"cheese" containing a high proportion of an unsaturated fat (corn oil).

The diet was palatable and well tolerated. Unlike most previous metabolic ward studies, in the present one the patients continued at work. The treatment was maintained for four months and observations were made during a control period of similar length. There was significant depression of the blood cholesterol (free and total), phospholipids, and plasma turbidity. In some cases the triglycerides were also reduced. The xanthomata diminished, particularly xanthoma tuberosum, which often disappeared. The blood-clotting and fibrinolysis time was influenced in most cases in a way presumably beneficial to the patient.

There was no clinical or electrocardiographic evidence of an improvement in myocardial ischaemia in the six patients with angina. Symptoms decreased in three of the six patients with intermittent claudication, but there was no improvement in the peripheral circulation of the foot, measured by plethysmography. The trial was perhaps too short for such changes to be detected, and the treatment is being continued.

In the condition studied the incidence of atherosclerosis is high and the prognosis poor when myocardial ischaemia or peripheral vascular disease develops. Such a diet forms a practical method of treatment, and is worthy of trial in the hope of preventing further manifestations of atherosclerosis.

I am grateful to Dr. C. J. Gavey, who has directed this trial. Professor N. F. Maclagan has supervised the biochemical aspect of the work, and the procedures were carried out under the guidance of Dr. J. D. Billimoria. The plethysmograph was designed and constructed in the department of clinical measurement, Westminster Hospital, under the direction of Dr. P. Cliffe. I gratefully acknowledge the helpful advice at this stage given by Professor W. J. H. Butterfield at Guy's Hospital. Dr. P. Armitage advised on the planning of the trial and analysis of the results. Serial photographs were taken under the direction of Dr. P. Hansell in the photographic department of Westminster Hospital. The diets were formulated by Miss P. Torrens, dietitian to the Westminster Hospital. I am grateful to Miss Jean E. Drysdale for allowing me to quote her unpublished results on blood-clotting and fibrinolysis. The research was carried out with the aid of a grant from the Board of Governors of Westminster Hospital. Messrs. Alfonal provided the margarine, milk, and cheese used in the trial.

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ERYTHEMA NODOSUM

BY

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"In erythema nodosum, many of the red patches are large and rounded. The central parts of them are very gradually elevated and on the 6th or 7th day, form hard and painful protuberances. From the 7th to the 10th, they constantly soften and subside without ulceration. On the 8th or 9th day, the red colour changes to bluish or livid, and the affected limb appears as if it had been severely bruised. This appearance remains for a week or ten days, when the cuticle begins to separate in scurf. The erythema nodosum usually affects the fore parts of the legs. I have only seen it in females, most of whom were servants. It is preceded by irregular shiverings, nausea, headache and fretfulness with a quick unequal pulse and a whitish fur on the tongue. These symptoms continue for a week or more, but they usually abate on the appearance of the erythema."—Robert Willan (1808).

The term "erythema nodosum" was introduced by Robert Willan, and the above description in his classic work *On Cutaneous Diseases*, published in parts between 1798 and 1808, is accompanied by a coloured illustration of the condition. He draws attention to the characteristic site, play of colours, and tenderness of the lesions; he refers to its predilection for females, and he underlines the constitutional upset which often precedes the rash. The description has not been bettered and is no less accurate to-day. We are still undecided

about its pathogenesis, confused on the relative frequency of its different causes, and have no better treatment than the Peruvian bark advocated by Willan.

During 1950–9 170 patients with erythema nodosum have been personally studied and the natural history followed. In presenting this series the general pattern is outlined irrespective of aetiology; and this is followed by analysis of possible causes or provocative factors.

Methods.—Chest radiographs were always done. Skin tests included Mantoux tests in 148 and depot tuberculin tests in 32 found to be Mantoux-negative; Kveim tests in 152 patients; and reactions to intradermal pine pollen extract in 20 patients. Several different Kveim antigens were in use; some prepared from sarcoid lymph nodes with the help of Dr. R. E. M. Thompson in the Bland-Sutton Institute of Pathology, and others kindly supplied by Dr. Louis Siltzbach, Mount Sinai Hospital, and by Dr. Carl Nelson, College of Physicians and Surgeons, New York City. Pine-pollen extract was kindly supplied by Dr. M. Cummings (Cummings and Hudgins, 1958) and reactions to 0.2 ml. were observed immediately, at the end of 24, 48, and 72 hours, and thereafter weekly for one month. Blood counts and sedimentation rates were routine, serum albumin and globulin levels with electrophoresis of the serum proteins were ascertained in 100 patients, serum calcium levels in 72, and serial anti-streptolysin O titres in 61. Biopsy material for histology was obtained in 32 patients from skin, lymph node, liver, or other sites, and in 23 instances direct from the erythema nodosum. 24-hour urine calcium levels were estimated in 11 patients.

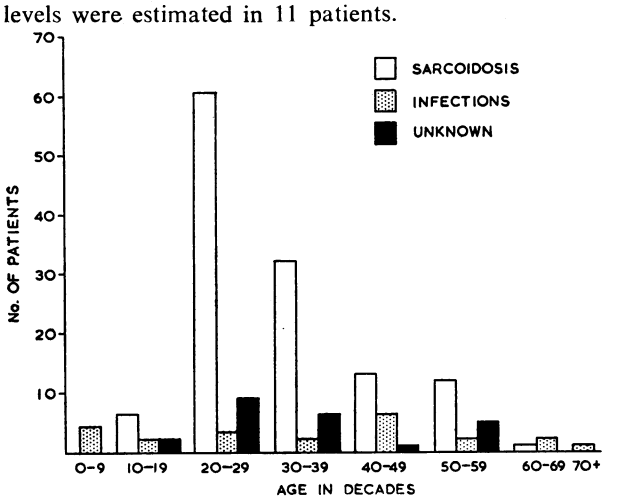

FIG. 1.—Age-groups in decades of 170 patients at onset of erythema nodosum due to sarcoidosis, various infections, and other conditions.

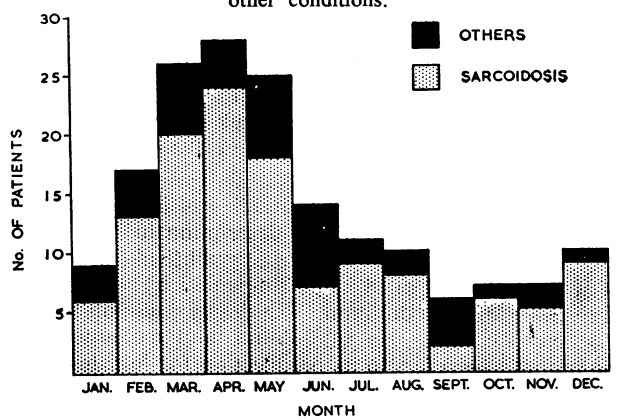

FIG. 2.—Month of presentation of erythema nodosum in 170 patients; 126 due to sarcoidosis and 44 grouped as other causes.

General Pattern of Erythema Nodosum

The group of 170 patients consisted of 126 females and 44 males aged 4 to 70 years, the majority being young adult women in the 20–29 decade (Fig. 1).

Erythema nodosum made its appearance at every season of the year, but was predominant during March, April, and May (Fig. 2). The characteristic red, hot, tender, shining, and symmetrical lesions were always present on the shins, frequently on the calves, knees, and buttocks, and in 12 instances also on the arms. Some constitutional disturbance was usual at the onset with swinging fever, even up to 105° F. (40.6° C.), for the first few days. The development of the skin lesions from the onset through the play of colours to the end of bruising occupied an average of three weeks (range 1 to 20 weeks) (Fig. 3). Recurrences were observed in 14 patients, usually within three months, but in two patients at 6 and 12 months.

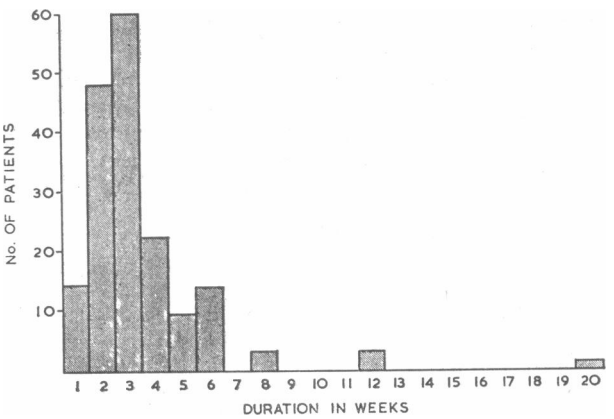

FIG. 3.—Duration of erythema nodosum.

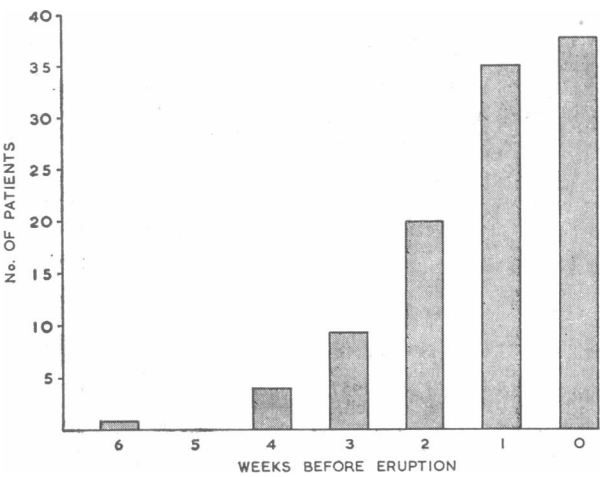

FIG. 4.—Duration of polyarthralgia preceding the development of erythema nodosum.

Polyarthralgia, usually of the ankles and knees but sometimes generalized, was experienced by 105 patients (62%); it most commonly occurred during the fortnight preceding or following the onset of erythema nodosum, but it could occur up to six weeks before (Fig. 4) or for eight weeks after the appearance of the eruption. Polyarthralgia preceding erythema nodosum may be indistinguishable from acute rheumatism, for the distribution of flitting pains, fever, sweating, and a grossly elevated sedimentation rate are common to both (James, 1958). The absence of a cardiac murmur and

normal electrocardiographic findings are helpful differential points, and the subsequent appearance of erythema nodosum is decisive.

Chest Radiographs

In 140 patients chest radiographs were abnormal, revealing bilateral hilar lymphadenopathy (124), bilateral hilar lymphadenopathy with diffuse pulmonary mottling (8), unilateral hilar lymphadenopathy (5), or pneumonia (3). In 26 of the 124 patients with bilateral hilar lymphadenopathy transient bilateral diffuse parenchymal mottling developed as the hilar nodes were subsiding.

In all instances the radiological abnormalities resolved in from 1 to 72 months; the majority with bilateral hilar node enlargement with or without parenchymal mottling did so within one year (average six months) (Fig. 5). Unilateral hilar adenopathy subsided in the course of six months, and the three instances of lobar pneumonia within three months.

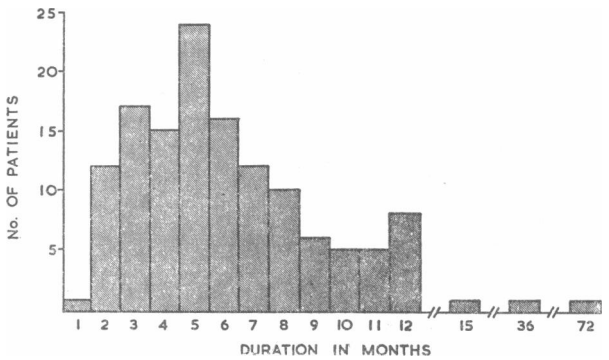

FIG. 5.—Duration of abnormalities in chest radiographs associated with erythema nodosum.

Skin Tests

In 148 patients in whom Mantoux tests were done, there was no response to 100 tuberculin units (T.U.) in 80; the reaction was positive in 68 patients—at levels of 1 T.U. in 7, of 10 T.U. in 35, and of 100 T.U. in 26 (Table I).

TABLE I.—*Results of Mantoux Tests*

Group	No. of Patients Tested	% Positive	Degree of Tuberculin Sensitivity		
			1 T.U.	10 T.U.	100 T.U.
Sarcoidosis ..	112	44	2	25	22
Infections ..	16	50	3	5	0
Unknown* ..	20	55	2	5	4
Total ..	148	46	7	35	26

* Group in which proof of a cause of erythema nodosum was lacking.

Depot tuberculin tests were positive in 24 of 32 patients with negative conventional Mantoux tests, revealing latent tuberculin hypersensitivity and suggesting that these Mantoux tests were negative because of depression of the cutaneous antigen-antibody reaction. The phenomenon was observed in 22 of 27 patients with erythema nodosum due to sarcoidosis and in 2 of 5 patients with infections (one with streptococcal infection and another with acute colitis).

Kveim tests were positive—yielding histological evidence of sarcoid tissue—in 107 of 152 patients with erythema nodosum.

In one of 20 patients injected intradermally with pine-pollen extract an erythematous reaction 5 by 4 cm. appeared at 24 hours and subsided gradually over four days. In the course of the ensuing fortnight a nodule became visible and palpable. Biopsy of this Kveim-like nodule at the end of one month revealed sarcoid tissue. This reaction was noted in a patient with sarcoidosis; the remaining 19 showed no reaction immediately or in the course of one month.

Other Investigations

Serum globulin levels about 3.5 g./100 ml. or electrophoretic patterns showing relating preponderance of α-, β-, or γ-globulin were noted in 34 of 100 patients in whom these investigations were performed. The sedimentation rate was consistently elevated at the time of the eruption, and readings of 80 mm. in the first hour were commonplace; it gradually fell as the erythema nodosum subsided even though hilar adenopathy persisted.

Serum anti-streptolysin O levels above 300 units, with a rise or fall in titre, were observed in 14 of 61 (23%) patients.

The 24-hour urine calcium level was less than 300 mg. in 11 patients in whom it was determined. Serum calcium levels above 11 mg./100 ml. were noted in 8 of 72 patients in whom they were determined; these 8 patients with hypercalcaemia all belonged to the sarcoidosis group.

Causes of Erythema Nodosum

The eruption itself offers no clue to its cause, and the differentiation is only suggested by a combination of evidence comprising clinical associations, histology, bacteriology, and some of the above-mentioned investigations. From these data, the 170 patients may be subdivided into three categories, comprising 126 patients with sarcoidosis, 21 with various infections, and 23 in whom proof of a cause is lacking.

Sarcoidosis

A group of 126 patients with features suggestive of sarcoidosis included 93 women, who predominated in a 3:1 ratio (Table II). They were all adult, aged 18

TABLE II.—*Features Delineating a Group of 126 Patients with Erythema Nodosum Attributed to Sarcoidosis*

	No.	%
Patients ..	126	100
Females ..	93	74
Age-group 29–29 years ..	62	49
Age-group 30–39 ,, ..	33	26
Bilateral hilar lymphadenopathy ..	116	92
Polyarthralgia ..	89	70
Peripheral lymphadenopathy ± splenomegaly ..	28	22
Ocular involvement ..	19	15
Other skin lesions ..	12	10
Positive Kveim test ..	107	94
Other histological evidence of sarcoid tissue ..	24	19
Mantoux test, negative 1: 100 ..	63	56
Abnormal serum globulin pattern ..	28	36
Hypercalcaemia ..	8	13

to 60 years, 62 (49%) of whom were in the 20–29 and 33 (26%) in the 30–39 decade. In one-half of this group there was clinical evidence of sarcoidosis other than erythema nodosum, comprising peripheral lymphadenopathy (23 patients), ocular involvement (19), other skin lesions (12), splenomegaly (5), enlargement of the parotid (1) or lacrimal (1) glands, cranial nerve palsy (1), and sarcoid deposits on the glottis (1). These changes subsided spontaneously within one year in all except one person who underwent enucleation of the left eye followed by right iridectomy for disabling chronic bilateral uveitis. Polyarthralgia preceded or accompanied erythema nodosum in 89 (70%) patients; it was common enough to be regarded as a feature of the syndrome.

Bilateral hilar lymphadenopathy (with diffuse pulmonary mottling in 8) was noted in 116, and unilateral hilar lymphadenopathy in the *x*-ray picture of one patient. These radiological changes reverted to normal in the course of a year.

Histological evidence of sarcoid tissue was obtained in all; by biopsy of skin (12 patients), lymph node (5), liver (4), enucleated eye (1), bronchus (1), glottis (1), and by means of the Kveim test in 107 of the 114 of this group. Sarcoid tissue was observed on two occasions in biopsy material direct from the erythema nodosum.

The Mantoux test was negative in 63 of 112 (56%) patients tested; positive reactions were usually in response to 10 or 100 T.U. but also to 1 T.U. on two occasions (Table I). Abnormal serum globulins were noted in 28 of 77 (36%) patients and anti-streptolysin O titres elevated above 300 units were found in 3 patients. Hypercalcaemia, occurring in 8 of 60 (13%) patients, subsided without treatment in the course of six months. Hypercalciuria did not occur in 10 subjects in whom 24-hour-urine calcium levels were determined.

Infections

These comprised streptococcal infections (12 patients), tuberculosis (4), pneumonia (3), dental abscess (1), and acute colitis (1).

Streptococcal Infection.—All 12 patients had a preceding upper respiratory infection, and elevated and changing anti-streptolysin titres were noted in the 11 in whom they were performed. Other suggestive evidence included recurrences of the eruption with another sore throat in two, enlarged tonsillar glands in two, and close contact with scarlet fever in one. The 12 patients included 9 females; there was no peak age incidence, for examples were noted in every decade from the first to the eighth. There was no obvious seasonal incidence, for a similar number of cases occurred in all four seasons. Associated features included polyarthralgia (6 patients), transient bilateral iritis (1), bilateral hilar lymphadenopathy (4), a negative Kveim test in all, a negative Mantoux test in 6 out of 8, and abnormal serum globulins in 2 out of 6. Raised anti-streptolysin levels with rising or falling serial titres in 11 patients were in the range 400 to 3,000 units.

Tuberculosis.—Four patients were presumed to have erythema nodosum due to tuberculosis, although tubercle bacilli were not isolated from laryngeal swabs, gastric washings, or biopsy material. Cervical lymph-node biopsy revealed tuberculous tissue in one middle-aged woman with extensive hilar lymph-node calcification. Another middle-aged woman converted and became Mantoux-positive at the time of development of erythema nodosum and unilateral hilar lymphadenopathy. A third woman, aged 25, displayed intense sensitivity to 1 T.U., and a chest radiograph revealed unilateral hilar lymphadenopathy. The fourth, a female child, also had unilateral hilar lymphadenopathy, and the Mantoux test eventually became positive. In all instances the chest *x*-ray abnormality subsided within six months, and only the patient with a tuberculous cervical lymph node was given anti-tuberculosis chemotherapy.

Other Infections.—In three instances erythema nodosum appeared during the course of protracted lobar pneumonia, which cleared gradually in the course of three months. As the pneumonia cleared, unilateral hilar lymphadenopathy became obvious in two patients, and this, also, in turn subsided uneventfully. No causal pathogenic organisms were isolated from sputa, but raised cold haemagglutinins were noted in one patient. Erythema nodosum recurred in crops in one patient, until a dental abscess was drained; thereafter there was no recurrence. Acute colitis necessitating colectomy was a possible provocative factor in another patient. The erythema nodosum subsided spontaneously in the course of two weeks despite continuing acute inflammation of the bowel.

Indeterminate

The only grounds for segregating 23 patients was their featurelessness. There was no preceding sore throat, and the anti-streptolysin titres were stationary and below 300 units in the 11 in whom they were performed. Skin biopsies showed no specific histology in 5, liver biopsy specimens were normal in 2, and the Kveim test was negative in the 18 instances in which it was done. There were abnormal chest radiographs in 13—bilateral hilar lymphadenopathy in 12 and unilateral hilar adenopathy in one. Thus with less rigid criteria most of these patients with erythema nodosum and bilateral hilar lymphadenopathy might be regarded as examples of sarcoidosis. Their only differences from some patients in the sarcoidosis group were the absence of suggestive clinical features elsewhere—for example, iritis, skin scars—and the negative Kveim tests. Their only difference from patients in the infections group was the absence of raised and changing anti-streptolysin titres or of evidence suggesting tuberculosis, focal sepsis, or colitis.

Discussion

It is disconcerting to investigate a large series of patients with erythema nodosum and to find such meagre evidence for distinguishing them on actiological grounds. The most clearly delineated group comprises those with erythema nodosum, bilateral hilar lymphadenopathy, and a positive Kveim test. The patients in this group were all adults, chiefly in the 20 to 40 years age-group, and predominantly female. These cases are regarded as instances of active early sarcoidosis. Their frequency undoubtedly reflects a personal interest in sarcoidosis, and for this reason the series cannot provide a representative cross-section of factors apt to provoke the development of erythema nodosum. Indeed, it is difficult to appreciate which series could be truly representative, for many factors influence the viewpoint, including the age-group of the material, the criteria for determining any single cause, and the range of investigations undertaken.

The most interesting recent series is that reported by Vesey and Wilkinson (1959), for it appears to be unselected and representative of dermatological experience. Erythema nodosum was considered to be a manifestation of streptococcal infection in one-half and of sarcoidosis in one-third of their series of 70 patients. The Kveim test was found to be specific and helpful, but these workers were handicapped by an insufficient supply of antigen. They felt that its routine use would have been very helpful in all cases of erythema nodosum of doubtful origin. In the present series the Kveim test has been the most helpful single test for segregating one group from erythema nodosum due to other causes. In the absence of histological confirmation by skin biopsy, it is in fact difficult to provide convincing proof of sarcoidosis by any other means. The results of aspiration liver biopsy and even scalene

lymph-node biopsy could be indistinguishable in tuberculosis. The Kveim test was positive in 94% of patients placed in the sarcoidosis group; if it is assumed that those placed in the unknown group with negative Kveim tests but with bilateral hilar adenopathy were also examples of sarcoidosis, then the Kveim test would be regarded as positive in 81% of the whole series.

Löfgren (1946) has emphasized the interplay of factors leading to the development of erythema nodosum. Mixed infection was evident in this series, for three patients with Kveim-positive bilateral hilar lymphadenopathy also had significantly raised anti-streptolysin O (A.S.O.) titres, whereas four patients assigned to the streptococcal group on the basis of a sore throat and high A.S.O. titres had bilateral hilar lymphadenopathy; one of these also had bilateral iritis. Overlapping examples such as these provide further argument in favour of the Kveim test for defining the various causes; without it, some examples of erythema nodosum due to sarcoidosis may be regarded as streptococcal on the basis of anti-streptolysin levels alone.

In this predominantly adult series, erythema nodosum due to tuberculosis was rare, possibly because such cases are well recognized beforehand and were not referred. The other reason may be that erythema nodosum is indeed a rare manifestation of tuberculosis in adults and that the association has been overemphasized. The principal value of the Mantoux test in the investigation of erythema nodosum is to note conversion from negative to tuberculin hypersensitivity. This would strongly favour primary tuberculosis, just as a persistently negative reaction would exclude the diagnosis. Degrees of sensitivity provide some information, although no categorical assumptions can be made. Most patients with Mantoux-positive sarcoidosis react only to 10 or 100 T.U. but two patients reacted to 1 T.U. (Table I). A positive depot tuberculin test in conjunction with a negative Mantoux test suggests an immunological defect; and this may be due to paucity of cellular antibodies derived from the reticulo-endothelial system (James and Pepys, 1956). Although the phenomenon was commonly observed in the group with sarcoidosis, it cannot be regarded as uniquely so, for it was also noted in one patient with a streptococcal infection and in another with acute colitis.

Whether the provocative seed be sarcoidosis, streptococcal infection, or tuberculosis, the ultimate development of erythema nodosum presumably depends also upon the type of soil. Erythema nodosum is common in women of the child-bearing years of life, indicating a hormonal factor. Irish girls working in London figured commonly in this series, whereas it is particularly seen among Puerto Rican migrants to New York (L. Siltzbach, 1960, personal communication); these observations suggest constitutional or racial predisposition. It is well recognized that regional factors also play a part as in erythema nodosum due to coccidioidomycosis, hisoplasmosis, and leprosy.

Cummings and Hudgins (1958) have accumulated evidence for a regional association between sarcoidosis and pine pollen to explain the frequency of this disease in the south-eastern United States. Pine-pollen allergy was considered as a possible factor in the present series of patients with erythema nodosum. There was no epidemiological evidence to support it. None the less, pine-pollen skin tests were done on 20 patients, for such a survey has not hitherto been reported in erythema nodosum. In only one patient pine-pollen extract behaved like Kveim antigen, provoking a nodule composed of sarcoid tissue. This patient had bilateral hilar lymphadenopathy and also a positive conventional Kveim test. She had contracted erythema nodosum while on holiday in pine-studded Bavaria. It is difficult at present to interpret the negative pine-pollen tests in the remainder, for McCuiston (1960) has noted that patients with sarcoidosis in Florida have depression of pine-pollen skin-test reactions similar to that observed with the Mantoux test and other delayed-type hypersensitivity reactions (Sones and Israel, 1954).

Irrespective of the causes observed in this series in Britain the prognosis of erythema nodosum and its associated clinical and radiological abnormalities is excellent. Since spontaneous recovery is the rule, there is rarely any indication for special treatment, such as with corticosteroids. It is sometimes tempting to prescribe them for symptomatic relief of patients with hectic fever or severe polyarthralgia, but steroids may interfere with some important immune mechanisms of which we are at present ignorant. It seems unnecessary to exhibit such potent drugs for a benign self-limiting condition.

Summary

During 1950–9, 170 patients with erythema nodosum have been studied. It has a seasonal incidence, presenting most often in the spring. It is three times commoner in women, and it particularly affects those of the child-bearing years of life. Polyarthralgia commonly precedes or accompanies it. The patients comprised 126 with evidence of sarcoidosis, 21 with various infections, and 23 in whom proof of a cause was lacking. Evidence delineating the sarcoidosis group included bilateral hilar lymphadenopathy, positive Kveim tests, and other histological evidence of sarcoid tissue. Streptococcal infection was suggested by raised and changing serum anti-streptolysin titres. Tuberculosis, pneumonia, a dental abscess, and acute colitis were uncommon associations. Since erythema nodosum itself affords no clue to the cause, the most informative investigations for distinguishing contributory factors include a chest radiograph, Kveim test, antistreptolysin titre, and Mantoux test.

A skin test, using pine-pollen extract, behaved like the Kveim test in 1 of the 20 patients in whom it was performed.

Irrespective of cause, the prognosis is excellent and there is rarely any indication for special treatment of the skin or other abnormal features.

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A booklet, *Factors in the Assessment and Education of Children with Cerebral Palsy*, has been published; it contains the addresses given at a conference organized by the British Council for the Welfare of Spastics and held in Bristol in November, 1958. It costs 4s. 6d., post free, from the Council at 13 Suffolk Street, Haymarket, London S.W.1.