negative Rose-Waaler tests. Three had psoriasis, the remaining 13 being free from skin or nail lesions.

One patient had an erosive arthritis with predominant terminal interphalangeal-joint involvement, absence of psoriasis, and negative Rose-Waaler tests. It is thought that this case is an example of psoriatic arthritis without psoriasis.

Four patients, only one of whom had psoriasis, had radiological features suggestive of psoriatic arthritis.

Criteria are presented to enable the diagnosis of psoriatic arthritis to be made in the absence of psoriasis.

Although the remaining patients had a joint disease clinically and radiologically indistinguishable from rheumatoid arthritis, all but one had consistently negative Rose-Waaler tests and none had subcutaneous nodules of rheumatoid type.

The importance of seeking a family history of psoriasis and of making a thorough examination for psoriasis in patients with sero-negative polyarthritis of undetermined aetiology is stressed.

The presence of even trivial psoriasis is important in patients with arthritis in view of the dangers of chloroquine therapy in this skin disease.

We are indebted to Professor J. T. Ingram and Dr. G. Holti for their encouragement and for permission to study some of the patients.

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URINARY WHITE-CELL EXCRETION AFTER IRON-SORBITOL-CITRIC-ACID

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During studies on the action of iron-sorbitol-citric-acid complex ("jectofer") in patients with hypochromic anaemia it was established that about one-third of the iron administered intramuscularly was excreted within 24 hours in the urine (Wetherley-Mein *et al.*, 1962; Pringle *et al.*, 1962). Scott (1962) has noted a possible provocation of an infection of the urinary tract in one patient with anaemia after treatment with iron-sorbitol. Recently provocative tests for the diagnosis of latent pyelonephritis have been established by the measurement of urinary white-cell excretion rates before and after the intravenous administration of a pyrogen (Pears and Houghton, 1958, 1959) or intravenous prednisolone phosphate (Little and de Wardener, 1962). The latter authors also found that three patients developed an exacerbation of a urinary infection after the administration of prednisolone phosphate. These observations suggested that iron-sorbitol might provoke a cellular response in states of renal infection. For this reason the urinary white-cell excretion rates were measured before and after the intramuscular administration of iron-sorbitol complex to normal subjects, patients with chronic infection of the urinary tract, and patients with non-infective renal disease.

Material and Methods

The cellular excretion in the urine was studied before and after the intramuscular injection of iron-sorbitol in

10 healthy subjects, in nine patients with present or past evidence of infection of the urinary tract (Table I), and in five patients with other renal disorders (Table II). The diagnosis of infection of the urinary tract was based on a typical clinical history as well as on quantitative bacterial counts (McGeachie and Kennedy, 1962)—that is, a bacterial count of more than 100,000 organisms per ml.

Urine was collected direct into a sterile container for the three-hour period immediately prior to the injection of iron-sorbitol and for two periods each of three hours in sequence after the injection. The urinary non-squamous white-cell excretion rate was counted in a Neubauer chamber after centrifugation of the urine, and the white-cell excretion rate per hour was calculated. Bacterial counts were performed on all the specimens by the method of McGeachie and Kennedy (1963). Iron-sorbitol 25 mg. was injected intramuscularly in all cases. In some patients an additional test was performed using 100 mg. of iron-sorbitol.

Results

The urinary white-cell excretion rates three hours before and three hours after the iron-sorbitol injection are shown in the Chart. In the 10 normal subjects the pre-injection urinary white-cell level ranged from 8,000 to 50,000 cells per hour and no significant alteration occurred after the injection of 25 mg. of iron-sorbitol. In 8 out of these 10 patients the test was repeated with 100 mg., again with