

ON ERYTHEMA NODOSUM

AND

ITS RELATIONSHIP TO TUBERCULOSIS.

A STUDY OF ONE HUNDRED AND THIRTEEN
CONSECUTIVE CASES.

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CONTENTS.

	Page
<u>INTRODUCTION</u>	1
<u>SECTION 'A'.</u>	
<u>HISTORICAL SURVEY</u>	2
(1) That Erythema Nodosum is a specific infectious disease	4
(2) That Erythema Nodosum is a manifestation of rheumatism or of B-haemolytic streptococcal infection	7
(3) That Erythema Nodosum is a manifestation of tuberculous infection	15
(4) That Erythema Nodosum is a symptom-complex resulting from bacterial infections, toxins, or chemical agents	28
<u>SECTION 'B'.</u>	
<u>PRESENT INVESTIGATION</u>	34
The Diagnosis of Erythema Nodosum	35
General Observations on the 113 Cases of Erythema Nodosum	36
Age and Sex Distribution	38
Seasonal Occurrence	42
Occupation	44
Contact History and Ascertained Contact to Tuberculosis	48
Skin Tuberculin Sensitivity	52
Mantoux Conversion	58

CONTENTS.

	Page
Chest Radiographical Examination	59
The Correlation of the Radiographical Findings and the Results of the Mantoux Test	80
Bacteriological Investigation	82
The Relationship of Erythema Nodosum to Tuberculosis	88
Recrudescence of Erythema Nodosum following tuberculin testing	103
Recrudescence following measles	104
Post-primary Erythema Nodosum	105
Recurrent Erythema Nodosum	107
Family History of Erythema Nodosum	108
The Association of Erythema Nodosum with drugs	112
The Treatment of Erythema Nodosum	113

SECTION 'C'.

<u>SUMMARY AND DISCUSSION</u>	115
<u>CONCLUSIONS AND RECOMMENDATIONS</u>	129
<u>REFERENCES</u>	131

PLATES

Plates 1 - 3	62
Plates 4 - 7	63
Plates 8 - 11	64
Plates 12 - 15	65

ON ERYTHEMA NODOSUM
AND
ITS RELATIONSHIP TO TUBERCULOSIS.

A Study of One Hundred and Thirteen
Consecutive Cases.

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INTRODUCTION:

The etiology of Erythema Nodosum has for many years been the subject of much discussion, and as yet, no final agreement has been reached. In the Scandinavian countries the opinion that it is in the main a tuberculous manifestation is widely held, but in this country, rheumatism is still thought by many authors to be the predominant cause.

Consideration of these divergent opinions has prompted me to investigate one hundred and thirteen consecutive cases of Erythema Nodosum seen at the Cardiff Tuberculosis Dispensary with a view to ascertaining if, in this country, tuberculosis is the significant etiological factor of this important disease.

The previous literature is reviewed; the present study is reported; the results of the investigation and their significance are presented, discussed and summarised.

Section 'A'.

HISTORICAL SURVEY.

The name Erythema Nodosum appears to have been introduced by Willan in his classical work "On Cutaneous Diseases", published in London in 1807. Hebra (1860) accepted Erythema Nodosum as a definite clinical picture, and did not include it in the more composite group described as Erythema Multiforme.

There has been no improvement on Hebra's classical description of the skin lesions in Erythema Nodosum in the later literature on the subject, and it is therefore justifiable to quote it in full:

"Light-red raised nodules, either round-topped or oval in shape, tender to the touch, and mainly situated on the legs. In many cases the eruption is preceded by a slight temperature elevation, or even chills; often, however, the patient has no previous warning of the disease before he sees or feels the nodes. They occur as a rule in various sizes, the smallest the size of a pea, and the largest, of a closed fist. The individual nodules are usually discrete, and first pale red with a faint gold tinge; at a later stage they turn dark red, then livid, and after the redness has disappeared, the lesions persist for a long

time in the form of yellowish pigmentation. These shiftings of colours are the same as those occurring after a bruise, and for this reason, the name dermatitis contusiformis has been used by some authors."

There appears to be general agreement about the clinical features of Erythema Nodosum, but in the ninety years that have elapsed since Hebra's precise description many theories have been advanced as to its etiology and pathogenesis; much discussion and argument still continues, and many divergent views are expressed. The numerous publications of the present century, especially those of the inter-war years, have thrown new light on the subject, for they have been aided by the tremendous advances made during this period in diagnostic measures, not only of tuberculosis, but of streptococcal and other infections. It should, therefore, be possible to discard those theories that are not founded on sound clinical and scientific investigation.

The causation of Erythema Nodosum may be discussed under the following heads:-

1. A specific infectious disease, "Nodal Fever".
2. A manifestation of rheumatism, or of B-Haemolytic streptococcal infection.
3. A manifestation of tuberculous infection.

4. A symptom-complex resulting from one of several bacterial infections, toxins, or chemical agents.

(1).

That Erythema Nodosum is a specific infectious disease, "Nodal Fever".

Lendon (1905, 1925) was a strong protagonist of the specific infectious theory and he was the first to use the term "Nodal Fever". He pointed out that Erythema Nodosum is not merely a skin disease, but is associated with a group of general symptoms. In support of his opinion he reported (1925) ten instances of apparent infection conveyed from one patient to another, and one in which five related adult females developed Erythema Nodosum at intervals of one to seven years. This, he considered, suggested the possibility of a "carrier" of the germ.

Symes (1921) was in general agreement with Lendon, but admitted that several of his cases of Erythema Nodosum had been associated with tuberculosis. He postulated that all acute specific infectious diseases should conform to the following criteria:-

1. Communicability from person to person.
2. Occurrence in epidemic outbreaks.
3. A seasonal incidence.

4. A constant age incidence.
5. A definite and orderly sequence of events during the illness, for example, a period of incubation, of prodromal illness, of febrile reaction, rash, convalescence, and relapses.
6. Conferment of immunity.

He recorded his personal experience of three instances in which two cases of Erythema Nodosum had occurred in the same house, and he quoted examples of several epidemics, the most notable being in Monmouthshire in August and September, 1920, when about fifty typical cases of Erythema Nodosum were observed in a small town. He believed that the seasonal incidence of Erythema Nodosum is constant - the largest number of cases occurring in the second quarter of the year, and the majority of the remainder in the last quarter. 63.2% of his cases were in the second and third decades of life. Both Lendon (1905) and Symes (1921) considered the incubation period to be about 12 to 14 days. Symes then concluded that Erythema Nodosum conforms to the criteria he had laid down for the behaviour of acute infectious diseases. Subsequently (1930), he modified this view, and brought forward evidence to show that 10 - 20% of his cases developed tuberculosis

} ? must be

within a short time of the skin eruption.

In more recent years, Keil (1939) in America, has supported the theory that Erythema Nodosum is an acute specific infectious disease.

It would be, however, unwise to accept the deduction put forward by either Lendon (1925) or Symes (1921). Their evidence in favour of the infectivity of Erythema Nodosum is very indefinite; for example, the occurrence of multiple cases in a house or school can equally well be explained by simultaneous infection from a patient with active pulmonary tuberculosis; further, sex and age incidence may occur in other types of disease, and whilst a slight seasonal preponderance appears to exist, cases of Erythema Nodosum do occur at all times of the year. Immunity, if produced at all, must be transient, for many examples of recurring attacks of Erythema Nodosum are given in the literature (Symes, 1929; Lendon, 1925; Wallgren, 1935; Löfgren, 1946).

Rosenow (1915) claimed to have isolated a Diphtheroid bacillus from the Erythematous nodes in eight cases, and to have reproduced the disease in animals by intravenous injection of this organism, but subsequent investigators have been unable to confirm these findings.

(2).

That Erythema Nodosum is a manifestation of rheumatism or of B-Haemolytic streptococcal infection.

Perry (1944) pointed out that the first to suggest a relationship between Erythema Nodosum and rheumatism was Bouillaud of Paris in 1840. This conception arose from the well-recognised fact that Erythema Nodosum is frequently associated with a sore throat and pains in the joints. Trousseau (1869) in a clinical lecture delivered at the Hôtel-Dieu, Paris, stated that Erythema Nodosum is "a specific and separate disease" and that it is probably "of the nature of rheumatism", but he was careful to declare "I have never seen redness or swelling in the situation of the affected parts; nor have I ever found signs of cardiac disease". Barlow (1883) was critical of the rheumatic theory. He had been unable to satisfy himself that an organic cardiac murmur occurred in cases of Erythema Nodosum or that a true arthritis developed. He thought the pains in the limbs were caused by tension in the nodes, which tend to occur in areas that do not readily yield. He concluded that "until we get evidence of the initiation of heart disease in an attack, or of the liability of persons who suffer from

Erythema Nodosum to subsequent undoubted rheumatism, I think we ought to hesitate before saying that Erythema Nodosum is closely related to rheumatism, much less convertible with it, although in some respects it runs parallel with it".

The traditional association between Erythema Nodosum and rheumatism dates back to a paper by Stephen Mackenzie read in 1886 to the Clinical Society, London, and published in that year in their transactions. For nearly fifty years, his hypothesis of this relationship has had, especially in this country, a considerable influence, and it is still quoted in practically every well-known text book of Medicine or Dermatology.

In the last two or three decades, however, the method in which his investigation was carried out, and the evidence on which he based his conclusions have been severely criticised by many authors (Gosse, 1913; Lendon, 1925; Walker, 1927; Landau, 1927; Perry, 1944; and Branwood, 1947).

Mackenzie reported on one hundred and eight cases of Erythema Nodosum, particulars about these having been collected from the records of four of the London Teaching Hospitals. It would appear that he had personally examined only

a small proportion of these patients, and that he relied on the observations of others for the greater part of his investigation. He concluded that "Erythema Nodosum is frequently, if not generally, an expression of rheumatism, even when no other definitely rheumatic symptoms are present". But he arrived at this conclusion on such flimsy evidence as a family history of rheumatism, the presence of fever and joint pains, and in many cases, a very doubtful heart murmur, which he admitted was often transitory. It is probable that these transitory murmurs were in the majority of cases febrile in origin.

Branwood (1947), reported the presence of a passive soft mitral systolic bruit in six of twenty cases of Erythema Nodosum, and in four of a control group of twenty young patients who were febrile. Further, no author has produced any evidence to show that patients with Erythema Nodosum are subsequently more prone to rheumatism than is the general population.

Recently, evidence has been produced to suggest a relationship between acute rheumatism and the streptococcus B-haemolyticus (Coburn, 1931; Collis, 1931; Gibson and Thompson, 1933).

Collis (1932) showed that a

marked local reaction is obtained in certain streptococcal infections to the intracutaneous injection of a soluble endotoxin of B-haemolytic streptococci, and he considered that this skin reaction has a high degree of specificity. Streptococcal infection is probably universal, and Collis, therefore, emphasized that only a strong skin reaction is significant. His findings have been supported by Coburn and Moore (1936), but Gibson and Thompson (1933) working in Edinburgh, noted that the intracutaneous reaction was not more frequent or marked in their rheumatic group than in a control non-rheumatic series, and they thought this test indicated only a previous infection with haemolytic streptococci. Wallgren (1938) was of the same opinion, for he found that nearly fifty per cent of his cases of Erythema Nodosum which he considered tuberculous in origin, had a positive reaction to Collis' streptococcal endotoxin, and there was no clinical evidence of rheumatism in these cases. It would appear, therefore, that a positive skin reaction to the B-haemolytic streptococcal endotoxin in itself is non-conclusive evidence that the streptococcus is the etiological factor of a suspected lesion.

Collis (1933) gave an account of a very comprehensive investigation carried out by him into the etiology of Erythema Nodosum.

Periodic radiographical examination of the chest, skin tests with tuberculin (Mantoux) and with his streptococcal endotoxin, bacteriological examination of gastric lavage fluid for tubercle bacilli, throat swabs for the presence of haemolytic streptococci, and clinical observation, were the methods he used. He considered that of 38 cases observed by him in London, 7 (18.4%) were streptococcal in origin, and of 11 in Dublin the corresponding figure was 1 (9.1%). He explained the pathogenesis of Erythema Nodosum as "a type of hyper-reactive tissue response to different bacterial allergens, and that the allergens responsible for the disease in London are commonly tuberculin and haemolytic streptococcal endotoxin".

Streptococcal agglutination tests were used by Frankel (1945) in an attempt to prove that this organism is the etiological factor of Erythema Nodosum. He gave details of 19 cases, all women between the ages of 25 and 70 years. Nine of these had periodic streptococcal agglutination tests carried out, and in seven the titre was initially considerably raised (1/5120 to 1/160 - the normal being up to 1/80). Towards the end of the illness the titre returned to within normal limits. Radiographical examination of the chests of the 19 cases was normal. The

author regarded all his cases as being streptococcal in origin.

Ernberg and Gabinus (1939) described an unusual outbreak of Erythema Nodosum which occurred in Stockholm in the spring of 1937. They reported that in the years 1928 to 1936 (inclusive) of 420 children with Erythema Nodosum, only 34 (8.1%) were tuberculin negative, but that of 34 seen in the first half of 1937, 20 (59%) were negative. They found a high incidence of pharyngeal infection in the 1937 cases, and it is possible that this was caused by B-haemolytic streptococci.

Wallgren (1938) stressed the difficulty of diagnosing atypical rheumatic infection especially in the absence of a cardiac lesion. He accepted Collis' (1933) evidence in favour of a streptococcal etiology of certain cases of Erythema Nodosum, but he considered that in Sweden this only rarely occurred. Of eight hundred cases of Erythema Nodosum observed by him, he regarded only one as due to acute rheumatism - this was a young boy with a negative tuberculin reaction, who developed wandering joint pains and endocarditis, verified electrocardiographically. In Bristol, Perry (1944) found only 10 cases of Erythema Nodosum in over 1,000 rheumatic patients, and he agreed with Wallgren's opinion that acute rheumatism was an uncommon cause of this condition.

On the other hand, Löfgren (1946) working in Stockholm, concluded that of 178 adult cases of Erythema Nodosum seen by him, 30 (16.9%) were of the streptococcal type. His study on the etiology of Erythema Nodosum is probably the most thorough yet carried out, especially with regard to bacteriological, serological and skin sensitivity tests. He based his diagnosis of acute streptococcal infection on, (a) the presence of a sore throat, (b) a strong skin reaction to a suspension of B-haemolytic streptococci, (c) a high antistreptolysin titre (200 units or over) and (d) the absence of evidence of recent tuberculous infection, at or subsequent to, the eruptive phase of Erythema Nodosum.

He, however, did not accept Wallgren's dictum (1938) "that it is only possible to prove a non-tuberculous etiology of Erythema Nodosum in a tuberculin negative patient", for eight of his thirty streptococcal type cases were Mantoux positive.

It is interesting to note that Löfgren (1946) found that of the tuberculous type cases of Erythema Nodosum, 15.4% had a sore throat, 12% a strongly positive reaction to B-haemolytic streptococcal endotoxin, and 32.6% a significantly raised antistreptolysin titre. If it is accepted that these criteria are evidence in

favour of an acute streptococcal infection, then it is necessary to assume a concomitant existence of tuberculosis and acute streptococcal infection. The presence of a dual infection at the time of the occurrence of Erythema Nodosum complicates the issue and makes it much more difficult to decide as to which of them is the true etiological factor of the eruption. Further, it raises the possibility that one of the infections may act as a provoking factor of what Löfgren calls "the basic infection" which is responsible for the specific hypersensitivity.

Löfgren observed the 30 streptococcal type cases for from one to three years, and none of them developed any signs of active tuberculosis in that period; this can be regarded as further evidence in support of the non-tuberculous etiology of this group.

It would appear that a strong case has been made, especially by Collis (1933) and Löfgren (1946) in support of acute B-haemolytic streptococcal infection being, in a small percentage of cases, the etiological factor concerned in the production of Erythema Nodosum.

(3).

That Erythema Nodosum is a manifestation of tuberculous infection.

Uffelmann (1872) separated Erythema Nodosum into two prognostic groups - an "ordinary" and an "omnious" type. The omnious type frequently gave a family history of tuberculosis, and some of them subsequently developed this disease, but the ordinary type appeared to produce little, if any, ill-effects.

It was not until the early part of the present century that any great interest was taken in the possible association between Erythema Nodosum and Tuberculosis, and only since about 1920 that a considerable amount of work, clinical and experimental, has been carried out to try and prove such an association. The advent of skin tuberculin testing in 1890 to demonstrate the existence of tuberculous infection, improved bacteriological methods to isolate the tubercle bacillus and the rapid development of radiographical technique, have combined to make in recent years, the approach to the problem a much more scientific one.

Pollak (1912) reported on 48 cases of Erythema Nodosum in children aged 1 - 13 years, all gave a positive tuberculin reaction,

and three developed active tuberculosis within a year of the eruption. Symes (1914) wrote a paper on "The Association of Erythema Nodosum and Tuberculosis", in which he described 20 cases of Erythema Nodosum, in 6 of whom clinical evidence of tuberculosis was found. He at that time suggested that Erythema Nodosum might be a toxic manifestation of chronic tuberculosis or an actual invasion of the skin by the tubercle bacillus.

The first outstanding investigation into the relationship of Erythema Nodosum and Tuberculosis was that of Ernberg, in 1921; this was conducted in a children's hospital in Stockholm. He reviewed the history and clinical condition of 39 cases of Erythema Nodosum, and found that, as a rule, they had a strongly positive tuberculin reaction, a family history of tuberculosis was noted in many, and that in some a moderate or high fever persisted for weeks after the eruption had disappeared. This last observation suggested to Ernberg that "there must be within the system, independent of the cutaneous eruption, a process which could give rise to fever". On inspection of their chest X-ray films, he found that in 35 of the 39 cases there was a pathological enlargement of the hilar glands, which at times was associated with a parenchymal lesion. He investigated the after-histories of 31 of these children, and

discovered that 13 of them had developed, usually inside a few months after the eruption, unmistakable signs of tuberculosis, such as phlyctenular conjunctivitis or miliary disease.

Further studies by Ernberg (1921, 1933) on the histological comparison between excised nodes from cases of Erythema Nodosum and excised positive skin tuberculin reactions from a control group, showed that there is a striking similarity in their appearances. He also produced, in several children with Erythema Nodosum, a recrudescence of the eruption by the sub-cutaneous injection of tuberculin. As a result of all these findings Ernberg suggested that in general Erythema Nodosum is a tuberculous manifestation, and that "the symptom-complex called Erythema Nodosum can be explained as an autogenous tuberculin reaction".

little
symptoms

Vetlesen (1922) of Oslo, reviewed 45 cases of Erythema Nodosum admitted to hospital during the years 1895 to 1915. He found that 12 (26.6%) of these had developed tuberculosis, but his follow-up was not very complete, and the clinical evidence on which the diagnosis of tuberculosis was made was at times not very convincing. He then searched the previous histories of 350 patients with pleurisy and noted that 18 (5.1%) had had Erythema Nodosum; and of

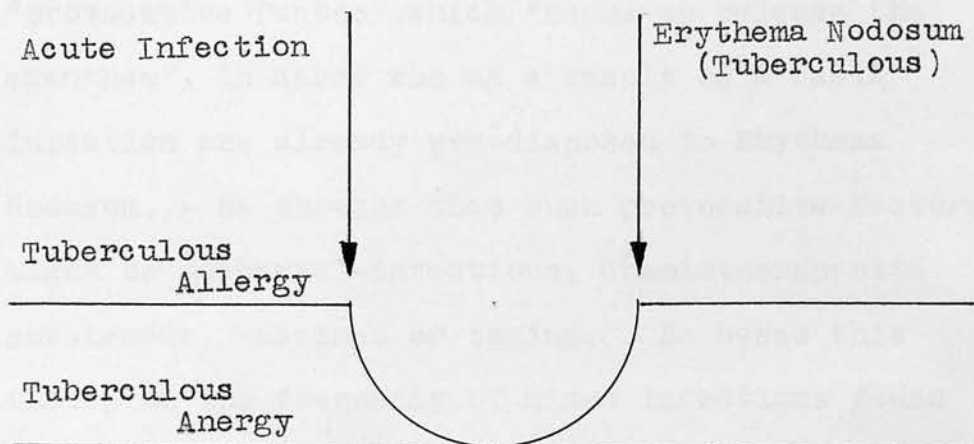
1,317 diagnosed cases of tuberculosis, 12 (0.9%) had previously suffered from Erythema Nodosum.

Since 1921 considerable support has been given by Scandinavian workers to the theory that tuberculosis is predominantly the etiological factor of Erythema Nodosum. Wallgren (1922) originally thought that it was a disease "sui generis", but that for some reason patients with tuberculosis were pre-disposed to it. In 1926, however, he agreed with Ernberg that Erythema Nodosum was a sign of tuberculous infection; he based this opinion on the observation that children with a negative tuberculin reaction just before the development of the eruption gave a positive result soon afterwards, and he suggested that the time of appearance of Erythema Nodosum coincides with the onset of tuberculous allergy (hypersensitivity) in a recently infected individual.

In a series of 266 sanatorium nurses observed in Oslo by Heimbeck (1928), 37 (14%) developed Erythema Nodosum at the time when their tuberculin reaction was converted from negative to positive as a result of a recent tuberculous infection. This finding of Heimbeck's has been supported by Punch (1941) and Daniels (1944) in this country, and Ustvedt (1947), Frostad (1944) and others in Europe. Daniels et alii (1948) in the Prophit Tuberculosis Survey of medical students

and nurses in London noted that of 782 Mantoux conversions to positive, only 14 (1.8%) were accompanied by Erythema Nodosum, a much smaller percentage than noted by Heimbeck in Oslo.

Wallgren (1935, 1938) considered that allergy (hypersensitivity) to tuberculin might be temporarily depressed by most acute infections, and he thought that this explained the occurrence of Erythema Nodosum in people who had been infected with tuberculosis a considerable time before the development of Erythema Nodosum - Post-Primary Erythema Nodosum. He concluded "a text-book example of this kind is the Erythematous eruption which measles may produce in a child infected with tuberculosis a long time previously. Measles gives rise to a change in the allergic state, producing first a decrease and then a new increase of tuberculous allergy, and the Erythema Nodosum appears as part of the phenomenon of the increase in allergy". He illustrated this change in allergy in schematic form as follows:



The pathogenesis of Tuberculous Erythema Nodosum was thought by Forman and Whitwell (1934) to be the result of a small number of tubercle bacilli being carried from a primary focus in the lungs or elsewhere by the bloodstream to the skin, and there producing an acute local reaction in a patient with a high degree of tuberculin hypersensitivity. They agreed with other workers that it is extremely rare to find tubercle bacilli in the Erythematous nodes, and they suggested that this is due to the bacilli being killed by the severity of the local reaction as is well-known to occur in the phenomenon described by Koch. They noted that there is a close similarity in the histological character of Erythematous nodes and in the skin reaction produced by Koch's re-inoculation in tuberculous animals.

Löfgren (1946), as already indicated, postulated an etiological factor, which he called "the basic infection" and a "provocative factor" which "seems to release the exanthem", in cases who as a result of a basic infection are already pre-disposed to Erythema Nodosum, - he thought that such provocative factors might be bacterial infections, chemiotherapeutic substances, vaccines or toxins. He based this theory on the frequency of mixed infections found

by him in patients with Erythema Nodosum, and also its association with certain drugs like sulphathiazole.

Tuberculin tests have been extensively used since the introduction of tuberculin by Robert Koch in 1890. Opinion is practically unanimous as to the specificity of these tests (Long, 1939; Topley and Wilson, 1936). A positive reaction shows that infection with the tubercle bacillus has at some time in the past taken place. A negative reaction is very strong evidence against the presence of tuberculous infection with the following exceptions:

1. In the presence of certain intercurrent acute infections, e.g. measles.
2. Occasionally with pregnancy.
3. Very acute tuberculosis.
4. Healed lesions.
5. Where infection with the tubercle bacillus has been so recent that tuberculin hypersensitivity has not had time to develop.

It has been suggested by Koch (1926) that Erythema Nodosum in itself may cause a temporary depression of tuberculin hypersensitivity so that a negative tuberculin reaction is given. His view has received little support, for cases of

Erythema Nodosum have been described in whom a negative reaction has persisted long after the acute phase of the illness has passed.

Many authors have reported a much higher incidence of positive tuberculin reactors in cases of Erythema Nodosum than occurs in the corresponding age groups of controls. (Pollak, 1912; Ernberg, 1921; Ernberg and Gabinus, 1939; Roosvall, 1936; Wallgren, 1938; Mascher, 1943; Ustvedt, 1947, and Koenigsberger, 1941). The occurrence of a high incidence of positive tuberculin reactors in cases of Erythema Nodosum is suggestive of an association between this condition and tuberculosis.

Bacteriological methods for the detection of the Tubercle Bacillus.

Meunier (1898) introduced the investigation of gastric lavage contents for tubercle bacilli, and this, with other bacteriological methods, has been fairly extensively used in the study of Erythema Nodosum.

Löfgren (1946) considered "that as a rule the finding of tubercle bacilli in connection with Erythema Nodosum is evidence of the presence of active tuberculosis of recent origin, and therefore constitutes an important aid when the etiological aspect is being considered".

Wallgren (1930) was the first to use the investigation of gastric fluid for the isolation of tubercle bacilli in cases of Erythema Nodosum. At that time he reported of 22 tuberculin positive cases, 14 were positive by guinea-pig inoculation using the gastric lavage contents.

TABLE I.

Results of Guinea-pig Inoculation of Gastric Lavage fluid in cases of Erythema Nodosum.
(Various Authors).

Author.	No. of Cases.	Negative.	Positive.	Per cent Positive.
Wallgren (1938).	119	57	62	52.6
Löfgren (1946).	174	110	64	36.8
Ustvedt (1947).	200	143	57	28.5
TOTAL:	493	310	183	37.1

? Control

Table I shows the results of guinea-pig inoculation of gastric lavage contents in cases of Erythema Nodosum obtained by various authors. It will be seen that these Scandinavian investigators obtained a considerable percentage of positive bacteriological findings for tubercle bacilli, using the gastric lavage method. No comparable investigation has been conducted in this country - with the exception of that by Collis (1933) which was on a much smaller scale.

Radiographical Findings.

The presence of radiographical evidence of enlarged hilar glands, often with a parenchymal lesion, was noted by Ernberg (1921) in a high proportion of his cases of Erythema Nodosum. This observation has been confirmed by many subsequent workers (Wallgren, 1938; Mascher, 1943; Perry, 1944; Löfgren, 1946; Branwood, 1947). Löfgren (1946) found that of his 178 unselected cases of Erythema Nodosum in adults, radiographical chest abnormality was present in 140 (78.7%). These abnormalities have been regarded as indicative of a tuberculous process. But Kerley (1942, 1943) denied that this was so, and suggested that they might better be attributed to the Sarcoids of Boeck. The relationship of sarcoidosis to tuberculosis is not finally settled, and most authors consider that the weight of evidence is against the pulmonary and hilar shadows seen in cases of Erythema Nodosum being essentially sarcoid in nature, and prefer to still regard them as the result of a tuberculous process.

The subsequent history of cases of Erythema Nodosum in regard to the development of active tuberculosis.

Numerous authors have shown that patients with Erythema Nodosum are prone to develop active tuberculosis, and in this respect

the work of Vetlesen (1922) has already been noted (page 17).

Hambro (1928) reported that of 62 cases observed by him, 27 (43.5%) subsequently had a pleurisy, and Mascher (1943) in a careful follow-up of 244 cases of Erythema Nodosum, that 97 (40%) had a pleural effusion, 14 (5.7%) pulmonary tuberculosis (five sputum positive), a few non-pulmonary tuberculosis, and 118 (48.3%) no evidence of an active lesion. In Löfgren's (1946) series of 178 adult cases, 50 (28.1%) developed active tuberculosis verified bacteriologically in 41 (82%).

Other workers have investigated the histories of diagnosed cases of tuberculosis to find what percentage of these have had Erythema Nodosum. Hambro (1928) noted that of 744 patients with tuberculosis, 62 (8.3%) had suffered from Erythema Nodosum, whilst of 256 patients with no evidence of active tuberculosis, none had had it. On the other hand, Lendon (1925) was of the opinion that there was no higher incidence of tuberculosis amongst his cases of Erythema Nodosum than in the general population, and that tuberculous sequelae were comparatively rare.

It is apparent from the foregoing account, and especially in the last three decades,

that a considerable amount of evidence has been brought forward in support of the tuberculous etiology of Erythema Nodosum. The results of the work of several authors in this country and in Scandinavia in respect of this association are shown in Tables II 'A' and II 'B' (page 27).

It will be seen that of 204 cases of Erythema Nodosum in this country, 103 (50%) were presumed to be tuberculous in origin, whilst in the Scandinavian countries, of 1068 cases, 795 (74%) were presumed to be tuberculous. The higher incidence of Tuberculous Erythema Nodosum reported from the Scandinavian countries may suggest that the etiological factors may vary in the two countries, but the more likely explanation is that these cases were much more thoroughly investigated in Scandinavia than here.

The Production of Erythema Nodosum
by B.C.G. Vaccination.

In view of the proposed re-introduction of B.C.G. Vaccination into this country, it is of interest to consider if it can produce Erythema Nodosum. Löfgren (1945) reported three cases of Erythema Nodosum following within 25 days B.C.G. Vaccination. All three patients gave a negative tuberculin reaction just before vaccination, but had been exposed to

TABLE II - ('A' and 'B').

The Frequency of Tuberculosis as an
Etiological Factor of Erythema
Nodosum (Various Authors).

'A' (In Great Britain).

Author	No. of cases	Child- ren. Adults Both.	Consid- ered Tuber- culous	Probably Tuber- culous	Total Presumed Tuber- culous
Symes (1930)	13	B	2 (15.4%)	-	2 (15.4%)
Collis (1933)	49	B	37 (75.5%)	-	37 (75.5%)
Perry (1944)	112	B	32 (28.1%)	28 (25%)	60 (53%)
Frankel (1945)	19	A	0 (0.0%)	-	-
Branwood (1947)	11	B	4 (36.4%)	-	4 (36.4%)
TOTAL:	204	All Ages	75 (36.8%)	28 (13.7%)	103 (50%)

'B' (In Scandinavia).

Ernberg (1921)	39	C	35 (90%)	-	35 (90%)
Vetlesen (1922)	45	B	12 (26.6%)	-	12 (26.6%)
Wallgren (1938)	362	C	248 (68.5%)	66 (18.2%)	314 (86.7%)
Mascher (1943)	244	A	198 (81%)	-	198 (81%)
Löfgren (1946)	178	A	78 (43.8%)	26 (14.6%)	104 (58.4%)
Ustvedt (1947)	200	B	110 (55%)	22 (11%)	132 (66%)
TOTAL:	1068	All Ages.	681 (63.7%)	114 (10.6%)	795 (74%)

tuberculous infection. Gastric lavage was positive by guinea-pig inoculation and the cultures showed that the tubercle bacilli were of the human type in the three cases. Löfgren considered that these three children had been infected with tuberculosis from a contact source just before vaccination, and that the Erythema Nodosum was not associated with B.C.G. Vaccination. He also thought that it was unlikely that it could produce Erythema Nodosum.

(4)

That Erythema Nodosum is a symptom-complex resulting from one of several bacterial infections, toxins, or chemical agents.

The occurrence of Erythema Nodosum in many diseases, apart from those already described, has been reported in the literature, but in the European countries the frequency of such occurrence is comparatively rare.

Erythema Nodosum has occasionally been seen in cases of pneumonia, syphilis, gonorrhoea, measles, whooping cough and other conditions (Löfgren, 1946). It is, of course, possible that some of these diseases have acted only as provoking factors of a basic tuberculous or B-haemolytic streptococcal infection.

In view of the theory put forward by Wallgren (1926), Collis (1933), and others, that Erythema Nodosum is a manifestation of hypersensitivity to different bacterial allergens (notably tuberculin, and B-haemolytic streptococcal endotoxin), it is of interest to note that in the literature, cases have been described of an association between Erythema Nodosum and other diseases which also produce hypersensitivity to specific allergens, namely: coccidioidomycosis, trichophytosis, and lymphogranuloma inguinale (climatic bubo).

Coccidioidomycosis - This disease is endemic in certain parts of North America, notably the San Joaquin Valley of California. It is caused by a fungus - *coccidioides immitis* - and is characterised by the formation of granuloma in the skin, lungs, and occasionally other organs. These granuloma may caseate and produce ulceration, and if the lungs are involved, may closely simulate tuberculosis. A positive skin reaction, varying in intensity, is given to an intracutaneous injection of coccidioidin, and appears to be diagnostic of the presence of this infection. Dickson (1937) found that about 5 per cent of cases of coccidioidomycosis developed Erythema Nodosum. Smith (1940) reported 453 patients with Erythema Nodosum in the San Joaquin Valley - 11 (2.4%) of these he thought

tuberculous in origin, and 432 (95.3%) due to coccidioidomycosis. He noted in the latter type a high predilection for females, and in several cases the occurrence of Erythema Nodosum was associated with a conversion of the coccidioidin reaction from negative to positive.

Trichophytosis - The occasional occurrence of Erythema Nodosum in this disease was noted by Bloch (1921). According to Muir and Ritchie (1937), an extract of the parasite trichophyton injected into the skin, may in deep-seated ringworm produce a local, focal and general reaction, not unlike that seen in tuberculosis after the injection of tuberculin.

literature on
skin grafts
syphilitic.

Lymphogranuloma inguinale - This disease is produced by a filterable virus, and a specific reaction (Frei) is obtained by an injection into the skin of diluted pus from a bubo. Kuznitsky (1926) and later others, have shown that Erythema Nodosum may occur in this disease.

It seems reasonable to conclude that in these three diseases - coccidioidomycosis, trichophytosis, and lymphogranuloma inguinale, a specific hypersensitivity may be the cause of the development of Erythema Nodosum. But this pathogenesis cannot be accepted for Erythema Nodosum occurring in syphilis, pneumonia, measles,

to what?

etc., for they do not produce specific allergens. It may be that they cause a temporary depression of hypersensitivity to either tuberculin or streptococcal endotoxin, and when this hypersensitivity returns, Erythema Nodosum is liable to appear.

The Association of Erythema Nodosum with Boeck's Sarcoid.

Kerley (1942, 1943) as a result of a study of 37 cases of Erythema Nodosum in adults, suggested that it was a manifestation of sarcoidosis and not of tuberculosis. He based this opinion on the following observations:-

1. None of his cases developed clinical tuberculosis.
2. Only one gave a family history of tuberculosis.
3. That excised nodes did not show any evidence of tuberculous histology.
4. That the radiological signs are not indicative of tuberculosis, but are identical with those seen in sarcoidosis.
5. In two cases eye lesions developed which were strongly suggestive of sarcoidosis.
6. In another two cases, skin lesions excised after the acute rash had

} - Histo not Sarcoid.

gone showed the histological characteristics of sarcoidosis.

7. The literature of sarcoidosis shows that 25% of cases gave a history of Erythema Nodosum.

In criticism of Kerley's study it may be said that only a few of his cases were tuberculin tested, and the duration of observation was insufficient to say that clinical tuberculosis did not develop. On the other hand, two of his cases were proved histologically, and the chest radiographical changes in 28 of his 37 cases must be considered suggestive of sarcoidosis. Cameron (1947) pointed out that with regard to sarcoidosis "in a strict sense the disease can only be diagnosed by histological examination of involved tissue, and a diagnosis apart from that is presumptive. Most radiographical diagnosis is, up to a point, presumptive, but the radiographical appearances of the sarcoid lung do often follow a pattern which is suggestive of the condition".

The etiology of sarcoidosis still remains obscure. Snapper (1938) thought it was due to an unknown virus. Hoyle (1947) concluded that "if it is not actually a tuberculous condition, it is very closely linked with it".

It may, therefore, be possible

that Kerley's assumption of an association between Erythema Nodosum and sarcoidosis is not evidence against a tuberculous etiology of Erythema Nodosum.

Toxic Agents.

The appearance of Erythema Nodosum shortly after an injection of diphtheria toxoid or vaccines, has been reported by Löfgren (1946), and in recent years during treatment with one of the sulphonamide drugs, especially sulphathiazole (Long, 1940; Loveman & Simon, 1940; Ustvedt, 1947). Long (1940) considered that the production of Erythema Nodosum by the sulphonamide drugs was due to sensitization, and Shaffer, Lentz and McGuire (1943) found that whilst simple, direct patch tests were negative to sulphathiazole, passive transfer tests gave a reaction to this drug. Löfgren (1946) noted that of his 178 cases of Erythema Nodosum, 23 developed after treatment with one of the sulphonilamides. He regarded 14 of these as of the tuberculous type, and 8 streptococcal in origin. He believed that "sulphonilamide medication does not constitute a real etiological factor in Erythema Nodosum, but that it produces this exanthem in cases which, because of the existing infection, especially early tuberculosis and infection with B-haemolytic streptococci, are ready to react with Erythema Nodosum". He arrived at no conclusion as to the exact mode of this provocation.

S E C T I O N B.PRESENT INVESTIGATION.

A Personal Study of One Hundred and
Thirteen Consecutive Cases of Erythema
Nodosum, with special reference to the
part played by Tuberculosis in its
Etiology.

Introductory Notes.

This investigation was carried out at the Cardiff Tuberculosis Dispensary, and the patients who formed the material for the Study dwelt in this City.

In order to form some idea of the extent of tuberculosis in Cardiff, the following statistical data for the year 1947 are given - the estimated population was 230,000; the number of deaths from all forms of tuberculosis was 185, giving a death rate of 0.80 per 1,000 population; 435 new cases of tuberculosis were notified. The tuberculosis death rate for England and Wales in the year 1947 was 0.549 per 1,000 population, and it will, therefore, be seen that in this respect Cardiff occupied a rather unenviable position.

Towards the end of 1945 the Medical Practitioners in the area were invited to

refer all their cases of Erythema Nodosum to the Tuberculosis Dispensary, and the present study is based on those seen during the years 1946 and 1947. It is considered that this series of cases of Erythema Nodosum did not constitute a selected group by virtue of being referred to the Tuberculosis Dispensary, for they were sent irrespective of any special indication of tuberculosis. A survey of the out-patient and in-patient records of the General Hospitals in the City showed that during the two years concerned, only 8 cases of Erythema Nodosum from Cardiff came under their observation, whilst 113 were seen at the Tuberculosis Dispensary. It is, however, impossible to estimate with accuracy the number of cases of Erythema Nodosum who were treated by their own doctors without reference to the Dispensary or elsewhere. But it is unlikely to have been large, for very free use of the Tuberculosis Dispensary is made by the medical practitioners in the area, as is shown by the fact that in the year 1947, of 6,037 new patients seen, only 393 (6.5%) were found to have active tuberculosis.

The Diagnosis of Erythema Nodosum.

For the purpose of this investigation, all patients in whom the rash had disappeared were discarded, as there was no way of substantiating the diagnosis. A classical

description of the skin lesion in Erythema Nodosum is that of Hebra (1860), which has already been quoted (page 2), and this formed the basis of diagnosis.

The differential diagnosis.

It was found that the skin lesion in Erythema Nodosum was so typical that the diagnosis was not difficult. Roxburgh (1941) gives the differential diagnosis as - from Bazin's disease "this is a chronic disease and affects the lower halves of the backs of the legs. It tends to recur every winter. The nodules are purple, relatively painless and often break down", - from Erythema Multiforme "in this the lesions are likely to be most marked on the hands or arms, and to be maculo-papular or vesicular. They are not painful or tender, and there is seldom any fever". Syphilitic nodes must not be forgotten. Here there are usually other signs of syphilis, and the Blood Wassermann and Kahn tests are almost invariably positive.

General Observations on the 113

Cases of Erythema Nodosum.

The nodes were confined to the lower limbs in 90 (80%) of the 113 cases, to the forearms in 7 (6%), and in the remaining 16 (14%) cases, occurred on both legs and arms. The well-

known predilection of the eruption for the extensor surfaces of the extremities was confirmed. Its duration averaged 17 days, the limits being 3 and 42 days.

A history of sore throat at, or just prior to the appearance of the nodes was given by 23 (20.4%) of the patients, limb pains were present in 70 (62%), but in only one case (0.9%) was joint swelling noted.

Investigation of the previous histories of the patients disclosed that 7 (6%) had had acute rheumatism, one 6 weeks before the occurrence of Erythema Nodosum, and the remaining 6 from one to ten years previously. In no case was a history of pulmonary tuberculosis obtained, but one had had a verified tuberculous gland in the neck four years before developing Erythema Nodosum. 2 (1.8%) gave a history of a previous attack of Erythema Nodosum, the intervals between the occurrences being two and four years respectively - the significance of recurrent Erythema Nodosum will be discussed later.

Clinical examination at the time of the eruption disclosed the presence of an apical systolic murmur in 12 (10.6%) of the cases. Two months later this murmur had disappeared in 5, but persisted in 7 cases. Four of these seven had given

a history of acute rheumatism. Six were Mantoux positive, and in three there was radiographical evidence of a recent primary tuberculous focus in the lung.

The Age and Sex Distribution of
the 113 Cases of Erythema Nodosum.

Table III (page 39) shows that of the 113 cases of Erythema Nodosum, 54 (47.8%) occurred in children (0 - 14 years), and 59 (52.2%) in adults (15 years and over); the incidence of the disease showing a gradual increase from 0 - 4 years (10.6% of the total cases) to a peak at 15 - 19 years (24.8% of the total cases), and then a fairly abrupt decline. The protagonists of the theory that Erythema Nodosum is a manifestation of primary tuberculous infection consider that its age incidence supports their view, for it is well-known that as age advances from birth to about 20 - 25 years, the rate of annual increment of primary tuberculous infection also increases, being accelerated in adolescence, until at the age of about 20 years, in an urban area, about 70 - 80% of the people are infected, and then there is a rapid decline in the rate of primary infection. Consideration of the sex distribution shows that 87 (77%) of the total cases were females, and 26 (23%) males. When, however, the total series is analysed into children and adults, a marked

TABLE III.

Age and Sex Distribution of the 113
Cases of Erythema Nodosum.

Age Group in Years	Males	Females	Per- sons	Percent- age all Ages
0-	6	6	12	10.6
5-	6	11	17	15.0
10-	11	14	25	22.1
Total 0-14	23(42.6%)	31(57.4%)	54	47.8
15-	3	25	28	24.8
20-	-	10	10	9.0
25-	-	13	13	11.5
35 & over	-	8	8	7.1
Total 15 & over	3(5.1%)	56(94.9%)	59	52.2
All Ages	26(23%)	87(77%)	113	100

alteration in the sex distribution is noted - in children, 57.4% were females and 42.6% males, but in adults, 94.9% were females and only 5.1% males.

Mackenzie (1886) arranged the ages of his 108 cases in decennia, and he found that the maximum incidence of the disease fell in the second decennia (36.1%), and the next in the third decennia (27.8%). But it is difficult to use his figures for comparison with the present series with regard to age distribution, as the method of collecting the material has differed, and it is probable that the ages of his cases were influenced by the type of hospital from which his material was obtained.

The difference in sex distribution noted in adults and children confirms the observation of Roosvall (1936) in Scandinavia, that the frequency of Erythema Nodosum was about the same in boys (40.8%) and girls (59.2%), whilst in adults the ratio was 12.1% of males to 87.9% females. Perry (1944) in this country, made a similar observation, finding that under the age of 15 years the proportion of boys to girls was fairly even (boys 36 - girls 31) whereas over this age, 43 cases occurred in females and only two in males. So far, no satisfactory explanation has been given for this marked difference in sex distribution of Erythema Nodosum in adult life.

Symes (1921) admitted that it was a weakness in his argument in support of Erythema Nodosum being a specific infectious disease, and he stated "there is no other infectious disease which shows this peculiar sex incidence".

Acute rheumatism and tuberculosis affect both sexes almost equally, although the latter disease tends to be more acute and fatal in young adult females than in males of the same age. (Picken, 1940). If either or both of these diseases constitute the basic etiology of Erythema Nodosum, it is necessary to assume the existence of some additional factor to explain its variation in sex incidence after puberty. Mascher (1943) suggested that exposure to cold air may have some influence in this respect, for the male tends to protect his legs with heavier clothing than does the female. Perry (1944) thought that sex endocrine factors may be partly responsible for the preponderance of females with Erythema Nodosum at and after adolescence. That such factors do exert an unfavourable influence on tuberculosis is accepted (Rich, 1946), but it is difficult to understand how they can have such a profound effect as to so greatly alter the sex ratio of Erythema Nodosum in adult life.

Seasonal Occurrence.TABLE IV.

The Seasonal Occurrence of the 113
Cases of Erythema Nodosum.

Year	No. of Cases	Quarter of the Year.			
		1st	2nd	3rd	4th
1946	61	16(26.2%)	18(29.5%)	8(13.1%)	19(31.1%)
1947	52	23(44.2%)	11(21.2%)	4(7.7%)	14(26.9%)
TOTAL	113	39(34.5%)	29(25.7%)	12(10.6%)	33(29.2%)

This table shows the occurrence of the cases in the different quarters of the year. For the two years together (1946 and 1947), 39 (34.5%) developed Erythema Nodosum in the first quarter, 29 (25.7%) in the second, 12 (10.6%) in the third, and 33 (29.2%) in the last quarter - that is, an incidence peak in the first quarter, a decline in the second, a marked decline in the third, and a rise in the fourth quarter, which suggests a slight but definite seasonal incidence of Erythema Nodosum. But when the cases are arranged in separate years, it is seen that in 1946, 26.2% of the cases that year occurred in the first quarter, 29.5% in the second, 13.1% in the third, and a slight peak, 31.1% in the fourth quarter. In 1947, a high incidence peak (44.2%) appeared in the first quarter, a much lower figure (21.2%) in the second, 7.7% in the third, and a rise again (26.9%) in the fourth quarter.

These figures show that in both 1946 and 1947 the seasonal incidence peak was in the winter months (but in 1946 only slightly so); that in the spring there was still a fairly high incidence, but in the late summer (third quarter) Erythema Nodosum was comparatively uncommon.

A seasonal occurrence of Erythema Nodosum has been suggested by many authors. Mascher (1943), in Sweden, found that the great majority of his cases occurred between the months of December and May. Symes (1921) stated that the seasonal incidence of Erythema Nodosum was very constant in Bristol, the largest number of cases occurring in the second quarter, and the next largest in the last quarter of the year. He thought that "this is due to the fact that the long, sunless winter months prepare the soil for infection".

It is probable that in winter there is a weakening of the body's resistance to many infections, and that confinement in houses, often badly ventilated, with the occurrence of frequent colds, predisposes to more primary tuberculous infections at this time of the year. Gosse (1913) noted that the disease in London was more common in March, April and May, with a secondary rise in July, September and October. On the other hand, Lendon (1925), in a review of 118 cases of Erythema Nodosum, discovered no seasonal incidence

in Australia. This may possibly be explained by the more equable climate in that country than occurs here.

Reference has already been made to Mascher's (1943) view that exposure to cold air may predispose to the development of Erythema Nodosum, and his opinion receives some support from the low incidence found in the third quarter of the year in the present study, for at this time the weather is usually warm.

To sum up, it appears that there is a slight seasonal incidence of Erythema Nodosum, the highest peak being in the winter months, but that this peak varies in different districts and countries at different times of the year.

The Occupations of the 113 cases of
Erythema Nodosum. (Table V, page 45).

It has not been possible to enumerate the patients with Erythema Nodosum according to the total number of people employed in each occupation in the city. The latest available information as to the distribution of occupations is that given in the 1931 Census, but since that date, Cardiff has rapidly developed, and many new industries and Government offices have been built. It is felt, therefore, that the working out of occupational risk in regard to Erythema Nodosum on the 1931

TABLE V.

Showing the Occupations of the 113
Cases of Erythema Nodosum.

Under School age.	12
At Primary or Secondary School.	46
Students (Arts).	2
Housewives.	17
Shop Assistants.	9
X Clerical.	14
Domestic Workers.	2
Waitress.	1
Nurse.	1
Fireman.	1
Factory hands.	3
Laundry workers.	2
Soldier.	1
Carpenter.	1
Hairdresser.	1

113

X Includes 6 from a large firm
of Football Pool Promoters.

Census figures would be unsound, and that it would not give a true picture of the situation.

Erythema Nodosum in Nurses.

It will, however, be seen (Table V) that of the 113 patients with Erythema Nodosum, only one was a nurse. The probable explanation of this is that nurses who report sick are usually investigated in their own hospitals. If it is accepted that primary tuberculous infection is frequently concerned in the etiology of Erythema Nodosum, then it is reasonable to anticipate a higher incidence of the latter disease in nurses than in the general population, for they are exposed to a greater risk of tuberculous infection. Ideally, Mantoux negative reactors should be excluded from any type of nursing where such a risk exists, but for at least the last ten years this has rarely been possible, owing to the shortage of nursing recruits. I have investigated the incidence of Erythema Nodosum in Mantoux negative and Mantoux positive nurses on the staff of two large tuberculosis institutions in South Wales.

Hospital 'A'.

The total number of nursing staff or entrants tested during the last six years was 524. Of these, 449 (86%) were Mantoux positive, and 75 (14%) Mantoux negative. None of the positive

reactors developed Erythema Nodosum; of the 75 negative reactors, only 13 were accepted on the staff; all the 13 subsequently became Mantoux positive, and in three (23%) of these this conversion was associated with the development of Erythema Nodosum.

Hospital 'B'.

The total number of nurses (1940 - 1948) Mantoux tested was 411, with 332 (80%) positive, and 79 (20%) negative reactors. No Mantoux positive nurses on entry, developed Erythema Nodosum. All 79 negative reactors were accepted on the staff. 8 (10%) of these developed Erythema Nodosum with conversion of the Mantoux reaction to positive.

In this respect, reference has already been made to the results obtained by Daniels et alii (1948) in their report on the Proffit Survey into Tuberculosis in young adults. They found that only 14 (1.8%) of 782 Mantoux conversions in nurses were associated with Erythema Nodosum. This smaller figure (1.8% compared with 10% and 23% in the present investigation) may partly be explained by the fact that the nurses reported in the Proffit Survey were employed in large general hospitals, only some of which admitted cases of tuberculosis, whilst those in the present study worked in tuberculosis

institutions.

This evidence, that nurses Mantoux positive on entry to hospital did not develop Erythema Nodosum, but that 10% in one hospital, and 23% in another, of the negative reactors did develop it on Mantoux conversion to positive, suggests an association between Erythema Nodosum and a primary tuberculous infection.

Contact History and Ascertained Contact
to Tuberculosis.

Table VI (page 49) shows the results of investigation into the contact history of the 113 cases of Erythema Nodosum, and the ascertainment of unsuspected contact in some of them. Of the 113 cases in the series, 45 (39.8%) gave a history of intimate contact (verified) with tuberculosis, in children this had occurred in 51.9% of the cases in that age, and in adults, in 28.8%. 68 (60.2%) of the total cases gave no history of intimate contact, and of these, contacts were examined to 20, with the ascertainment of unsuspected household contact in 6 (30%); so that of the 113 cases, a history of intimate contact with tuberculosis and ascertainment of unsuspected contact was found in 51 (45.1%) of them.

Contact history was not accepted unless verified by reference to the Dispensary

TABLE VI.

Incidence of History of Intimate Contact with Tuberculosis in the 113 Cases of Erythema Nodosum; and the Results of Contact Examination in 20 of the Cases with no History of Intimate Contact.

(1)	(2)	(3)	(4)	(5) X	(6) X	(7) X	(8) @
	No. of Cases	History of Intimate Contact.	No History of Intimate Contact.	Cases with no History of Contact to whom Contacts Examined.	Source of Tuberculous Infection Found.	No Contact History. Contacts not Examined.	Source of Tuberculous Infection Found. (History or in Contacts Examined.)
Children 0-14 years	54	28(51.9%)	26(48.1%)	13(50%)	5(38.5%)	13(50%)	33(61.1%)
Adults 15 & over	59	17(28.8%)	42(71.2%)	7(16.7%)	1(14.3%)	35(83.3%)	18(30.5%)
All Ages	113	45(39.8%)	68(60.2%)	20(29.4%)	6(30%)	48(70.6%)	51(45.1%)

X Percentage expressed to No. of cases in column (4) @ Percentage expressed to No. of cases in column (2)

) Percentage expressed to No. of cases in column (5)

@ These figures are incomplete, for contact examination was carried out in only 20 of the 68 cases with no history of intimate contact.

Register or the Notification Register of the Medical Officer of Health. By intimate contact is meant household contact, or a prolonged contact to infection in the place of employment, etc. Originally the cases of Erythema Nodosum were divided into two groups with regard to contact history - (a) those who had been in intimate contact with tuberculosis, and (b) those in casual contact, that is, contact with cases of tuberculosis of a more temporary nature. It was assumed that intimate contact was more likely to lead to massive infection with tubercle bacilli than was casual contact, and it was hoped to ascertain if this had any influence on the immediate and later findings with regard to the development of tuberculosis. But this grouping had to be discarded, for it was found, as might have been expected, that the number in the casual group was so small as to be of no statistical value.

It is, however, of interest to note that six of the cases of Erythema Nodosum were employed as female clerks in a local firm of Football Pool promoters. On investigation it was found that the Manager of this firm had recovered from tuberculosis some years previously, and in gratitude he was sympathetically inclined to employ patients with this disease, so that of a total of 600 girls employed, 94 (15.7%) had tuberculosis,

many of them sputum positive cases. The work was at the weekends only, and was, therefore, attractive to those unfit for full work. The offices were well-ventilated but overcrowded, and the opportunities for infection must have been considerable.

A disappointing feature of the present investigation is that, in spite of every persuasion, contacts were only examined to 20 (29.4%) of the 68 cases with no history of intimate contact with tuberculosis. There can, however, be little doubt, in view of the fact that of the 20 cases to whom contacts were examined, 6 (30%) had been exposed to an unsuspected source of tuberculous infection, that had contacts been examined to all 68 cases, approximately the same proportion (30%) would have revealed a source of infection. Nevertheless, the fact that 45 (39.8%) of the 113 cases of Erythema Nodosum gave a history of intimate contact with tuberculosis is significant, for in 1947, of 283 cases of pulmonary tuberculosis diagnosed at the dispensary, only 70 (24.7%) gave such a history. It will be seen, therefore, that there is a considerably higher percentage of tuberculosis contact (39.8) in the cases of Erythema Nodosum as compared with that (24.7) for the diagnosed cases of pulmonary tuberculosis in the year 1947.



Mascher (1943) reported that of 335 cases of Erythema Nodosum, he succeeded in examining contacts to 222 of them. He found that of these 222 cases, a source of tuberculous infection existed in the family in 53 (24%), at place of employment or otherwise in 76 (34%), in 44 (20%) the search was incomplete, and in 49 (22%), no contact with tuberculosis was ascertained.

It has been impossible, in the present study, to estimate with any accuracy, the time elapsing from the initial tuberculous infection to the time of development of Erythema Nodosum, for in nearly all the cases with contact history, exposure had lasted for several months. Frostad (1944) noted that of 47 cases of Erythema Nodosum, 15 (32%) gave a history of contact with tuberculosis, and that in 8 of the 15, he estimated the interval between exposure to infection and the occurrence of Erythema Nodosum varied from less than one month to a maximum of six months.

The Skin Tuberculin Sensitivity in the 113 cases of Erythema Nodosum.

In this investigation, the intracutaneous tuberculin test (Mantoux) was used throughout, for it is generally accepted to be the most reliable method (Rich, 1946). Koch's Old Tuberculin (O.T.) standardised by the manufacturers

against the Medical Research Council Standard Tuberculin was used in various dilutions. In order to avoid possible severe local reactions, 0.1cc of a 1/10,000 dilution (0.01 m.g.) was initially used. If this gave a negative reaction it was followed by 0.1 cc of 1/1,000 dilution (0.1 m.g.) and if this was also negative, the test was repeated with 0.1 cc of 1/100 dilution (1 m.g.). The result of the test was read 72 hours after it was performed. The standard adopted for a positive reaction was the presence on the third day of an area of induration at the site of the injection, at least 5 millimetres in diameter. The reaction was usually associated with surrounding erythema. This standard was altered with the use of a dilution of 1/100 O.T. to at least 10 millimetres oedema for a positive reaction to be recorded.

The intensity of the positive reaction was measured as follows:

Strongly positive +++	-	At least 10 m.m. oedema to 0.1 cc 1/10,000 O.T.
Moderately positive ++	-	(a) 5 to 10 m.m. oedema to 0.1 cc 1/10,000 O.T.
		or (b) at least 10 m.m. oedema to 0.1 cc 1/1,000 O.T.
Weakly positive +	-	(a) 5 to 10 m.m. oedema to 0.1 cc 1/1,000 O.T.
		or (b) at least 10 m.m. oedema to 0.1 cc 1/100 O.T.

A negative reaction was recorded if

the oedema was less than 10 millimetres to a dilution of 1/100 O.T.

In two cases a fairly severe reaction (vesiculation) resulted from the use of 0.1 cc 1/10,000 O.T. It would probably have been wiser to have used a 1/100,000 dilution for the initial test, but as the patients were out-patients, it was felt desirable to avoid inconvenience to them by too frequent attendances at the dispensary.

Table VII 'A' (page 55) shows the results of the Mantoux tests and the degree of the reaction in the 113 cases of Erythema Nodosum. Of the 113 cases, 101 (89.4%) were Mantoux positive, in age groups 0 to 4 years 91.7% were positive, 5 to 9 - 94.1%. 10 to 14 - 92%, 15 to 19 - 85.7%, 20 to 24 - 90%, 25 to 34 - 92.3%, and aged 35 years and over - 75% were positive. It will be noted that in childhood, the percentage (72) of strong tuberculin reactors was slightly greater than in adults (60.8).

In order that some comparison of the results of the Mantoux test (Table VII 'A') may be made with control groups, Table VII 'B' and VII 'C' are given below. No group tuberculin surveys of people beyond the age of 19 years have been made in Cardiff, but this is probably of little importance for comparative purposes, as it may be assumed that

TABLE VII(A).

The Results of the Mantoux Tuberculin Test, and the Degree of the Reaction, in the 113 Cases of Erythema Nodosum Distributed in Age Groups.

Age Group Years.	No. of Cases.	Mantoux Negative	Mantoux Positive	Mantoux Positive, Degree of Reaction.		
				Strong + + +	Moderate + +	Weak. +
0 -	12	1 (8.3%)	11 (91.7%)	10	0	1
5 -	17	1 (5.9%)	16 (94.1%)	11	5	0
10 -	25	2 (8%)	23 (92.0%)	15	8	0
0 - 14	54	4 (7.4%)	50 (92.6%)	36 (72.0%) ✕	13 (26.0%) ✕	1 (2.0%) ✕
15 -	28	4 (14.3%)	24 (85.7%)	16	8	0
20 -	10	1 (10%)	9 (90%)	5	3	1
25 -	13	1 (7.7%)	12 (92.3%)	7	4	1
35 & over	8	2 (25%)	6 (75%)	3	2	1
15 & over	59	8 (13.6%)	51 (86.4%)	31 (60.8%) ✕	17 (35.3%) ✕	3 (5.9%) ✕
All Ages	113	12 (10.6%)	101 (89.4%)	67 (66.3%) ✕	30 (29.7%) ✕	4 (4.0%) ✕

✕ Percentages expressed to number Mantoux positive.

the percentage of positive reactors in the older age groups is much the same as reported in other surveys for urban areas, for example, Hart (1932), working in London, found that of 134 people aged 21 years and over, 93% were tuberculin positive.

TABLE VII 'B'.

The Results of the Mantoux Test (1/1000)
in a Control Group of Children in a
General Hospital in Cardiff.

Age Group Years	Mantoux Negative	Mantoux Positive	No. of Cases	Percentage Positive
0 - 4	220	20	240	8.3
5 - 9	144	28	172	16.3
10 - 14	80	30	110	27.3
0 - 14	444	78	522	14.9

This hospital does not admit known or suspected cases of tuberculosis. Table VII 'B' shows the results of a tuberculin survey (Mantoux 1/1,000) of nearly all the children admitted in the years 1946 and 1947. It will be seen that, of 522 children aged 0 - 14 years, 78 (14.9%) were tuberculin positive; at the age 0 - 4 years of 240 cases 20 (8.3%) were positive, aged 5 - 9 years, of 172, 28 (16.3%), and aged 10 - 14 years, of 110 cases, 30 (27.3%) were positive. Comparison in the appropriate age groups with the Erythema Nodosum cases is: aged 0 - 4 years control group, 8.3% Mantoux positive - Erythema Nodosum cases

91.7% positive, the corresponding figures for age group 5 - 9 years being 16.3% and 94.1%, and 10 - 14 years, 27.3% and 92%.

TABLE VII 'C'.

The Results of the Mantoux Test (1/1000) in an Unselected Group of Air-Training Corps Boys (Tytler and Graham 1942 - Unpublished.)

Age Group Years.	Mantoux Negative	Mantoux Positive	No. of Cases	Percentage Positive
15 - 18	117	163	280	58.2

This table shows the results of a tuberculin survey (Mantoux 1/1,000) of an unselected group of Air Training Corps boys aged 15 - 18 years, carried out in Cardiff in 1942. Of 280 boys tested, 163 (58.2%) were Mantoux positive. Comparison with the Erythema Nodosum cases in the same age group shows that whilst in the control group 58.2% were positive, in the Erythema Nodosum cases 85.7% were Mantoux positive.

It is, therefore, seen that there was a significantly higher percentage of tuberculin positive reactors in the Erythema Nodosum cases below the age of 20 years, than occurred in the control groups at the same period of life, and this must be considered strong evidence in favour of a predominantly tuberculous etiology of Erythema Nodosum.

The significance of the intensity of the tuberculin reaction in the 113 cases of Erythema Nodosum will be discussed in a later section.

Mantoux-conversions from negative
to positive in the 113 cases of
Erythema Nodosum.

In only 3 (2.7%) of the 113 cases was there proof of a negative Mantoux reaction in the year preceding the eruption, and all three were positive at the time of the appearance of Erythema Nodosum. A girl aged 15 years had been Mantoux tested as a contact three months before she developed Erythema Nodosum, and was negative to a dilution of 1/100 O.T. She was strongly positive to a dilution of 1/10,000 when the rash appeared. The remaining two cases were children who had been in the general hospital where Mantoux testing is carried out as routine. Both were negative reactors - one developed Erythema Nodosum five months later, and the other after nine months, and both became strongly Mantoux positive. The fact that only three of the 113 cases under review had been Mantoux tested previously, is a sad reflection on the neglect of this method of investigation in this country.

As already indicated, the existence

of a negative tuberculin reaction a short time before the occurrence of Erythema Nodosum, followed by a positive result during or just after the eruption, must be considered definite evidence that infection with the tubercle bacillus has taken place, and very strong evidence in favour of the Erythema Nodosum that occurred being tuberculous in origin. In the Scandinavian countries tuberculin testing has been extensively carried out during the last 12 - 15 years; it is not surprising, therefore, that Ustvedt (1947) reported that of his 200 cases of Erythema Nodosum, 58 (29%) had shown Mantoux conversion at the time of the eruption, and Löfgren (1946) noted that of his 178 adult cases, 10 gave a history of a negative tuberculin reaction in the 12 months preceding the Erythema Nodosum, and another 7 had been positive at some time before.

Chest Radiographical Examination.

Procedure adopted - All the 113 cases of Erythema Nodosum had a full-sized (15" x 12" or 12" x 10") X-ray film taken of the chest on their first visit to the dispensary, then at about six-weekly intervals for the first six months, and every three months subsequently (with the exception of the three who ceased attending).

A standardised technique was used throughout, so that, as far as possible, the films

should be of uniform quality, making serial comparison more easy. Postero-anterior views were taken, the tube-film distance was five feet, a milliamperage of 300 was used, the kilovoltage was varied between 55 and 65 according to the thickness of the chest, and the time exposure from 1/20th to 1/10th of a second.

Description of the Abnormal Shadows seen.

For convenience of description, these can be divided into three main groups:-

1. Unilateral or bilateral hilar enlargement with or without a parenchymal lesion.
2. A parenchymal (pulmonary or pleural) lesion without hilar enlargement.
3. A calcified primary complex.

In no case was any evidence of chronic pulmonary tuberculosis (i.e. disease) found, as indicated by fibrosis or partial calcification.

1. Unilateral or bilateral hilar enlargement with or without a parenchymal lesion - the hilar shadows were often enlarged to two to three times the size of normal limits, and frequently with a marked increase in density as well. When a parenchymal lesion was present, it was usually localised, was always single, and it varied in size from about $\frac{1}{4}$ " to 1" in diameter. But at

times this shadow was larger and more diffuse to begin with, later shrinking and becoming more circumscribed. It occurred in any part of the lung field, with some predilection for the mid and lower zones, and when associated with unilateral hilar enlargement, the two shadows were invariably regionally related.

2. A parenchymal lesion with no hilar enlargement - this group is sub-divided into (a) those with a parenchymal lesion as described above, but without any obvious hilar enlargement, (b) a rarer type with much more generalised shading, usually situated in the upper zone of one or both lungs, very occasionally with early cavitation, and (c) pleural involvement, usually an effusion (proved by exploration).

3. A calcified primary complex - by this is meant a localised calcified parenchymal shadow associated with calcified regional nodes. This was found in only 3 (2.7%) of the 113 cases on their initial examination.

In only one case was cardiac enlargement noted.

X-ray plates exemplifying some of these appearances are inserted in the pages immediately following.

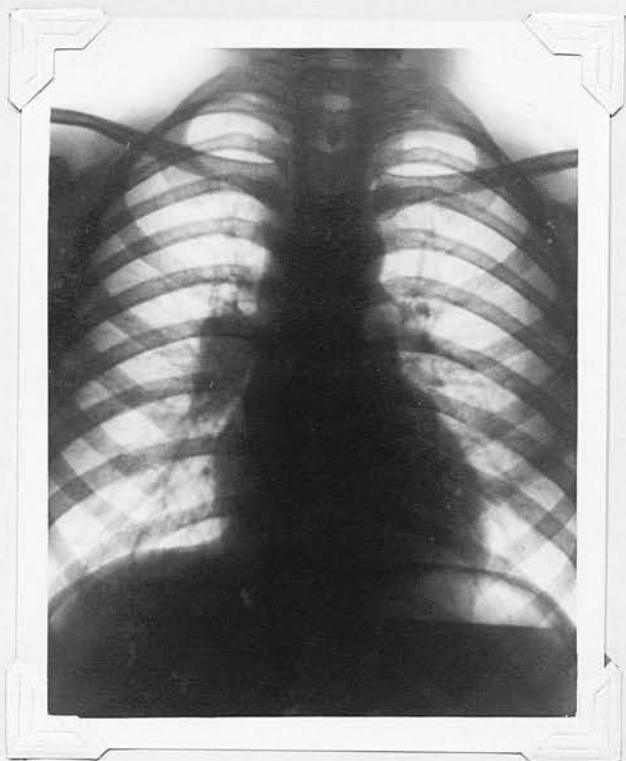


PLATE I

R. root shadow moderately enlarged.

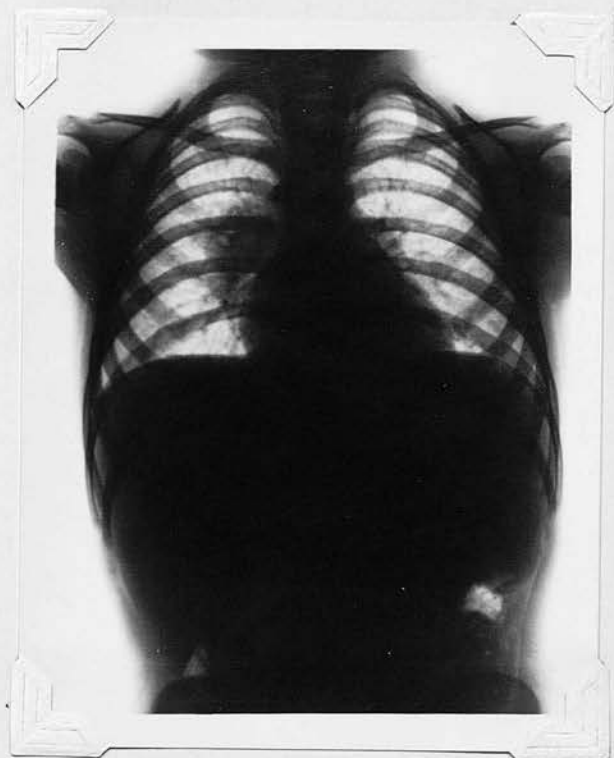


PLATE II

R. root shadow markedly enlarged.

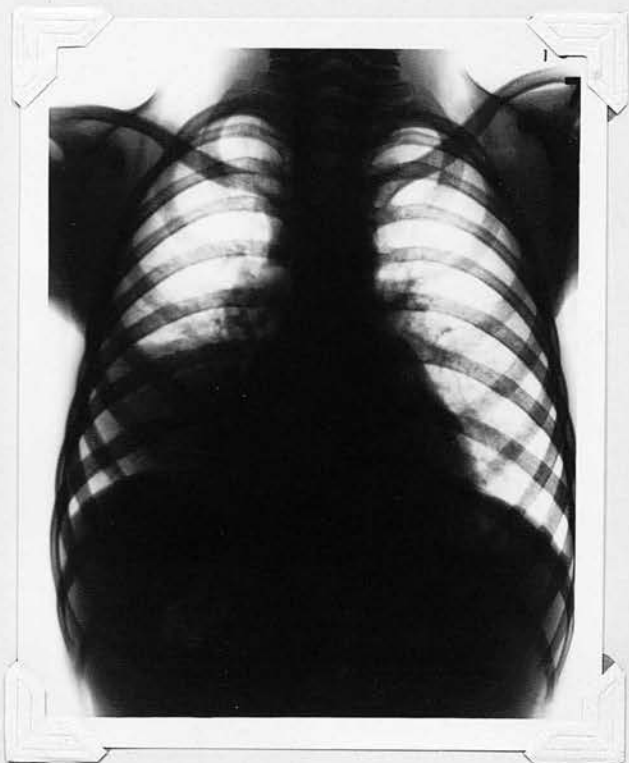


PLATE IIIa

R. root enlarged. Dense opacity R. lower zone.



PLATE IIIb

R. lateral of IIIa. Atelectasis R. middle lobe.

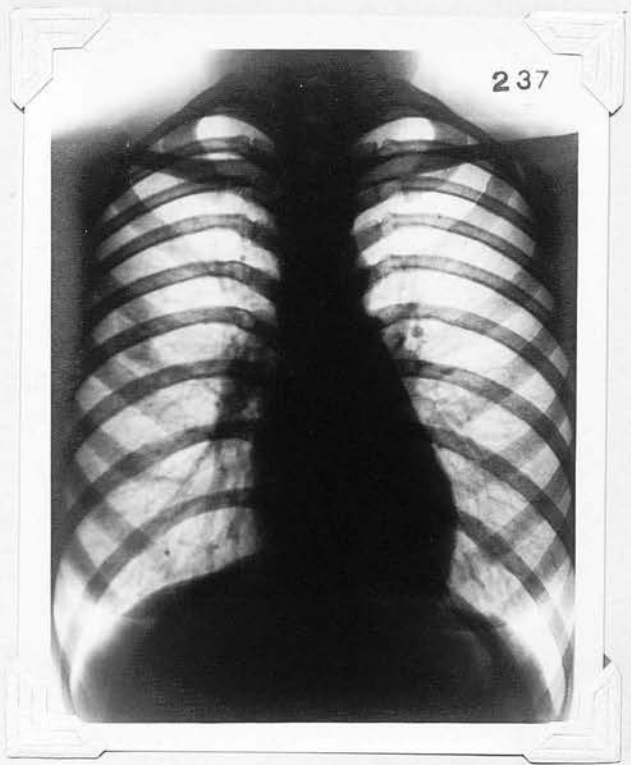


PLATE IV

Round focus R. mid-zone.
R. root dense.

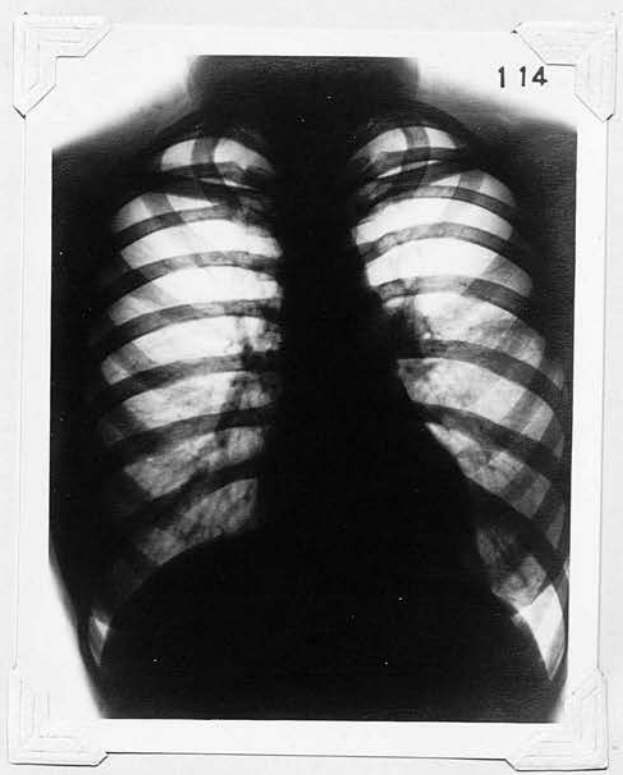


PLATE V

Ill-defined focus L. mid-zone.
L. root enlarged.

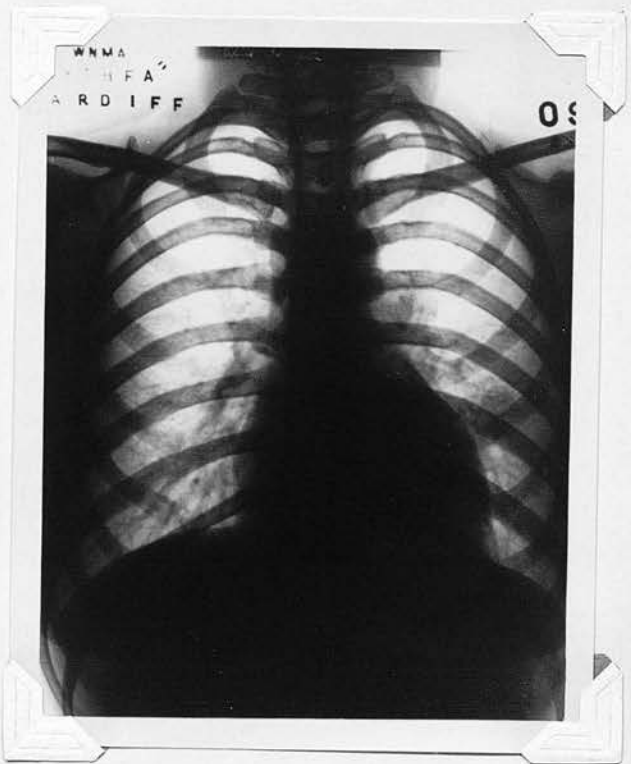


PLATE VI

Round focus L. lung
level 3rd space.



PLATE VII

Slight bilateral root
enlargement.

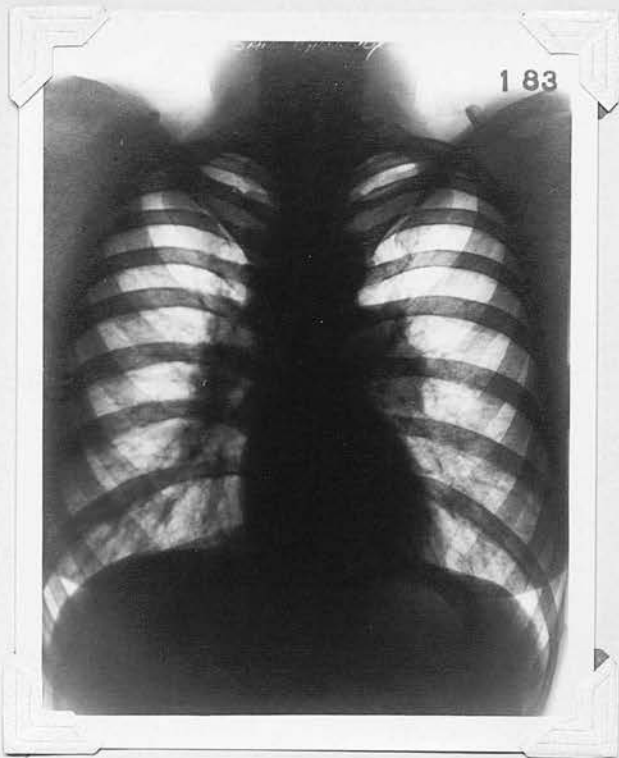


PLATE VIII

Marked bilateral root enlargement.

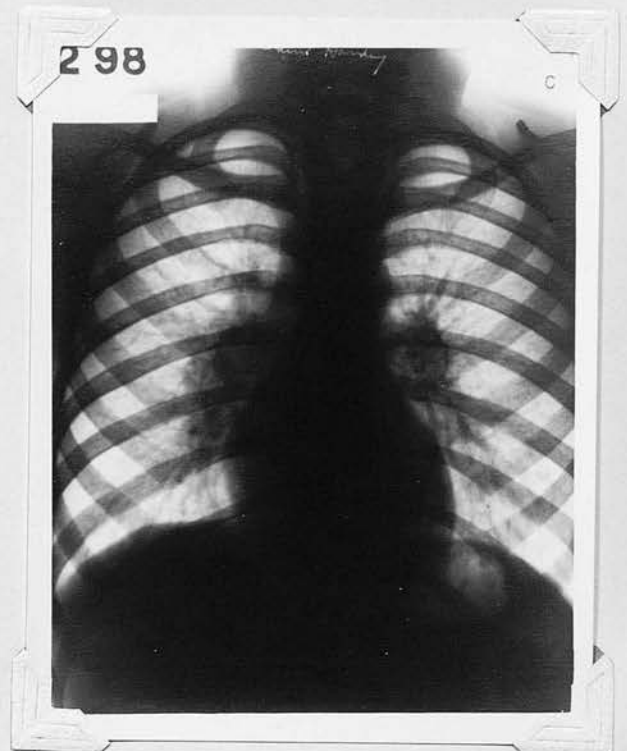


PLATE IX

Very marked bilateral root enlargement.

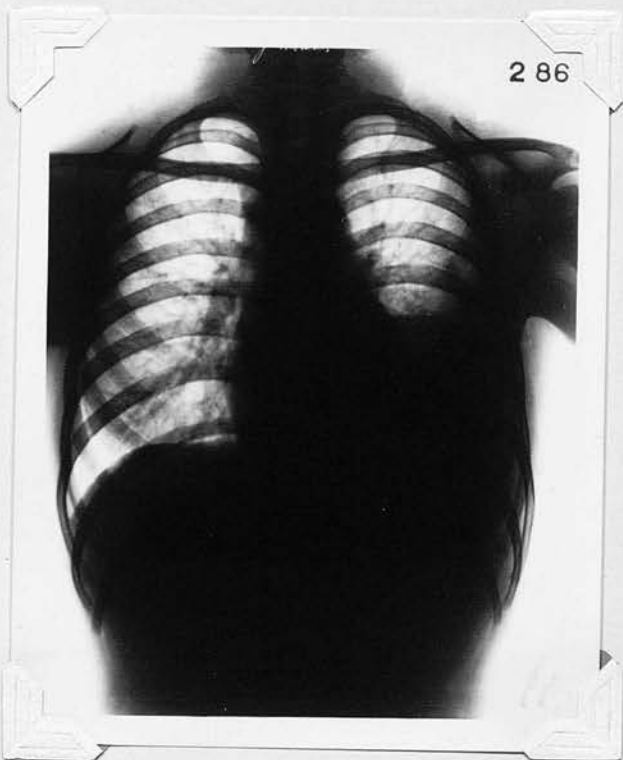


PLATE X

L. pleural effusion.

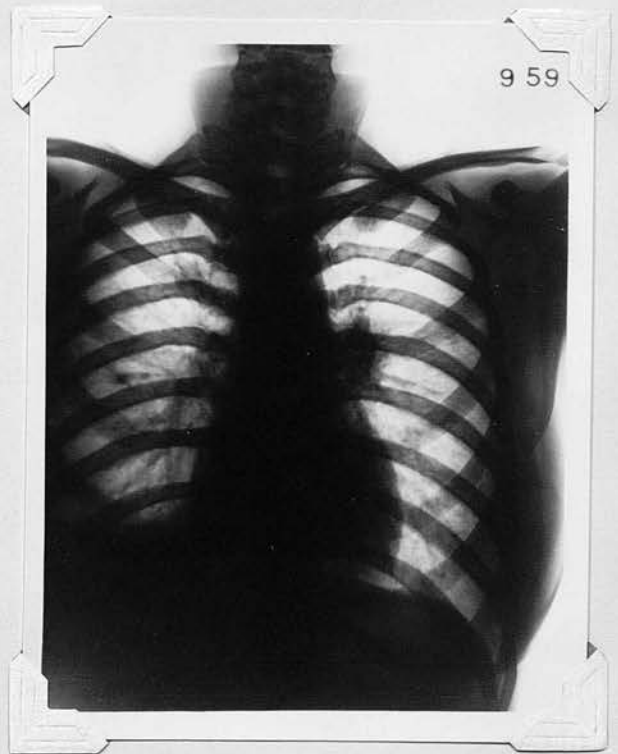


PLATE XI

L. root enlarged.
R. pleural effusion.

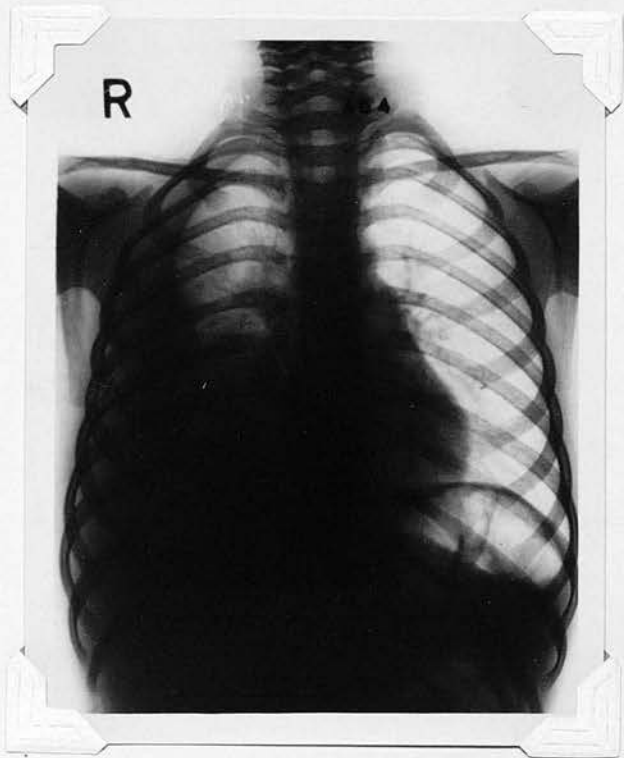


PLATE XII

Large R. pleural effusion.

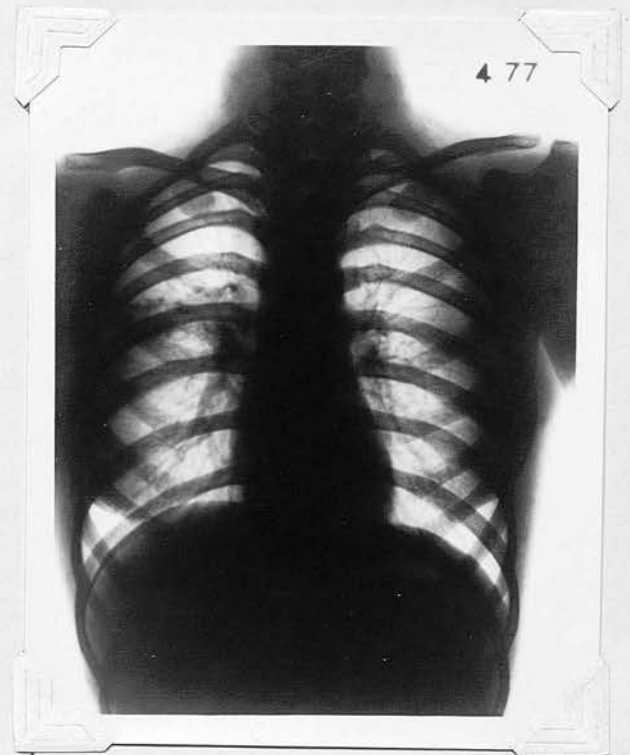


PLATE XIII

R. root enlarged.
Shading R. mid-zone.



PLATE XIV

Shading upper zone R. lung.

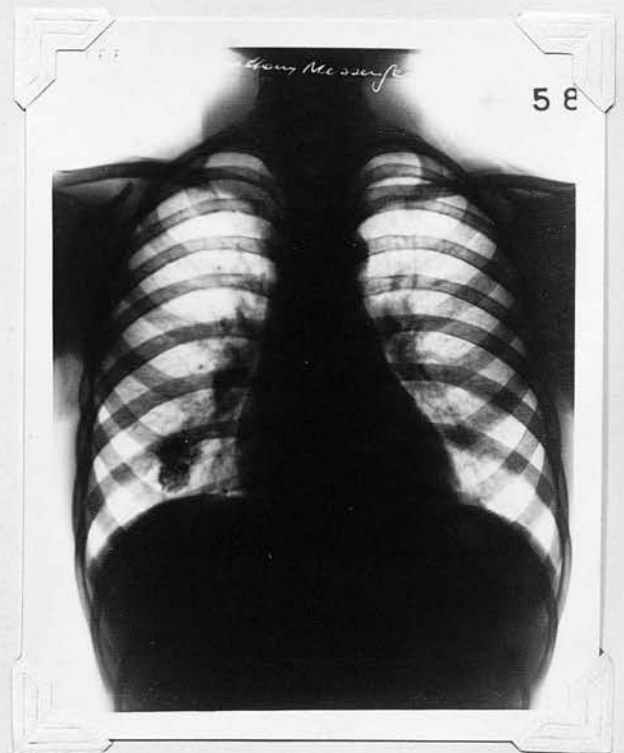


PLATE XV

Large calcified primary
complex R. lower zone.

The Interpretation of the abnormal shadows.

Complete agreement exists as to the great value of radiography in the discovery of many chest diseases, but it is acknowledged that a diagnosis based on an X-ray film alone can never be conclusive. Nevertheless, most chest diseases do produce a fairly characteristic pattern, so that a diagnosis can be presumed with a fairly high degree of accuracy. The final proof must depend on bacteriological and pathological tests, but when these are not possible, a presumed diagnosis can be supported by clinical observation, skin sensitivity tests, and other methods.

Consideration of the radiographical findings in this series of cases of Erythema Nodosum suggests a presumptive diagnosis of recent tuberculous infection or disease (with of course, the exception of the three cases showing calcified primary foci.) A localised parenchymal lesion with regional hilar enlargement is typically seen in a recent primary tuberculous infection, (Macpherson, 1939), and hilar enlargement alone is no evidence against primary tuberculosis as its cause; or is a localised parenchymal lesion unassociated with glandular involvement, for as Rich (1946) has pointed out "X-ray studies during life are notoriously inadequate in bringing to view all primary lesions in the lungs". When bilateral

hilar enlargement occurs alone, it is necessary to assume the existence of a radiographically invisible primary focus, in each lung, as bronchopulmonary glands in the hilum have no direct connection with those in the other lung (Miller, 1919). Blacklock, (1932) in a post mortem study, found that of 148 children with primary lung foci, in 15 (10%) these were multiple, and in five subjects they occurred in both lungs. That bilateral pulmonary primary complexes do occasionally occur is supported by personal experience.

Direct contact

Those cases with more generalised shadows in one or both lungs, and occasionally with cavitation as well, were typical of established tuberculous disease, and the majority were verified bacteriologically. This type of lesion occurred during the subsequent observation period, and in no case was associated with the eruptive phase of the Erythema Nodosum.

Finally, it is generally accepted that in this country the presence of a calcified complex is very strong evidence indeed of previous tuberculous infection.

It must, however, be admitted that as Kerley (1942, 1943) has suggested, it may be possible that some of the abnormal chest shadows

seen in cases of Erythema Nodosum may be a manifestation of sarcoidosis, more especially the bilateral hilar enlargement type. No cases in the present series showed evidence of generalised nodular opacities with a reticular background and hilar enlargement, which is the composite picture usually seen in sarcoidosis, and in no case was a possible radiographical diagnosis of sarcoidosis supported on clinical grounds.

Tables VIII 'A' (page 69), VIII 'B' (page 71), VIII 'C' (page 73), VIII 'D' (page 74), VIII 'E' (page 76) and VIII 'F' (page 79), show the result of the radiographical examination of the series of cases of Erythema Nodosum and the type of lesion found.

Table VIII 'A' (page 69) shows the results of the radiographical observation of the 110 (excludes three who ceased attending) cases of Erythema Nodosum with regard to the development of initial chest abnormality. It does not, of course, show subsequent changes in the abnormal. Of the 110 cases observed for 1 - 3 years, 34 (30.9%) were normal throughout, and 76 (69.1%) showed immediate or delayed abnormality. Of the 53 children, 43 (81.1%) were abnormal, and of 57 adults, 33 (57.9%) abnormal. In the age group 0 - 4 years, 11 (91.7%) of 12 were abnormal; 5 - 9 years, 12 (70.6%) of 17; 10 - 14 years, 20

TABLE VIII(A).

The Results of Radiographical Chest Observation of the 110 Cases of Erythema Nodosum with regard to the Development of Initial Chest Abnormality
(Excludes 3 Immediate Normals Ceased Attending.)

Age Group Years.	No. of Cases	Normal Throughout	Abnormal (Immediate or Delayed)
0 -	12	1 (8.3%)	11 (91.7%)
5 -	17	5 (29.4%)	12 (70.6%)
10 -	24	4 (16.7%)	20 (83.3%)
0 - 14	53	10 (18.9%)	43 (81.1%)
15 -	28	8 (28.6%)	20 (71.4%)
20 -	10	5 (50.0%)	5 (50.0%)
25 -	13	6 (46.2%)	7 (53.8%)
35 & over	6	5 (83.3%)	1 (16.7%)
15 & over	57	24 (42.1%)	33 (57.9%)
All Ages	110	34 (30.9%)	76 (69.1%)

(83.3%) of 24; 15 - 19 years, 20 (71.4%) of 28; 20 - 24 years, 5 (50%) of 10; 25 - 34 years, 7 (23.8%) of 13, and aged 35 years and over, 1 (16.7%) of six cases was abnormal. It will be noted that the percentage of "abnormals" in children (81.1) was considerably greater than occurred in adults (57.9), and when analysed further into age groups, that there was a high incidence of abnormals up to the age of 20 years and much less beyond that age. In this respect, it is of interest to note that Perry (1944) in Bristol made a similar observation, but in his series of 112 cases, the discrepancy of abnormals between children (43%) and adults (7%) was much more marked. The possible significance of these observations will be discussed later.

Table VIII 'B' (page 71) shows the interval in months between the occurrence of Erythema Nodosum and the first ascertainment of chest abnormality. Of 54 children, 33 (61.1%) were immediately abnormal, 53 of the 54 continued under observation, and 10 (18.9%) later became abnormal, 6 (60%) of the 10 inside 3 months, 2 (20%) in 3 - 6 months, 1 (10%) in 6 - 9 months, 1 (10%) in 9 - 12 months, and none became abnormal beyond 12 months.

Of the 59 adults, 22 (37.3%) were immediately abnormal. 57 of the 59 continued

TABLE VIII(B).

Showing the Interval in Months between the Occurrence of Erythema Nodosum and the First Ascertainment of Chest Radiographical Abnormality.

(1)	(2) No. of Cases.	(3) Immediate Abnormals	(4) No. of cases Continued under Observation.	(5) Delayed Abnormals	(6) * Time of Ascertainment (Months)				12 Months & over
					< 3 Months	3 -	6 -	9 -	
Children 0 - 14 years	54	33 (61.1%)	53	10 (18.9%)	6 (60%)	2 (20%)	1 (10%)	1 (10%)	0 (0.0%)
Adults 15 and over	59	22 (37.3%)	57	11 (19.3%)	6 (54.5%)	3 (27.3%)	1 (9.1%)	1 (9.1%)	0 (0.0%)
Children and Adults	113	55 (48.7%)	110	21 (19.1%)	12 (57.1%)	5 (23.8%)	2 (9.5%)	2 (9.5%)	0 (0.0%)

* Percentages expressed to Figures in Column (5).

under observation, and 11 (19.3%) later became abnormal, 6 (54.5%) of the 11 inside 3 months, 3 (27.3%) in 3 - 6 months, 1 (9.1%) in 6 - 9 months, and 1 (9.1%) in 9 - 12 months; again none occurring beyond this time.

At all ages of the initial 113 cases, 55 (48.7%) were immediately abnormal. 110 continued under observation, and 21 (19.1%) of these later became abnormal. 12 (57.1%) of the 21 within 3 months, 5 (23.8%) in 3 - 6 months, 2 (9.5%) in 6 - 9 months, and 2 (9.5%) in 9 - 12 months, none developing abnormality beyond this time.

Table VIII 'C' (page 73) shows the types of chest abnormality seen on first ascertainment in the 55 immediate abnormal. Of the 33 immediate abnormal in children, 15 (45.4%) showed unilateral hilar enlargement alone, 10 (30.3%) unilateral hilar enlargement with a lung lesion, 3 (9.1%) bilateral hilar enlargement alone, 3 (9.1%) bilateral hilar enlargement with a lung lesion, and 2 (6.1%) a lung or pleural lesion alone, the corresponding figures for adults being 22; 7 (31.8%); 8 (36.3%); 1 (4.6%); 1 (4.6%); and 5 (22.7%), and at all ages - 55; 22 (40%); 18 (32.7%); 4 (7.3%); 4 (7.3%); and 7 (12.7%).

Table VIII 'D' (page 74) shows the

TABLE VIII (C).

The Incidence of Different Types of Chest Abnormality at the Time of First Ascertainment in the 55 "Immediate" Radiographical Abnormals found in the 113 cases of Erythema Nodosum.

Age Group Years	Immediate Abnormals	C H E S T A B N O R M A L I T Y.					
		T Y P E S	O F	C H E S T	A B N O R M A L I T Y.	Lung or Pleural lesion Alone.	
		Unilateral Hilar Enlargement Alone.	Unilateral Hilar Enlargement with a lung lesion.	Bilateral Hilar Enlargement Alone.	Bilateral Hilar Enlargement with a lung lesion.		
0 -	9	5	2	0	1	1	
5 -	10	2	3	2	2	1	
10 -	14	8	5	1	0	0	
0 - 14	33	15(45.4%)	10(30.3%)	3(9.1%)	3(9.1%)	2 (6.1%)	
15 -	14	5	7	0	1	1	
20 -	2	0	1	0	0	1	
25 -	5	2	0	1	0	2	
35 & over	1	0	0	0	0	1	
15 & over	22	7(31.8%)	8(36.3%)	1(4.6%)	1(4.6%)	5(22.7%)	
All Ages	55	22(40.0%)	18(32.7%)	4(7.3%)	4(7.3%)	7(12.7%)	

TABLE VIII (D).

The Incidence of Different Types of Chest Abnormality at the time of First Ascertainment in the 21 "Delayed" Radiographical Abnormals found in the 110 Observed Cases of Erythema Nodosum.

Age Group Years	Delayed Initial Abnormals	T Y P E S						A B N O R M A L I T Y.		
		Unilateral Hilar Enlargement Alone.	Unilateral Hilar Enlargement with a lung lesion.	Bilateral Hilar Enlargement Alone.	Bilateral Hilar Enlargement with a lung lesion.	Bilateral Hilar Enlargement with a lung lesion.	Lung or Pleural lesion Alone			
0 -	2	0	1	0	0	0	1	0	0	1
5 -	2	1	0	0	0	0	0	0	0	1
10 -	6	1	2	1	1	0	2	0	0	2
0 - 14	10	2 (20%)	3 (30%)	1 (10%)	1 (10%)	0 (0.0%)	4 (40.0%)	0 (0.0%)	0 (0.0%)	4 (40.0%)
15 -	6	1	3	0	0	0	2	0	0	2
20 -	3	0	2	0	0	0	1	0	0	1
25 -	2	0	1	0	0	0	0	1	0	0
35 & over	0	0	0	0	0	0	0	0	0	0
15 & over	11	1 (9.1%)	6 (54.5%)	0 (0.0%)	0 (0.0%)	1 (9.1%)	3 (27.3%)	1 (9.1%)	1 (9.1%)	3 (27.3%)
All Ages	21	3 (14.3%)	9 (42.8%)	1 (4.8%)	1 (4.8%)	0 (0.0%)	7 (33.3%)	1 (4.8%)	1 (4.8%)	7 (33.3%)

types of chest abnormalities seen on first ascertainment in the 21 delayed abnormal. Of 10 delayed abnormal in children, 2 (20%) showed unilateral hilar enlargement alone, 3 (30%) unilateral hilar enlargement with a lung lesion, 1 (10%) bilateral hilar enlargement alone, none bilateral hilar enlargement with a lung lesion, and 4 (40%) a lung or pleural lesion alone, the corresponding figures for adults being 11; 1 (9.1%); 6 (54.5%); 0 (0.0%); 1 (9.1%); and 3 (27.3%), and for all ages 21; 3 (14.3%); 9 (42.8%); 1 (4.8%); 1 (4.8%); and 7 (33.3%).

Table VIII 'E' (page 76) is a summary of Tables VIII 'C' and VIII 'D'. It shows the types of lesions seen on first ascertainment of immediate or delayed chest abnormality. Of 43 immediate or delayed abnormal in children, 17 (39.5%) showed unilateral hilar enlargement alone, 13 (30.2%) unilateral hilar enlargement with a lung lesion, 4 (9.3%) bilateral hilar enlargement alone, 3 (7%) bilateral hilar enlargement with a lung lesion, and 6 (14%) a lung or pleural lesion alone.

The corresponding figures for adults being 33; 8 (24.2%); 14 (42.5%); 1 (3%); 2 (6.1%); and 8 (24.2%), and for all ages 76; 25 (32.9%); 27 (35.5%); 5 (6.6%); 5 (6.6%); and 14 (18.4%).

TABLE VIII (E).

Summary of the Incidence of Different Types of Chest Abnormality at the Time of First Ascertainment in the 76 Radiographical Abnormals Found in the 110 Observed Cases of Erythema Nodosum. (Tables VIII (C) and (D) combined)

Age Group Years	Initial Abnormality or Delayed	T Y P E S O F			C H E S T A B N O R M A L I T Y.			Lung or Pleural lesion Alone
		Unilateral Hilar Enlargement Alone.	Unilateral Hilar Enlargement with a lung lesion.	Bilateral Hilar Enlargement Alone.	Bilateral Hilar Enlargement with a lung lesion.	Bilateral Hilar Enlargement with Pleural lesion Alone		
0 -	11	5	3	0	1	2		
5 -	12	3	3	2	2	2		
10 -	20	9	7	2	0	2		
0 - 14	43	17 (39.5%)	13 (30.2%)	4 (9.3%)	3 (7%)	6 (14%)		
15 -	20	6	10	0	1	3		
20 -	5	0	3	0	0	2		
25 -	7	2	1	1	1	2		
35 & over	1	0	0	0	0	1		
15 & over	33	8 (24.2%)	14 (42.5%)	1 (3%)	2 (6.1%)	8 (24.2%)		
All Ages	76	25 (32.9%)	27 (35.5%)	5 (6.6%)	5 (6.6%)	14 (18.4%)		

Observations on Tables VIII ('B', 'C', 'D' and 'E').

It is worthy of note that a high percentage (48.7%) of the 113 cases (Table VIII 'B') showed a chest abnormality at the time of the eruption of Erythema Nodosum. 110 continued under observation, and 21 (19.1%) of these later became abnormal, the risk of doing so diminished with time so that none became abnormal after 12 months. It seems likely that a considerable percentage of these delayed abnormalers were abnormal at the time of the occurrence of Erythema Nodosum (if they represented a primary tuberculous infection) for Macpherson (1939) in a review of 830 children with positive tuberculin tests noted "that there were many who developed small deposits of calcification either in the lung tissue or in the hilum glands while under observation, but who never had any detectable lesion at the early stage of the disease".

Consideration of the nature of the 55 immediate abnormal shadows (Table VIII 'C') shows that 40% of these were unilateral hilar enlargements, 32.7% unilateral hilar enlargements with a lung lesion, 7.3% bilateral hilar enlargements, 7.3% bilateral hilar enlargements with a lung lesion, and 12.7% a lung or pleural lesion alone, giving 47.3% with hilar enlargement alone, and 40% hilar enlargement with a lung lesion.

It is felt that these findings strongly suggest that the abnormal shadows represented a recent primary tuberculous infection. When the nature of the shadows in the 21 delayed abnormals is considered (Table VIII 'D') it is noted that hilar enlargement with or without a lung lesion was present in 66.7% of them, and that a lung or pleural lesion alone was found in 33.3% (compared with 12.7% in the immediate abnormals). The higher percentage of cases with a lung or pleural lesion in the delayed abnormals is not surprising, for the infection had had a longer time in which to progress and involve the pleura, etc.

The results of the chest radiographical observation (1 - 3 years), of the 110 cases of Erythema Nodosum (excludes three who ceased attending).

Table VIII 'F' (page 79) shows that of 53 children with Erythema Nodosum, 43 (81.1%) had a chest abnormality. In 13 (30.2%) of these the abnormal shadows cleared; in 2 (4.7%) they did not change; in 15 (34.9%) they showed evidence of healing by contraction and/or calcification, and in 13 (30.2%) they went on to progressive disease. Of 57 adults, 33 (57.9%) were abnormal, in 10 (30.3%) the abnormality cleared, in 4 (12.1%) it had not changed, in 8 (24.2%) it showed evidence of healing, and in 11 (33.3%) it went on to progressive disease, and at all ages of the 110 cases 76

TABLE VIII (F).

The Results of the Chest Radiographical Observation (1 - 3 years) of 110 Cases of Erythema Nodosum (Excludes the three who ceased attending).

	No. of Cases	Normal Throughout.	Abnormal	F A T E			O F		T H E A B N O R M A L S			Total Progressive Disease
				Becoming Normal	No Change	Healing. Contraction. Calcification.	Progressive Disease		Pleural			
							Parenchymal.					
Children 0 - 14 years	53	10 (18.9%)	43 (81.1%)	13 (30.2%)	2 (4.7%)	15 (34.9%)	8 (18.6%)	5 (11.6%)	13 (30.2%)			
Adults 15 +	57	24 (42.1%)	33 (57.9%)	10 (30.3%)	4 (12.1%)	8 (24.2%)	6 (18.2%)	5 (15.2%)	11 (33.3%)			
ALL AGES	110	34 (30.9%)	76 (69.1%)	23 (30.3%)	6 (7.9%)	23 (30.3%)	14 (18.4%)	10 (13.2%)	24 (31.6%)			

(69.1%) were abnormal, 23 (30.3%) of these became normal, 6 (7.9%) showed no change, 23 (30.3%) showed evidence of healing, and 24 (31.6%) progressed. It will, therefore, be seen that the fate of the abnormal shadows differed little in children and adults; in the former 30.2% and in the latter 33.3% went on to progressive disease.

With regard to becoming normal, and evidence of healing of the shadows, it must be remembered that the period of observation varied from 1 to 3 years, had all the cases been observed for the full period, it is probable that a number of the becoming normal group would have moved to the healing by calcification group.

The Correlation of the Radiographical Findings
and the Results of the Mantoux Test.

It will be seen (Table IX, page 81) that of the 53 children with Erythema Nodosum, 10 were radiographically normal throughout, of these 6 (60%) were Mantoux positive. 43 were radiographically abnormal and all of these were Mantoux positive. Of 57 adults 24 were X-ray normal and 16 (66.7%) were Mantoux positive, 33 were abnormal and again all were Mantoux positive; at all ages (110 cases) 34 were X-ray normal, 22 (64.7%) were tuberculin positive, 76 X-ray abnormal and 100% of these were tuberculin positive.

TABLE IX.

The Correlation of the Radiographical Findings and the Results of the Mantoux Test in 110 of the 113 Cases of Erythema Nodosum (3 ceased attending).

	X-ray Normal Throughout	M A N T O U X		X-ray Abnormal	M A N T O U X		Number of Cases.
		Positive	Negative		Positive	Negative	
Children 0 - 14 years	10	6 (60%)	4 (40%)	43	43 (100%)	0 (0.0%)	53
Adults 15 & over	24	16 (66.7%)	8 (33.3%)	33	33 (100%)	0 (0.0%)	57
All Ages	34	22 (64.7%)	12 (35.3%)	76	76 (100%)	0 (0.0%)	110

The presence of an abnormal chest shadow with a positive tuberculin reaction in younger children is presumptive evidence that the shadow is tuberculous in origin, but in adults this is not necessarily so. In infants and young children a positive Mantoux reaction must indicate a recent tuberculous infection and it is wise to regard with great suspicion an abnormal chest shadow appearing at or about this time. But tuberculin surveys in this country (Hart, 1932; Coutts, 1947) show that in an urban area 70% to 80% of the population in adult life are infected with the tubercle bacillus so that in the older age groups primary infection may have been of long duration, it not being possible to know at what age it took place, and, therefore, a positive reaction is no decisive evidence in favour of a suspected lung lesion being tuberculous in origin in these ages.

Observation on the Bacteriological
investigation for Tubercle Bacilli in the series
of cases of Erythema Nodosum.

Sputum, if present, was examined for tubercle bacilli by the direct method and if there was any suspicion of a lung lesion, concentration, culture and guinea-pig inoculation were also carried out. Examination of the faeces in the writer's experience has been of little value in the

diagnosis of early pulmonary tuberculosis, and this method was, therefore, not used. On the other hand the value of examination of the stomach contents for tubercle bacilli is now well established and many workers have found this method diagnostically helpful when minimal pulmonary lesions existed (Collis and Brockington, 1933; Munro, 1938; Davies and Doherty, 1942). Reference has already been made (page 23) to the use of this method by Scandinavian workers in the investigation of cases of Erythema Nodosum and to the fact that they found a high percentage of positive results (Wallgren, 1938; Löfgren, 1946; Ustvedt, 1947). After careful consideration it was decided not to use gastric lavage in the present study unless the patient was admitted to hospital, and this decision was a reluctant one for it was appreciated that the most reliable diagnostic evidence of active tuberculosis is the finding of the tubercle bacillus. But as Tytler (1945) has pointed out the method of gastric lavage "is better suited to institutional than to dispensary work". The technique is simple, but it is liable to be rather frightening to the patient and as it was important to keep as many as possible of them under dispensary observation for some time it was felt that the scientific advantage gained by doing gastric lavage was likely to be offset to the patients' disadvantage, by frightening some of them

away. Here it is pertinent to say that it was often difficult to persuade patients with Erythema Nodosum of the possible seriousness of the condition.

All the bacteriological examinations were carried out at the Central Tuberculosis Laboratory, Cardiff.

The results - negative findings are omitted as they were no evidence against the existence of tuberculous disease. Of the 8 cases in children with radiographical progressive pulmonary disease, 3 were sputum positive and 3 were positive by gastric lavage (culture and guinea-pig inoculation), of 6 similar cases in adults 3 were sputum positive. 5 cases of pleural effusion occurred in children and in 2 of these the fluid was positive for tubercle bacilli, and of the 5 pleural effusion cases in adults 2 were also positive. In all the 10 pleural effusion cases the cytology of the fluid, that is a high preponderance of lymphocytes, suggested a tuberculous etiology. It will thus be seen that of the 24 cases of Erythema Nodosum with radiographical progressive disease, 13 (54.2%) were proved tuberculous bacteriologically.

A further 3 cases in the series developed non-pulmonary tuberculosis and all 3 were verified by the finding of tubercle bacilli, so that

of the 113 cases of Erythema Nodosum in 16 (14.2%) tuberculosis was proved. This finding is considerably lower than that reported by Wallgren (1938) - 52.6%; by Löfgren (1946) - 36.6%; and by Ustvedt (1947) - 28.5% positive for tubercle bacilli. The probable explanation of this is that the gastric lavage method of investigation was not extensively used in the present study, if it had been it is reasonable to expect that a higher percentage of those with progressive disease would have been proved bacteriologically and that some of those presumed tuberculous would have also been positive.

Throat cultures for haemolytic streptococci, estimation of the antistreptolysin titre, and tests for skin sensitivity to streptococcal endotoxin, were not carried out, as an investigation of any relationship between Erythema Nodosum and streptococcal infection was not a main aim of this study.

The Development of Non-Pulmonary Tuberculosis
in the series of 113 cases of Erythema Nodosum.

It has been noted above that of the 113 cases of Erythema Nodosum, 3 (2.7%) developed non-pulmonary tuberculosis - 1 meningitis and 2 cervical adenitis. The meningitis occurred in a girl aged 7 years; she was seen in February, 1947,

with Erythema Nodosum, her Mantoux test (1/10,000) was strongly positive at that time, but there was no known or ascertained contact with tuberculosis and X-ray of her chest showed nothing abnormal there. Exactly six months later (in August, 1947) she died of tuberculous meningitis. The cerebro-spinal fluid was positive for tubercle bacilli of the bovine type, and post mortem examination showed an ulcer in the lower end of the ileum associated with enlarged and diseased mesenteric glands, which, on microscopic examination, proved to be tuberculous; no evidence of a pulmonary lesion was found. The 2 cases of cervical adenitis were in children aged 6 and 8 years, in one of these the adenitis was present at the time of the occurrence of Erythema Nodosum and in the other it appeared three months later. Both were strongly Mantoux positive (1/10,000), and had no X-ray evidence of a chest lesion and no known or ascertained contact with tuberculosis. Pus from the enlarged glands was positive for bovine type tubercle bacilli on culture. One of these cases had an interesting family history of Erythema Nodosum which will be described later (page 109). There can be no doubt that the child who died of tuberculous meningitis had had an active and progressive primary focus in the small intestine and that the infection became generalised from this focus. It is possible that in the other two cases the

cervical adenitis represented the glandular component of a primary tuberculous focus in the naso-pharynx, although no evidence of this was found clinically. It must, however, be pointed out that Pagel (1942) considered that only about 3% of cases of tuberculous cervical adenitis are the direct result of a naso-pharyngeal primary infection. Wallgren (1932) reported 2 cases of Erythema Nodosum associated with primary non-pulmonary tuberculosis, both had cervical adenitis, in one there was an ulcer on the gums proved tuberculous by guinea-pig inoculation, and in the other histological examination of the tonsils showed typical tubercle formation.

Of the 54 children with Erythema Nodosum in the present investigation, 50 (92.6%) were tuberculin positive and of these 50, 43 (86%) had abnormal chest shadows suggestive of a primary tuberculous infection, in a further 3 (6%) the evidence supported a non-pulmonary infection leaving only 4 (8%) in whom the site of the primary infection was not found. It is agreed that radiography may fail to show primary lung foci, nevertheless the possibility that the focus is extra-pulmonary must always be considered in investigating cases of Erythema Nodosum and this point does not appear to have been sufficiently stressed in the literature.

The Relationship of Erythema Nodosum
to Tuberculosis.

Table X (page 89) shows the relationship of the 113 cases of Erythema Nodosum to tuberculosis and the conclusions reached are the results of the analysis of the investigations already described.

Definition of terms used.

(1) "Presumed tuberculous" - the association of a positive Mantoux reaction with radiographical evidence of a lesion in the chest suggestive of a primary infection, and where this lesion has not progressed to active clinical disease.

(2) "Notified tuberculous" -

(a). The presence of a positive Mantoux reaction with radiographical evidence of a progressive lesion in the chest, verified at times bacteriologically, and

(b) the occurrence of non-pulmonary tuberculosis verified bacteriologically.

Of the 54 children with Erythema Nodosum 4 (7.4%) were considered non-tuberculous (Mantoux negative), in 4 (7.4%) a positive Mantoux test was the only evidence of tuberculosis, 30 (55.6%) were presumed tuberculous on account of a positive Mantoux test with an abnormal chest

TABLE X.

The Relationship of the 113 Cases of Erythema Nodosum to Tuberculosis.

	No. of Cases	Non-Tuberculous. Mantoux Negative.	Mantoux Positive only Evidence of Tuberculosis.	Presumed Tuberculous. Mantoux Positive and X-ray Positive.	NOTIFIED TUBERCULOUS.			Total Notified Tuberculous.	Presumed or Notified Tuberculous.
					Pulmonary		Non-Pulmonary		
					Mantoux Positive. X-ray Progressive Disease.	Mantoux Positive. X-ray Positive. Verified Bacteriologically.	Mantoux Positive. Verified Bacteriologically.		
Children 0 - 14 years.	54	4 (7.4%)	X 4 (7.4%)	30 (55.6%)	5 (9.3%)	8 (14.8%)	3 (5.6%)	16 (29.6%)	46 (85.2%)
Adults 15 years & over.	59	8 (13.6%)	φ 18 (30.5%)	22 (37.2%)	6 (9.8%)	5 (8.5%)	0 (0.0%)	11 (18.6%)	33 (55.9%)
Total:	113	12 (10.6%)	22 (19.5%)	52 (46%)	11 (9.2%)	13 (11.5%)	3 (2.7%)	27 (23.9%)	79 (69.9%)

X Includes one case who ceased attending.

φ Includes two cases who ceased attending.

shadow, and a further 16 (29.6%) were notified tuberculous giving a total of 46 (85.2%) presumed or notified tuberculous; of the 59 adults, 8 (13.6%) were non-tuberculous, in 18 (30.5%) a positive Mantoux was the only evidence of tuberculosis, 22 (37.2%) were presumed tuberculous, and 11 (18.6%) notified, giving for adults 33 (55.9%) presumed or notified tuberculous, and at all ages of 113 cases of Erythema Nodosum 12 (10.6%) were non-tuberculous. In 22 (19.5%) a positive Mantoux test was the only evidence of tuberculosis, 52 (46%) were presumed tuberculous and 27 (23.9%) were notified tuberculous, giving a total of 79 (69.9%) presumed or notified tuberculous at all ages.

It will be noted that the percentage of presumed or notified tuberculous cases in children (85.2) was considerably higher than occurred in adults (55.9). Does this mean that tuberculosis is more often the cause of Erythema Nodosum in children than in adults, or does it only mean that evidence of tuberculous infection in the chest is more obvious in the former and, therefore, more easily ascertained? Attention has already been drawn to the fact that in the present series of cases there was a high incidence of radiographical chest abnormality up to the age of 20 years and beyond this age the incidence was

much less. It is well known (Macpherson, 1939) that in young children the glandular component of a primary complex is more enlarged than in older children or in adults, and it is probable that radiographical evidence of recent primary infection is more easily obtained in children than in older ages, but it has already been pointed out that the incidence of primary tuberculous infection as shown by tuberculin testing surveys increases yearly from birth to about the age of 20 to 25 years and then rapidly decreases. If it is accepted that Erythema Nodosum is essentially a manifestation of primary tuberculous infection, then it is not surprising that there is a relation between age and the development of this type of Erythema Nodosum (with the exception of adult males who are relatively immune to it) and, therefore, this would suggest that beyond the age of 20 to 25 years other etiological factors are of increasing importance. This observation is supported by Löfgren's findings (1946) that the incidence of the tuberculous type of Erythema Nodosum was "78.1, 55.6 and 30.3 per cent respectively in the age groups 15 to 24, 25 to 34, and 35 to 44 years. In the 15 to 19 year group the incidence was 96.2%".

Perry (1944) reported a study of 112 cases of Erythema Nodosum (67 children and 45 adults) in the neighbouring city of Bristol. He

considered 32 (28%) "certainly" tuberculous (Mantoux positive, X-ray positive and/or subsequent tuberculous history) and this group would appear to correspond fairly closely to the presumed or notified cases (69.9%) in the present investigation. Perry, unlike the writer, accepted a positive Mantoux reaction alone as sufficient evidence to classify some of his cases as probably tuberculous and it is thought that this group is, therefore, not comparable with the presumed tuberculous (positive Mantoux, X-ray positive) of the present study. He reported 51 (45.0%) as not tuberculous (Mantoux negative), compared with 10.6% in this investigation. His high percentage of negative Mantoux reactions (76% of his adults were negative) may partly be explained by the fact that he used only a dilution of 1/10,000 (0.01 m.g.) tuberculin for his Mantoux tests.

What are the possible explanations for the discrepancy in the Bristol and Cardiff results?

(1) A difference in the standard for X-ray interpretation adopted by either investigator, for example, assessment of what constitutes root enlargement is notoriously difficult, but it seems unlikely that any such variation could account for the marked discrepancy in the results that occurred.

(2) Perry did not give any information as to the method of collecting his material, but it is probable that most of his cases were observed in general hospitals and, therefore, constituted a selected group, those with any suspicion of tuberculosis having been seen at the local tuberculosis dispensary; it is considered that the present series were an unselected group.

(3) That the etiology of Erythema Nodosum may vary in different districts or from year to year. Collis (1933) has shown that the etiological factors of Erythema Nodosum varied to some extent in London and Dublin. In London he found that 71% of his cases were tuberculous in type and 18.4% streptococcal; in Dublin 90.9% were tuberculous and 9.1% streptococcal. He considered that the variation of his results between the two cities was due to the fact that tuberculosis is extremely common in Dublin, whilst streptococcal infections are particularly prevalent in London. Reference has already been made to the report of Ernberg and Gabinus (1939) in which they recorded that in Stockholm from 1928 to 1936 only 8.1% of their 420 cases (children) of Erythema Nodosum were Mantoux negative, but that in the spring of 1937 of 34 seen, 59% were negative.

The extent of tuberculous infection in an area can be roughly estimated by the

mortality from the disease. In Cardiff in the year 1947 the death rate per thousand population from all forms of tuberculosis was 0.80 and for Bristol the corresponding figure was 0.64, but it has been impossible to find any reliable figures as to the extent of streptococcal infection in the two cities and, therefore, no final conclusions can be reached as to what part prevalence of these infections in the cities concerned can explain the discrepancy in the results, but it seems reasonable to suggest that the greater prevalence of tuberculous infection in Cardiff (as indicated by the higher mortality) compared with Bristol, contributed in some degree to the greater incidence of tuberculosis found in the cases of Erythema Nodosum in the former city.

The Proportions in whom Tuberculosis
was "Notified or Presumed".

Table XI 'A' (page 95) shows the proportions irrespective of age and sex in whom tuberculosis was "notified or presumed" in each six months subsequent to the date first seen, and it, therefore, gives the number exposed to risk in each period. This number was calculated by allowing for those who ceased attending (three), the one death, and the fact that once a case was notified or presumed tuberculous he ceased to be at

TABLE XI(A).

The Proportions in whom Tuberculosis was
'Notified or Presumed' in each
Six Months Subsequent to the Date First Seen.

Both Sexes - All Ages Combined.

Period of Exposure (Months) (1)	No. Exposed to risk. (2)	No. Notified or Presumed T.B. (3)	Rate (Per cent) (3) ÷ (2)
0 -	111.5	75	67.265
6 -	35	4	11.429
12 -	31	-	-
18 -	29	-	-
24 -	19	-	-
30 -	11	-	-

risk of being notified or presumed tuberculous; thus 111.5 persons were exposed to risk in the first 6 months, of these 75 (67.3%) were notified or presumed tuberculous, in the next six months 35 were exposed to risk and 4 (11.4%) of these were notified or presumed tuberculous, 31 were exposed to risk in the next six months, none developed tuberculosis (notified or presumed) and none did so of those exposed to risk subsequently. An important point in this analysis is that no persons were notified or presumed after an interval of one year from entry into the experience, in other words, if still normal after one year from the date first seen they did not develop tuberculosis either presumed or notified. The significance of this observation is that all cases of Erythema Nodosum in whom there is any evidence of tuberculous infection, that is Mantoux positive, should continue under observation for at least one year.

Tables XI 'B', 'C', 'D' and 'E' (page 97) give the figures comparable to Table XI 'A' (page 95) when the data are sub-divided for children and adults, and by sex for children, the fact that there were only three male adults precluded any sex distinction for adults. The aim of this sub-division is to ascertain if there was any sex or age predilection to the development

TABLES XI ('B', 'C', 'D' and 'E').

The Proportions in whom Tuberculosis was
'Notified or Presumed' in each Six
Months Subsequent to the Date First Seen.

Children and Adults and by Sex in Children.

TABLE XI(B) - MALE CHILDREN.

Period of Exposure (Months)	No. Exposed to Risk.	No. Notified or Presumed T.B.	Rate (Per cent)
0 -	22.5	18	80
6 -	4.0	1	25
12 -	3.0	-	-
18 -	3.0	-	-
24 -	-	-	-
30 -	-	-	-

TABLE XI(C) - FEMALE CHILDREN.

0 -	31	26	83.871
6 -	5	1	20.000
12 -	4	-	-
18 -	4	-	-
24 -	2	-	-
30 -	2	-	-

TABLE XI(D) - MALE & FEMALE CHILDREN.

0 -	53.5	44	82.243
6 -	9	2	22.222
12 -	7	-	-
18 -	7	-	-
24 -	2	-	-
30 -	2	-	-

TABLE XI(E) - ADULTS.

0 -	58	31	53.448
6 -	26	2	7.692
12 -	24	-	-
18 -	22	-	-
24 -	17	-	-
30 -	9	-	-

of tuberculosis in the cases of Erythema Nodosum under review. It will be seen from these tables that of 22.5 male children exposed to risk in the first six months, 18 (80%) were notified or presumed tuberculous, the corresponding figures for female children being 31 and 26 (83.8%). In the next six months four male children were exposed to risk and 1 (25%) was notified or presumed and for female children 5 and 1 (20%). For children of both sexes combined of 53.5 exposed to risk in the first six months 44 (82.2%) and of 9 in the next six months 2 (22.2%) were notified or presumed tuberculous. Of 58 adults at risk in the first six months 31 (53.4%) were presumed or notified tuberculous, the corresponding figures for the next six months being 26 and 2 (7.7%). It is, therefore, apparent that an approximately equal percentage of male and female children with Erythema Nodosum developed presumed or notified tuberculosis, and that, as already pointed out, for children as a whole the percentage that did so was considerably greater than that in adults.

The Degree of Tuberculin Sensitivity and
the Development of "Presumed or Notified"
Tuberculosis.

It was thought of interest to correlate the degree of tuberculin sensitivity found in 110 of the cases of Erythema Nodosum and

the occurrence of presumed or notified tuberculosis. Examination of Table XII (page 100) shows that of 66 cases with a strongly positive Mantoux reaction in 10 (15.2%) no other evidence of tuberculosis was found, 31 (46.9%) were presumed tuberculous, 25 (37.9%) were notified tuberculous giving a total of 56 (84.8%) presumed or notified tuberculous. The corresponding figures for the 29 moderately positive reactors being 8 (27.6%), 19 (65.5%), 2 (6.9%) and 21 (72.4%). The number of cases (three) with a weak reaction being too small to be of any statistical value; as expected, none of the 12 Mantoux negative reactors showed any evidence of tuberculosis.

It is, therefore, seen that there is a significant association between a high degree of skin tuberculin sensitivity and the occurrence of tuberculosis of a recent type in the cases of Erythema Nodosum. It has already been noted (Table VII 'A', page 55) that of the 101 cases under review who gave a positive tuberculin reaction, in 67 (66.3%) it was of strong intensity, in 30 (29.7%) moderate, and in 4 (4%) of weak intensity. It is recognised that the degree of tuberculin sensitivity following infection with the tubercle bacillus depends on a number of factors, for example - the number and virulence of the bacilli, age and race of the patient, inherent resistance,

TABLE XII.

The Correlation of the Degree of Tuberculin Sensitivity and the Occurrence of 'Presumed or Notified' Tuberculosis in 110 of the 113 Cases of Erythema Nodosum. (3 ceased attending)

Degree of Tuberculin Sensitivity	No. of Cases	No other/ or no Evidence of Tuberculosis.	Presumed Tuberculous.	Notified Tuberculous Pulmonary Non-pulmonary.	Presumed or Notified Tuberculous.
Strong + + +	66	10(15.2%)	31(46.9%)	25(37.9%)	56(84.8%)
Moderate + +	29	8(27.6%)	19(65.5%)	2(6.9%)	21(72.4%)
Weak +	3	1(33.3%)	2(66.6%)	0(0.0%)	2(66.6%)
Negative	12	12(100%)	0(0.0%)	0(0.0%)	0(0.0%)
TOTAL.	110	31(28.2%)	52(47.3%)	27(24.5%)	79(71.8%)

and temporarily the presence of certain inter-current infections of which measles and influenza are the most notable. It seems reasonable to expect that, generally, tuberculin hypersensitivity should be more marked in a recent tuberculous infection compared with one of longer duration, for the latter has had an opportunity of localisation and healing, and experience of tuberculin surveys in children supports this view. Blacklock (1947) recorded that of 1732 clinically non-tuberculous children the percentage who reacted to a higher dosage of tuberculin only (1 m.g. or 10 m.g.) increased as age advanced, but, of course, if tuberculous infection is progressive, no matter its age, then skin tuberculin sensitivity is usually but not always pronounced. Attention has already been drawn (page 18) to Wallgren's theory (1926) that the development of Erythema Nodosum coincides with the onset of "tuberculous allergy" as he then called it, and the high percentage (66.3) of strongly positive tuberculin reactors found in the present series of cases lends support to this view.

It is considered that the high incidence of strongly positive Mantoux reactors in the presumed or notified cases of Erythema Nodosum is evidence in favour of the correctness of the diagnosis of tuberculosis as the etiological

factor, for as Rich (1946) has pointed out "it is quite true that a relatively high degree of sensitivity is often associated with progressive tuberculosis. This, however, is by no means invariably the case; and on the other hand minute lesions may induce high sensitivity. Nevertheless, a strongly positive reaction to very small doses of tuberculin tends to support the opinion, derived from other methods of clinical study, that the patient probably has active tuberculosis, although the evidence provided by even a strong reaction can never be more than supporting evidence". Ustvedt (1947) was of the opinion that a recent primary tuberculous infection was "highly probable" when an intense tuberculin reaction was combined with a characteristic X-ray picture. It is interesting to note that Daniels et alii (1948) in the report of the Proffit Tuberculosis Survey recorded that "the higher the sensitivity shown at the first positive test after conversion, the greater the subsequent incidence of tuberculosis. In those who reacted strongly to 0.01 m.g. the incidence was over 10% and was three and a half times as high as in those who reacted only to 0.1 or 1.0 m.g." This would support the observation made by Rich & McCordock (1929) as a result of animal study, that a high degree of tuberculin hypersensitivity was an unfavourable factor (Blacklock, 1947).

Some further Clinical and Other
Observations on the present series
of Cases of Erythema Nodosum.

(1)

Recrudescence of the eruption following
tuberculin testing.

This occurred in only one of the 113 cases of Erythema Nodosum. A girl aged 5 years with a fading eruption was Mantoux tested, 0.1 cc 1/10,000 O.T., with a strongly positive result. She became "feverish" twenty-four hours after the injection, the nodes on the legs became reactivated and she developed fresh ones on the forearms. In this case it seems reasonable to associate the recrudescence of the Erythema Nodosum and the production of new nodes on the forearms with the tuberculin injection, and to assume that it was the result of stimulus by a very small dose of tuberculin in a patient with a marked hypersensitivity to the allergen concerned. Wallgren (1938), Arnaud (1939) and many others have given examples of the re-appearance of a fading or recently disappeared nodal eruption as a result of provocation by tuberculin. In the case just described there was no radiographical evidence of a chest lesion, otherwise it would have been of

interest to observe if a focal reaction had occurred as well.

(2)

Recrudescence of the eruption following measles.

A girl aged seven years was seen on 15.12.47. with a fading Erythema Nodosum rash; her Mantoux test was strongly positive (1/10,000) and radiographical examination of her chest showed a circular shadow about 1" in diameter towards the base of the right lung with enlargement of the regional hilar glands. She was seen again in four weeks' time when the rash had completely gone; fourteen days later she developed measles and seven days later the nodes had reappeared and they persisted for about a month, followed in three months' time by radiographical and clinical evidence of progressive pulmonary tuberculosis. V Pirquet (1911) was the first to draw attention to the lowering of skin tuberculin sensitivity during an acute attack of measles and his observation has been confirmed by many others, more especially by Wallgren (1935 and 1938). It is still uncertain whether this is a specific depression of skin tuberculin sensitivity or due to a mechanical action produced by measles on the cutaneous capillaries (Rich, 1946). The recrudescence of the Erythema Nodosum is assumed to coincide with

the rising again of tuberculin hypersensitivity.

(3)

Post-primary Erythema Nodosum - by this is meant its occurrence with evidence of an old tuberculous infection.

Attention has already been drawn to the fact that of the 113 cases of Erythema Nodosum under review three (2.7%) showed a calcified primary complex in the chest on initial X-ray examination and that 1 (0.9%) had had a tuberculous gland in the neck (verified bacteriologically) four years previous to the development of Erythema Nodosum. All 4 cases were Mantoux positive, 3 moderately so and 1 weakly positive. Subsequent radiographical examination showed no evidence of progressive pulmonary tuberculosis in any of them. The presence of a calcified shadow in the lung or hilum is regarded in this country as almost diagnostic of a previous tuberculous infection. It is known that in certain parts of America coccidioidomycosis may produce a similar type of calcified lesion (Arnson, Saylor & Par, 1942), but this disease is practically unknown in this country. There are two possible explanations for the occurrence of post-primary Erythema Nodosum -

1. that it is a manifestation of tuberculosis but not necessarily of

- primary tuberculous infection, and
2. that some other etiological factor is concerned.

As already stated, these four patients did not develop any evidence of active tuberculosis whilst under observation and they continued in good health; one had given a history of an acute tonsillitis ten days before the development of Erythema Nodosum, for which she was treated with a sulphonamide drug (the exact preparation was not ascertained), and in the other three cases nothing untoward was noted. Löfgren (1946) found that of his 178 adult cases of Erythema Nodosum 30 (17.0%) had evidence of an old tuberculous infection. His criteria for the diagnosis of old tuberculous infection were -

1. a positive tuberculin test
at least six months before the
attack of Erythema Nodosum;
2. radiographical evidence of
calcified foci in the lungs or
abdomen or fibrotic pulmonary
changes.

He considered that in 16 of 30 cases of post-primary Erythema Nodosum the condition was the result of an acute throat infection with B-haemolytic streptococci. According to Wallgren (1938) post-primary Erythema Nodosum is rare in children, it having occurred in only 16 (2%) of his 800 cases; he believed that it is a tuberculous manifestation

and that it resulted from a depression of allergy (hypersensitivity) produced by an acute infectious disease.

(4)

Recurrent Erythema Nodosum - by recurrent Erythema Nodosum is meant the occurrence of the eruption with an interval of at least 3 months between attacks and this definition, therefore, excludes a recrudescence produced by tuberculin or other agents. Two patients in the present series of 113 cases gave a history of a previous attack of Erythema Nodosum; and in no case had there been more than two attacks. Both cases were females over 30 years of age, one had had Erythema Nodosum four years previously, and the other two years before the last eruption. They were Mantoux positive, one strongly and one moderately so; radiographical examination of the chest showed nothing abnormal and there was nothing in their history or clinical course to suggest a possible etiology of the Erythema Nodosum. It is, of course, possible that each attack of Erythema Nodosum may have been caused by a different factor but this must be a matter of conjecture.

Symes (1929) described the case of a female patient who had her first attack of Erythema Nodosum at the age of 18 years and her

ninth when she was 42 years old - in cases with a frequent occurrence of the condition he used the term "chronic Erythema Nodosum". Of a total of 124 cases observed by Lendon (1925) in Australia he found that second attacks had occurred in nine and that the interval between the attacks varied from one to sixteen years. As already noted, he thought Erythema Nodosum a specific infectious disease and its recurrence an indication that as such it conferred little or no immunity. Löfgren (1946) reported that of his 178 adult cases of Erythema Nodosum, 18 (10%) had had an earlier attack - 15 patients once, 2 twice and 1 three times; in six of these he considered that the last attack was the result of a recent primary tuberculous infection and the remaining 12 as probably not related to tuberculosis, but the latter group being also tuberculin positive, he did not exclude the possibility that their first attack of Erythema Nodosum may also have resulted from a primary tuberculous infection.

(5)

A family history of Erythema Nodosum.

Two patients in the present series gave a history of Erythema Nodosum having occurred some time before in a member of the family; it is probable that little reliance can be placed on the

? Nodular
vasculitis.

presence or absence of a family history of Erythema Nodosum for the diagnosis may not have been correct and conversely Erythema Nodosum may have been present and ignored, but in three (2.7%) families concerned in the present investigation cases of Erythema Nodosum occurred in the household within a few days or weeks of each other and all these cases were clinically verified -

Family 'A'. This family consisted of the parents and 7 children aged from 6 to 17 years. On 27.5.47. 3 of the children were referred to the Tuberculosis Dispensary, Margaret aged 9 years and Clifford aged 12 years had Erythema Nodosum; Janice 8 years old, an enlarged gland in the neck of fourteen days' duration and a week later she also developed Erythema Nodosum. All the 3 cases gave a strongly positive Mantoux reaction (1/10,000) and chest radiographical examination was negative initially and continued so throughout the observation period. The rest of the family were tuberculin positive but in them no clinical or radiographical evidence of active tuberculosis was found. Four weeks later pus aspirated from Janice's enlarged gland was positive for tubercle bacilli and culture showed that these were bovine in type. Bacteriological examination on two occasions of the milk supplied to the home was negative for tubercle bacilli and that at school was pasteurised. No history of a holiday in the

country was obtained and no contact with a known case of tuberculosis found. The negative bacteriological report on the milk supplied is no evidence that this was at all times safe, and the fact that three of the younger children developed Erythema Nodosum at the same time suggests an almost simultaneous infection of all three. The absence of known contact with pulmonary tuberculosis and the positive culture for bovine tubercle bacilli would suggest that milk had been the source of the infection. It is, however, interesting to note that the youngest child in the family, aged 6 years, although strongly Mantoux positive, did not also develop Erythema Nodosum.

Family 'B'. On 1.12.47. a brother and sister, both with Erythema Nodosum, were seen; the boy was 6 years old and the girl 4 years, and they were the only children in the family. Both gave a strongly positive Mantoux reaction and both had radiographical evidence of a recent pulmonary primary tuberculous infection. Two months later the boy had clinical tuberculosis of the lungs (gastric lavage positive for tubercle bacilli of the human type); the girl continued in good health whilst under observation and X-ray examination of her chest showed that her lung focus was steadily retrogressing. The parents were examined

fourteen days after the children were first seen, no evidence of active tuberculosis was found in the father, but the mother had extensive acute bi-lateral pulmonary tuberculosis from which she died two months later.

Family 'C'. This family consisted of the parents and three children. The mother had been diagnosed as having pulmonary tuberculosis (sputum negative) one year previously when she refused sanatorium treatment and to have her contacts examined. On 10.2.47. her daughter aged 5 years developed Erythema Nodosum and on 2.4.47. her son aged 3 years the same condition. Both were seen in the eruptive phase, were strongly Mantoux positive and had radiographical signs of a primary tuberculous focus in the lungs which in both went on to progressive disease (in one the gastric lavage fluid was positive for human type tubercle bacilli). The remaining child in the family, a boy aged 8 years, was examined as a contact and apart from a positive Mantoux reaction no evidence of tuberculosis was found in him; the father was also non-tuberculous, but the mother had now extensive disease of both lungs with a positive sputum and there can be no doubt that she had been the source of the infection in the family.

Symes (1921) reported 3 personal examples of more than one case of Erythema Nodosum

occurring in the same household within three days of each other, and Lendon (1905 and 1925) collected 10 instances in which it had appeared shortly after contact with a patient suffering from it. Both these authors thought that this indicated that Erythema Nodosum was an infectious disease and that there might be a familial predisposition - that a familial predisposition to Erythema Nodosum exists seems likely - but it appears much more probable that infection is not from case to case but rather from a common source.

(6)

The association of Erythema Nodosum with certain drugs.

In the present series of 113 cases 12 (10.6%) gave a history of having been treated with one of the sulphonamide drugs just prior to the development of Erythema Nodosum, the exact type of the drug used was ascertained in only 7 of the 12 cases. In 3 it was sulphathiazole, and in the remaining 4 sulphamezathine. Four of the patients treated with a sulphonamide drug had had a sore throat, 3 had had a pyrexia of unknown origin, and in 5 the indication for this medication was not obvious. Of the 12 sulpha treated cases, 8 (67.7%) were presumed or notified as tuberculous and in 4 (33.3%) no etiological factor was found.

Clinically in every case the eruption was typical of that seen in Erythema Nodosum. So far no conclusive evidence has been produced to show if the Erythema Nodosum is merely a simple toxic manifestation of the drug due to sensitisation or as suggested by Löfgren (1946) the result of the sulphonamide acting as a provoking agent on an infection, for example, tuberculosis or B-haemolytic streptococci, which of itself is capable of producing Erythema Nodosum. Whatever the exact relationship between the therapy and the eruption may be it would appear unwise to ignore such types of Erythema Nodosum, for as already stated 8 (66.7%) of the 12 cases under consideration were thought to be of the tuberculous type.

The Treatment of the 110 Cases
of Erythema Nodosum (excludes the
3 ceased attending).

All the cases with a positive Mantoux reaction who continued under observation were regarded as possibly tuberculous in origin and treated as such. Bed rest for an initial period of 6 weeks was advised no matter the result of chest radiographical examination. The patient was then recalled for a further assessment of his or her clinical condition and X-ray examination. Subsequent treatment was guided by the results of these investigations; those with no symptoms or

chest abnormality were allowed by slow graduated stages to return to a normal but quiet life; others with any symptoms the least suggestive of tuberculosis and/or with an abnormal chest shadow were advised further bed rest, the duration of which depended on individual case assessment. Some developed clinical tuberculosis and for these bed rest was continued until hospital or sanatorium admission was obtained. It is not suggested that all the patients in this group adhered to the instructions given, for the domicilliary treatment of tuberculosis by rest is notoriously much less efficiently carried out than when the patient is hospitalized.

Those cases that gave a negative tuberculin reaction to a dilution of 1/100 O.T. were considered to be non-tuberculous and no routine treatment was prescribed for them, although they continued under Dispensary observation.

S E C T I O N C.

Summary and Discussion.

It is still commonly held in this country that Erythema Nodosum is in the main, a manifestation of rheumatism, and this belief continues to be fostered by some of the more modern text books on Medicine or Dermatology.

The present study was particularly concerned with ascertaining if, as is taught in the Scandinavian countries, tuberculosis is the predominant factor concerned in the production of Erythema Nodosum.

It is now proposed to bring together and to briefly review the methods of investigation used in this study, and to further discuss the significance of the results obtained from these.

During the years 1946 and 1947 113 clinically verified cases of Erythema Nodosum domiciled in the city of Cardiff were seen at the Tuberculosis Dispensary. These constituted the material for the study, and it was considered that they represented an unselected group as the medical practitioners had been asked to refer all cases of Erythema Nodosum irrespective of any suspicion of tuberculosis.

To establish or otherwise an association between Erythema Nodosum and tuberculosis, the following methods were used:-

1. Investigation of "intimate" contact history to tuberculosis, and in a number of cases examination of contacts to find if an unsuspected source of tuberculous infection existed.
2. Tuberculin testing (Mantoux 1/10,000 to 1/100) to ascertain if there was a significantly higher incidence of positive reactors in the cases of Erythema Nodosum than occurred in control groups, and to correlate the intensity of the reaction with the subsequent findings.
3. Radiographical examination of the chest at the time of the eruption and at fixed intervals to the end of the observation period; for the purpose of this study this period terminated in December, 1948, but the majority of the cases continued to be observed.

4. Bacteriological examination of the sputum where present and of the gastric lavage fluid in a few cases when clinical tuberculosis was suspected.
5. A follow-up of 110 of the 113 cases of Erythema Nodosum for a period which varied from 1 to 3 years to find if a significant number were presumed or notified tuberculous.

The Results of these Investigations and
their Significance.

1. Intimate exposure to tuberculous infection.

Of the 113 cases of Erythema Nodosum 45 (39.8%) gave a verified history of close contact with tuberculosis; in 39 of these contact had been a household one and in 6 it had occurred in an office which employed a large number of tuberculous patients. Examination of household contacts when no contact history was obtained was carried out in only 20 of the 68 cases - this small number was due to the reluctance of the others to have their contacts examined; of the 20 cases to whom it was done in 6 (30%) an unsuspected source of tuberculous infection was discovered. It is anticipated that if the contacts to the

remaining 48 cases had been examined a similar proportion (30%) of these would have disclosed a source of infection.

Contact history was investigated to all the 283 cases in the city, diagnosed as suffering from pulmonary tuberculosis at the dispensary in the year 1947 and 70 (24.7%) had had intimate exposure to infection. It is, therefore, seen that for the cases of Erythema Nodosum the percentage (39.8) with such a history was considerably greater than that (24.7) noted in the routine notifications, and this is considered some evidence in favour of a tuberculous etiology of Erythema Nodosum. The explanation of the higher incidence of tuberculous contact history in the Erythema Nodosum series compared with the routine notified cases is probably that the former occurred in younger age groups than the latter, and it is well known that as age advances the source of tuberculous infection is increasingly difficult to find, due to a greater contact with the outside world.

These findings emphasize very strongly the advisability of carrying out contact examination to all Mantoux positive cases of Erythema Nodosum.

2. Tuberculin testing - the Mantoux test

(1/10,000 - 1/100 O.T.) was used throughout this investigation. 101 (89.4%) of the 113 cases were positive and 12 (10.6%) negative. No tuberculin surveys of control groups beyond the age of 19 years had been carried out in the area, but below this age a very significantly higher incidence of positive Mantoux reactors occurred in the cases of Erythema Nodosum than in the controls, viz. age 0 - 4 years Erythema Nodosum cases 91.7% positive: controls 8.3% positive; the corresponding figures for age group 5 - 9 years being 94.1% and 16.3%; 10 - 14 years 92% and 27.3%, and 15 - 19 years 85.7% positive in the Erythema Nodosum cases compared with 58.2% in the control group.

Of the 101 positive reactors 67 (66.3%) were strongly so, 30 (29.7%) moderately, and 4 (4.0%) weakly positive.

These results would suggest that tuberculosis is closely concerned in the causation of Erythema Nodosum, but that in the 12 (10.6%) negative reactors to a dilution of 1/100 O.T., some other condition must have been the etiological factor.

3. Radiographical examination of the chest.

The results of this examination showed that at the time of the eruption or later 76 (69.1%) of the 110 cases observed had abnormal

pulmonary and/or hilar shadows, the great majority of which were typical of those generally accepted as representing a recent primary tuberculous infection. When the radiographical findings and the results of the Mantoux test were correlated (Table IX, page 81) it was noted that all 76 X-ray abnormalities were Mantoux positive, whilst of the 34 normals 22 (64.7%) were Mantoux positive, and 12 (35.3%) negative. This observation makes it possible that all the abnormal shadows were tuberculous in origin.

Three cases (2.7%) had a calcified primary complex in the chest indicating an older tuberculous infection and in no case was there any radiographical evidence of established pulmonary tuberculosis of long duration.

4. Bacteriological examination - This method of investigation was incomplete for gastric lavage was not carried out as a routine. Of the 24 cases of Erythema Nodosum considered to have pulmonary tuberculosis 13 (54.2%) were proved bacteriologically and all 3 of the cases of non-pulmonary tuberculosis were positive for tubercle bacilli.

5. The subsequent history of the 110 cases of Erythema Nodosum (excludes the 3 ceased attending.)

Of the 110 cases of Erythema Nodosum 27 (24.5%) were diagnosed and notified as clinically

tuberculous (24 pulmonary and 3 non-pulmonary). In two of the non-pulmonary cases of tuberculosis the cervical glands were involved, and the third developed meningitis from which she died; this was the only death in the series.

All the 27 cases who developed clinical tuberculosis did so within twelve months of the eruption, it seems, therefore, that the first year is the danger period and this emphasizes the importance of keeping all Mantoux positive cases of Erythema Nodosum under very careful observation for at least this time.

To summarize - of the 113 cases of Erythema Nodosum 27 (23.9%) were notified as tuberculous - 16 (60%) of the 27 were verified bacteriologically; a further 52 (46%) were presumed tuberculous on account of a positive tuberculin reaction and chest radiographical evidence of a recent primary focus; in 22 (19.5%) the only evidence in favour of tuberculosis was a positive Mantoux test, but it is probable that some of these cases were tuberculous; and 12 (10.6%) with a negative reaction were non-tuberculous.

It is here of interest to note that of the 66 (of the 110 cases observed) who gave a strongly positive Mantoux reaction, 56 (84.8%) were presumed or notified tuberculous, and of 29 with a

moderate reaction 21 (72.4%) were presumed or notified tuberculous, the number (3) with a weak reaction is too small from which to draw any conclusions. The marked intensity of the reaction found in so many cases would in itself suggest a recent tuberculous infection.

It must be accepted that the only absolute proof of tuberculous disease in the living is the finding of the tubercle bacillus in an exudate, discharge, or tissue. But as Tattersall (1944) has pointed out "apart from the evidence of a positive sputum test, there is no single symptom, sign or other manifestation which is conclusive in itself and an accurate diagnosis of early tuberculosis can only be reached by careful sorting of the many strands of evidence which make up the fabric as a whole". It is considered that in the present investigation of 113 cases of Erythema Nodosum the high percentage (39.8) who had been in intimate contact with tuberculosis, the very high incidence of positive Mantoux reactions (89.4%), the frequency of radiographical evidence of abnormal chest shadows (69.1% of the 110 cases observed) suggestive of a primary tuberculous infection, and the fact that 23.9% developed tuberculous disease, are very strong evidence in favour of the Scandinavian theory that Erythema Nodosum is predominately a manifestation of tuberculous infection. It is not, however,

suggested that all cases of Erythema Nodosum are tuberculous in origin but the writer agrees with Collis (1934) that "I would willingly, however, give up ever mentioning those rare and comparatively unimportant cases of the streptococcal (wrongly called rheumatic) type, if thereby I could persuade my colleagues of the necessity of regarding every case of Erythema Nodosum as potentially tuberculous until proved otherwise".

The Occurrence of Erythema
Nodosum in Relation to the Age
of Tuberculous Infection.

It has already been pointed out (page 18) that Wallgren (1926) thought that Erythema Nodosum occurred at the time of the onset of tuberculin allergy (hypersensitivity), that is within two to three months of the initial infection; fairly strong evidence in favour of this view is found in the present investigation;

(i) Of the 101 Mantoux positive cases 67 (66.3%) gave a strong reaction and this is highly suggestive of a recent tuberculous infection, for generally as the age of the infection increases the degree of tuberculin sensitivity decreases (Blacklock, 1947);

(ii) Radiographical examination of the chest showed (Table VIII 'B', page 71) that at the time of the erythematous eruption 55 (48.7%) of the 113 cases had an abnormal chest shadow which was

considered suggestive of a recent primary tuberculous focus and it is probable that some of the 21 (19.1% of the 110 observed) delayed abnormalities were initially abnormal, but were not radiographically apparent.

(iii) Of the 113 cases only 4 (3.5%) had any evidence of an old tuberculous infection and in these it is possible that the eruption was of a non-tuberculous origin. No cases showed any initial signs of chronic tuberculous disease.

(iv) The fact that all the 27 cases (23.9%) who developed progressive tuberculosis in the present series did so within 12 months of the occurrence of the eruption is further evidence in favour of a recent tuberculous infection being concerned in the production of Erythema Nodosum.

Wallgren (1935) reported that in approximately 50% of instances the clinical appearance of bone and joint tuberculosis was within the first year of infection (not necessarily associated with Erythema Nodosum), and in 75% within two years. There seems no reason to doubt that this time interval also applies to the development of pulmonary tuberculosis.

(v) In the writer's investigation into the occurrence of Erythema Nodosum in nurses in two large tuberculosis hospitals in South Wales, it was found that none of those who gave a positive Mantoux

reaction (449 in Hospital 'A' and 332 in Hospital 'B') developed Erythema Nodosum, but that of the 13 negative reactors accepted on the staff of one hospital, 3 (23%) developed Erythema Nodosum later, of 79 in the other hospital 8 (10%) developed it, and in all the cases that did so it was associated with a Mantoux conversion to positive. This observation must be considered strong evidence in favour of the tuberculous type of Erythema Nodosum being associated with the initial infection with tubercle bacilli.

The Age and Sex Distribution
of the 113 Cases of Erythema
Nodosum.

It was noted (Table III, page 39) that the incidence of the disease showed a gradual increase from the age group 0 - 4 years (10.6% of the total cases) to a peak (24.8% of the total cases) at 15 - 19 years and then a fairly rapid decline. If it is agreed that Erythema Nodosum is usually associated with a recent primary tuberculous infection, then this age distribution is not surprising for it is well known that below the age of 20 years initial tuberculous infection is particularly frequent and that beyond it the percentage of annual increments must be considerably less (Coutts, 1947). In childhood Erythema Nodosum had little or no sex predilection (57.4%

females, 42.6% males) but in adult life (15 years and over) females were more markedly chosen (94.9% compared with 5.1% in males). No satisfactory explanation was found for this adult sex distribution; Picken (1940) has shown that in Wales for the years 1936 - 1939, the incidence peak of pulmonary tuberculosis occurred in both sexes in the same age group (15 - 24 years) and it, therefore, seems unlikely that the infection rate materially differed in the two sexes. It is thought that whilst sex endocrine factors may play some part in the development of Erythema Nodosum in adult females they cannot completely explain the very marked predilection of Erythema Nodosum for this sex.

The Prognosis in Mantoux Positive

Erythema Nodosum.

Wallgren (1938) considered that "Erythema Nodosum in itself is not a sign of any special malignancy. Everything considered, primary tuberculous infection behaves in exactly the same way whether there is Erythema Nodosum or not. On the contrary, it may be regarded as a favourable symptom for the individual, in that the eruption helps in the diagnosis of a tuberculous infection at a very early stage, and thus making it possible to commence appropriate treatment immediately". The present writer has failed to

find any reliable information as to the ultimate prognosis of primary tuberculous infection in the white races, with the exception of selected population groups like medical students and nurses. In spite of a fairly careful regime of bed rest at home 27 (23.9%) of the cases in the present series developed clinical tuberculosis. It is accepted that in an urban district in this country the great majority of people (over 90%, Hart (1932)) sooner or later become infected with the tubercle bacillus and, therefore, if 23.9% of the new primary infections each year went on to progressive disease, then the morbidity of tuberculosis would be greatly in excess of what is shown by notification. It would appear from the findings of this study that primary tuberculous infection, if associated with Erythema Nodosum, is more likely to result in tuberculous disease than when it occurs alone.

Should Erythema Nodosum be Notified
to the Medical Officer of Health as
a Tuberculous Condition?

In this country the two main objects of notification of tuberculosis are -

(i) that the local health department shall know the extent of the disease and the problem it has to deal with, and (ii) that the patient may obtain assistance with regard to treatment and supervision.

The advantages of notification of Erythema Nodosum would be that the case comes under the supervision of a tuberculosis dispensary so that the occurrence of progressive disease would be detected at an early stage; that he or she would be subjected to some control by periodic visits from a health nurse, and that facilities for contact examination would be available. The chief disadvantage is that certain cases of non-tuberculous Erythema Nodosum would be notified as tuberculous by the medical practitioners. There can be no doubt that in practice notification is likely to affect adversely the patient's prospects of obtaining employment and it, therefore, should only be carried out when the diagnosis of active disease is established. The writer believes that these difficulties could be overcome by making Erythema Nodosum a disease that is "intimated" to the Medical Officer of Health. Intimation of tuberculous infection in which the activity is in doubt has been suggested by the Joint Tuberculosis Council (1945). Those who were Mantoux negative would be referred to a general hospital and all others kept under observation at the dispensary, notification being only used when clinical tuberculous disease was discovered. In this way the patient would obtain the advantages of notification with none of its disadvantages.

Conclusions and Recommendations.

1. Of the 113 consecutive cases of Erythema Nodosum investigated 27 (23.9%) developed clinical tuberculosis and of those that did so 16 (60%) were verified bacteriologically, an additional 52 (46%) were presumed tuberculous on account of a positive Mantoux reaction and radiographical signs in the chest, giving a total of 79 (69.9%) notified or presumed tuberculous.
2. It is, therefore, considered that tuberculosis is the predominant etiological factor in the production of Erythema Nodosum.
3. It is not, however, suggested that all cases of Erythema Nodosum are tuberculous in origin for in the present series of cases 12 (10.6%) were Mantoux negative to a dilution of 1/100 (1 m.g.) O.T. and in 22 (19.5%) the only evidence of tuberculosis was a positive tuberculin reaction.
4. All cases of Erythema Nodosum should be "intimated" to the Medical Officer of Health so that they may be investigated and observed as to a tuberculous etiology, but only those in whom clinical tuberculosis is diagnosed should be notified.
5. The fact that the 27 cases who developed tuberculous disease (as distinct from

infection) did so within 12 months of the eruption emphasizes the importance of maintaining observation of all Mantoux positive cases of Erythema Nodosum for at least this time.

6. The finding of a high incidence of notified or presumed tuberculosis in this series of cases of Erythema Nodosum would suggest that contact examination should be carried out to ascertain, if possible, the source of the infection.

7. Evidence has been produced to support the theory that Erythema Nodosum of the tuberculous type is related to the development of specific hypersensitivity and that its occurrence, therefore, indicates a recent primary infection. It is recommended that these cases should be treated by adequate bed rest to lessen the risk of developing clinical tuberculosis.

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