ERYTHEMA NODOSUM: AN ACUTE
SPECIFIC FEVER.*

BY

J. ODERY SYMES, M.D.,

SENIOR PHYSICIAN, BRISTOL GENERAL HOSPITAL; PRESIDENT OF THE
BATH AND BRISTOL BRANCH OF THE BRITISH MEDICAL ASSOCIATION.

I PROPOSE briefly to review the evidence that can be adduced in favour of regarding erythema nodosum as an acute specific infectious fever comparable in every way to the zymotic fevers.

The matter is one of very great importance from a national point of view on account of the varied theories that have been held with regard to the nature and causation of the disease. Briefly, these theories are:

1. That erythema nodosum is a manifestation of acute rheumatism.
2. That it is a cutaneous manifestation of a general intoxication due to several widely different causes.
3. That it is tuberculous in origin, a septicaemia due to attenuated tubercle bacilli.
4. That it is a manifestation of syphilis.

Obviously, if erythema nodosum could be proved to be an early manifestation of tuberculosis or of acute rheumatism, it would enable us to take precautionary measures in the case of persons who have suffered from it, and possibly so to avert later attacks of phthisis or carditis—two conditions which levy so heavy a toll upon the young adult life of the community.

It is not my present purpose to criticize these theories, but it is necessary to make a few brief remarks in regard to them.

The cases of erythema nodosum associated with syphilis have been reported chiefly in German and French journals, and these have been published with the view of showing that the disease is of syphilitic origin without considering the possibility of a symbiosis. Altogether the evidence is far from convincing.

The rheumatic origin of erythema nodosum is still taught in English textbooks, but the evidence brought forward in its support is not very satisfactory. In the following table I briefly summarize the chief differences between erythema nodosum and acute rheumatic fever:

Erythema Nodosum.	Acute rheumatic Fever.
Age incidence: Second and third decades	5-10 years.
Seasonal incidence: Second and last quarters	Third quarter.
Some evidence of infectivity and epidemic occurrence	Very little.
Relapses and recurrences rare	Frequent.
Endocarditis rare	Frequent.
No relief of fever or arthritis from salicylates	Relief.
Phlyctenulae in about one-third of the cases	None.

In a series of 48 cases seen at the Bristol General Hospital down to 1907, there was the possibility of a rheumatic connexion in 22.9 per cent. if one took into account a family or personal history of rheumatic fever, chorea, and growing pains, and regarded all cardiac bruits, of whatever nature, as due to a rheumatic carditis.

From 1907 to 1920 I made the closest inquiries and the most careful examination as to the existence of rheumatic symptoms in 50 consecutive cases of erythema nodosum seen in hospital and private practice. In this series the result is much the same—that is to say, 25 per cent. gave either a family history or a personal history of acute rheumatism, or had a cardiac bruit whilst under observation. In the majority of these cases a note was made of the fact that the bruit was probably haemic. Amongst practising physicians the view that erythema nodosum is a rheumatic disease is fast disappearing. It is kept alive only by the medical textbooks which copy the statement from one to the other.†

* Abstract of a Presidential address delivered before the Branch, June, 1921.

† I discussed this matter more fully in an article contributed to the *Lancet*, January 26th, 1907; and in the *Practitioner* for August, 1913. Gosse contributed a most convincing paper controverting the rheumatic view.

The question of the association of erythema nodosum and tubercle cannot be dismissed so easily. The French school led by Poncet and Landouzy, and to a lesser degree the Germans, maintain the tuberculous origin of the disease; but in this country the view more commonly held is that erythema nodosum is more likely to develop in tuberculous subjects, or that an attack of erythema nodosum (just like an attack of measles) may light up afresh a latent tuberculous focus.

In April, 1914, I published in the *BRITISH MEDICAL JOURNAL* an account of 6 cases of erythema nodosum associated with tuberculosis; since that date, in other 30 cases tuberculous lesions have been found in 2 only; both were cases of tuberculous glands in children. In private practice I have followed cases of erythema nodosum for four, ten, and fourteen years, and no signs of tuberculosis have arisen. I have not succeeded in exciting or re-exciting the lesions of erythema nodosum by the intradermic injection of tuberculin, nor have I found von Pirquet's reaction invariably positive in children with erythema nodosum. Inquiries made at tuberculosis sanatoriums do not show that cases of erythema nodosum are of frequent occurrence. Of especial value is the reply of Sir Henry Gauvain, medical superintendent of the Treloar Homes for Crippled Children, who writes to me: "As far as my memory serves me, I have not seen more than half a dozen cases of erythema nodosum out of 2,500 children treated here during the last twelve years."

Time will not permit me to go further into the discussion of this matter, but it is one of great interest and would well repay further investigation. I wish to confine myself strictly to discussing, "What facts are there supporting the view that erythema nodosum is a definite infective disease?"

If erythema nodosum be a specific infectious fever we should expect it to present definite epidemiological and clinical features, namely:

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, and convalescence. Relapses.
6. Conferment of immunity.
7. To a lesser extent, we should look for alterations in the leucocyte count, a fall of the blood pressure, and the presence of organisms in blood, urine, or tissues.

Some infectious diseases present those characteristics better than others. For instance, there is a wide difference between a group of diseases such as measles, scarlet fever, and chicken-pox, and a group such as influenza, anterior poliomyelitis, and encephalitis lethargica; and erythema nodosum could be classified best with the latter group.

Infectivity.

With regard to the infectivity of the disease, I have records of three instances in which two cases of erythema nodosum have occurred in the same house within three days of one another. Whilst such incidents lend support to the view that they were the result of a common infection, it might equally be true that both cases arose from some toxic source shared in common.

In 1907 I saw a boy with erythema nodosum, his sister having suffered from the same disease three weeks previously. On July 12th we discharged a boy from the Bristol General Hospital convalescent from erythema nodosum, and admitted his sister suffering from the same disease on August 31st. The rash was well developed. An interesting series of cases occurred at the Bristol General Hospital last year. Two ladies (sisters) developed the rash of erythema nodosum—one, a medical student, on March 20th, and the other on March 22nd. There can be no doubt that they were infected from some common source, for the medical student had been suffering from an attack of measles from March 3rd to March 17th, and had been separated from her sister. The medical student first returned to her hospital work about March 27th—long before her nodes had disappeared.

On April 8th a nurse in the ward in which this student was working developed pains in the limbs with fever, and the erythema nodosum rash appeared on April 12th. The night nurse of the same ward had a sore throat about April 15th; and after a period of indefinite malaise developed fever and arthritis on May 2nd and erythema

nodosum rash on May 8th. The interval between the date of the lady medical student's return and the first appearance of symptoms in the nurses was twelve and nineteen days. If these nurses were infected from the student, then the incubation and prodromal periods must have been very brief. I am inclined to think that the prodromal period in this disease may very occasionally be limited to one or two days only.

Multiple cases have been noted by other observers, amongst whom I may mention Lendon and Gosse. Unfortunately they do not enable us to fix with any degree of accuracy the incubation period of the disease, because erythema nodosum is frequently characterized by a long prodromal period with or without fever. This prodromal stage may last from one to three weeks before the rash appears, and is often so ill-defined that it is impossible to say when the illness began. Taking all these difficulties into account, it seems probable that the incubation period is about fourteen days.

Epidemicity.

Small outbreaks of erythema nodosum are reported from time to time in the medical papers, and tend to confirm the view that the disease is infective in character. Joynt¹ reported 9 cases of erythema nodosum which occurred amongst 300 convalescent cases of measles. His report, however, might equally well be quoted in support of the view that the disease is a general toxæmia excited by measles or other malady.

A more convincing report was that of Langford Symes,² physician to the Orthopaedic Hospital of Ireland. In a home of 100 young girls he saw 12 cases of erythema nodosum between May 14th and June 14th. There was no antecedent zymotic illness. The incubation period appears to have been about fourteen days.

Recently a very large outbreak of erythema nodosum has come under my notice. It has not been reported in the medical press, and I am indebted to Dr. R. E. Roberts, M.O.H. of the Mynyddislwyn Urban District Council, for the following particulars. In that urban district about 50 cases were observed during a period of five weeks in August and September, 1920. The majority occurred in a small area comprising two or three streets. There was febrile disturbance and the characteristic rash on legs, face, and neck. No case of erythema nodosum had occurred in these same streets in Dr. Roberts's recollection for fifteen years. The majority of the patients were between the ages of 12 and 20 years, and both sexes were equally affected. No two cases arose in the same house. One case, in which the rash took on the characters of erythema multiforme, was of a serious nature, but ultimately recovered.

I have plotted curves from a number of cases of erythema nodosum seen year by year in the skin department of the Bristol General Hospital from 1899 to 1914, and also from the yearly number of cases seen by me from 1908 to 1914. The number of cases seen is so small that the value of the curves is not great, but they seem to show that erythema nodosum tends to recur in epidemic form every three or four years, and both curves agree in showing an exceptionally large number of cases in 1913. Such variations are the rule in other infectious diseases, as, for instance, measles and whooping-cough.

Seasonal Incidence.

In Bristol the seasonal incidence of the disease is very constant. The second quarter of the year is the period in which the largest number of cases occur, and there is another rise of lesser degree during the last quarter. The curve somewhat resembles that of measles—a disease with which erythema nodosum is not uncommonly associated. Gosse found that in London the disease was most common in the months of March, April, and May, with a rise again in July, September, and October. Hebra, Hegler, and other Continental writers also gave April, May, and October as the months of greatest prevalence.

Age Incidence.

The age incidence is even more definite, the majority of cases occurring in the second and third decades of life, chiefly during youth and adolescence. Thus, of the cases up to 1907, 63.2 per cent. occurred during the second and

third decades of life, and of cases subsequent to 1907, 65 per cent. The youngest patient was aged 3 and the oldest 63 years.

Sex Incidence.

The sex incidence of this disease is a stumbling-block to the infective theory. The disease attacks females three times as frequently as males.

Lendon says that before puberty (which he fixes at 15 years) this difference is not very obvious. My own figures support this statement, and I have confirmation of his views from Dr. Kenneth Wills, who has looked up the age and sex of 53 consecutive cases attending his skin clinic. Ten of them were males, and all of these were under 15 years; of 43 females, 22 were under 15 years. It is obvious that erythema nodosum is of rare occurrence in males after puberty.

I know of only one other infective disease in which there is a marked difference in the incidence upon the two sexes—namely, chorea. In chorea, which is a cerebral form of rheumatic fever, the incidence on girls is more than twice as great as that on boys, and, like erythema nodosum, it is rarely seen in males after the age of puberty.

Goodall and Washbourne state that in scarlet fever more females are attacked than males at all ages, and C. B. Ker says that after 10 years of age diphtheria is more common amongst females, but in neither disease is the difference very considerable.

The overwhelming preponderance of attacks in females at the higher ages is an argument against both the rheumatic and the tuberculous theories of causation. It supports the views of those who regard erythema nodosum as an evidence of general blood dyscrasia, more particularly as the highest incidence is at or about puberty.

A Definite and Orderly Sequence of Events.

The definite sequence noted clinically in erythema nodosum is much more suggestive of a specific fever than of a toxæmia due to one or more causes. The incubation period is from ten to fourteen days. (Dr. Lendon writes me that in his experience the average is about eleven days.) This is followed by a lengthened prodromal period (one to three weeks), and then by a period of fever lasting for from one to three weeks. It is generally during the first week of the fever that the characteristic rash appears. The rash is confined to the arms, legs, and head, comes out in successive crops, chiefly on the extensor surfaces, and goes through definite stages of fading and desquamation. Occasionally cases occur in which the characteristic nodes are followed or accompanied by the papules and vesicles of erythema multiforme, and this can fairly be advanced as an argument against the specific nature of the disease. Time will not permit me to discuss this theory of the relation of erythema nodosum to erythema multiforme, but I may say that one never sees greater variations in the rash than one is accustomed to see in other specific fevers, as, for instance, between that of a mild case of small-pox and that of the malignant form of the disease.

Angina is so common an early symptom as to suggest that the specific infective agent gains entry by the tonsils.

Although the malaise of the febrile period is less than in other fevers, convalescence is generally prolonged. Relapses are not uncommon, especially if the patient be allowed up too soon. Arthritis is rather more frequent than in other acute fevers, and the only distinctive sign—other than the rash—is the presence of phlyctenules in the conjunctiva.

The blood pressure is low, as in fevers generally, and there is slight leucocytosis; the average white cell count in the present series was 11,000 per c.mm. The increase is greater amongst the lymphocytes than the polymorphonuclear cells. This leucocytosis is a point in favour of a bacterial origin, but my many attempts to grow an organism from the blood, cerebro-spinal fluid, affected tissues, and from the urine, have failed, both in aerobic and anaerobic media.

Immunity.

The degree of immunity conferred by an attack of erythema nodosum is not high. In the present series of fifty cases, one patient—a girl of 18 years—stated that she had suffered from a similar attack just twelve months previously. Another patient had two well marked attacks, both when under my care, the first in 1915, and the second

in 1920. I saw the sister of this patient in a severe attack in March, 1920, and in February, 1921, she had a still more serious attack, in which some of the nodules became vesicated and ulcerated. The mother of the two girls had erythema nodosum in 1886, and her oldest daughter died in 1889 during an attack of tonsillitis and erythema nodosum with endocarditis and pericarditis. There was a strong rheumatic family history, and several members of the family had suffered from multiple attacks of scarlet fever, measles, and diphtheria, so their case might be used equally well as an argument for or against the theory of infection.

Certainly second attacks are more common in this disease than in scarlet fever, but they are not of such frequent occurrence as to support the view that the disease is a blood dyscrasia due to rheumatism, tuberculosis, or other chronic constitutional weakness. I have not heard of a person suffering from more than two attacks.

Conclusion.

I do not regard the evidence I have been able to bring forward as conclusive. The strong points in favour of the theory that erythema nodosum is an infectious fever are the proof that it may be transferred from person to person and may occur in small localized outbreaks and in epidemic waves. Equally convincing is the evidence of a definite seasonal incidence and constant age incidence. The systematic distribution of the rash, the evidence of relapses, and conferment of immunity are also favourable to this view. On the other hand, one has to explain the constant association of erythema nodosum with other diseases, such as tuberculosis, measles, and minor conditions of ill health.

The heavy incidence of the disease on girls at and about the age of puberty is difficult to explain on any ground of infection, and we also have to decide whether erythema nodosum and erythema multiforme are but two phases of the same disease, or whether they are two clear and distinct entities.

REFERENCES.

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MOUNTAIN CLIMATES IN HEALTH AND DISEASE.

BY

BERNARD HUDSON, M.D.CAMB., M.R.C.P.LOND.,
SWISS FEDERAL DIPLOMA,
MONTANA, VALAIS, SWITZERLAND.

THE object of this note is to set out, briefly and concisely, the principal physiological and therapeutic effects of high altitudes upon the organism. As one ascends to a higher altitude the barometric pressure falls, there is a lower tension of oxygen in the air, and at the same time there is a fall in temperature. There is also increasing dryness of the air, which becomes more marked the higher one goes. As a result of the absence of moisture in the air the radiant power of the sun increases, and this is helped by the freedom from smoke and (in winter, at any rate) from dust. During the winter, when the snow is down, the radioactive power of the sun appears to be even greater than during the summer. Much interesting information may be obtained on this subject from the classical work, *The Therapeutics of Climate*, by the late Dr. W. R. Huggard of Davos.

Upon the healthy person the general effects of altitude are as follows: The tissue changes go on more rapidly, the respirations and pulse are quickened, and the body temperature tends to be slightly higher than at sea level; one is living at a greater rate, so to speak, in the mountains. Another important point is that at sea level the normal red blood count is approximately five million corpuscles per cubic millimetre, and the percentage of haemoglobin about 90; at an altitude of, say, 5,000 ft., the blood, in order to compensate for the diminished tension of oxygen in the air, becomes richer both in red cells and in haemoglobin, the ordinary estimation of a healthy person at this altitude being seven million red cells per cubic millimetre, and about 100 per cent., or even more, of haemoglobin. The essential facts here appear to be the change in the percentage of haemoglobin, and this is directly proportional to the altitude, and thus, of

course, to the diminished oxygen tension of the air. The highest percentage of haemoglobin ever recorded is, I believe, 150 per cent., which was reached by one observer at a height of 12,000 ft. There is, however, another factor to be considered in regard to the process of "acclimatization." Under the lowered pressure of a high place, and, of course, proportional to the height, the internal pressure of the body gases is altered, and is always tending to equalize with the external pressure, and until this is accommodated there is increased internal pressure, which may help in producing many of the sensations experienced at first, even at a moderate height—say, 5,000 ft. This process of acclimatization takes from a week to a fortnight to accomplish itself, however, and as a result on first going to a high altitude people often feel uncomfortable and short of breath on slight exertion, and may experience cardiac palpitations and sleeplessness, with lassitude and malaise.*

At high altitude persons breathe deeper, and there is a tendency to expand the lung more than at sea level. The vital capacity also is increased. This feature is valuable in the treatment of chronic pleuritis with adhesions, and in pulmonary disease of the fibrotic type generally; also in adenoids.

From this brief summary of the chief physiological effects of altitude, it is plain that we have here a valuable and powerful therapeutic aid, if applied with care and common sense and to the correct type of case. My remarks are based upon observations made at an average height of 5,000 ft. above sea level, which, taking it all round, appears to be the most advantageous altitude as a therapeutic agent. The modern tendency of treatment is to try to increase the reactive power of the patient, rather than to attempt a direct attack on the disease itself, and this is clearly the line of procedure to take up in such a disease as pulmonary tuberculosis, where direct attack is often impossible. Since the increased metabolism at high altitudes must tend to heighten the reactive power and power of resistance, this therapeutic agent offers the best means at present available for the treatment of pulmonary tuberculosis in properly selected cases. I will first endeavour, therefore, to sketch out the types of case most likely to benefit from a stay in the mountains, and then will enumerate certain cases which should never under any circumstances be sent there.

Healthy people may thus derive great benefit from a holiday in a mountain station, and perhaps the three weeks that many spend at Christmas time in some of the Alpine resorts give the greatest possible value, as regards a holiday, that can be obtained, especially to the hard-worked professional man.

Tuberculosis: Indications and Contraindications.

Tuberculosis is, perhaps, the condition most closely associated with mountain treatment, and it is certain that there must be some good reason for the great reputation which the mountains have won for the cure of tubercle, more especially tubercle of the lungs. First, it is clear from what has already been said, that the main general principle the physician should bear in mind when deciding whether a particular patient is a suitable type of case for a high altitude must be his reactive power. And this is where the judgement of the doctor must be carefully exercised, but the following few remarks may serve as a guide in forming an opinion.

To begin with, there is no doubt that the best type of pulmonary tuberculosis to treat in the mountains is an early case in a young or middle-aged subject, if of a good general constitution, and with sufficient resistance and vitality to react properly to the increased rate of metabolic activity which occurs at an altitude. But later cases of a chronic and partially arrested type undoubtedly do very well in the mountains, especially those in which the disease appears to have come to a standstill and the patient is "sticking"; the mountain climate seems to give this type of case just the necessary amount of stimulus or "kick" to enable him (or her) to improve.

The patients who should never be sent are those in the

* An interesting account of mountain sickness and the sensations experienced at great altitudes—for example, 8,000 to 20,000 ft.—will be found in *Travels amongst the Great Andes of the Equator*, by Edward Whymper, where the effects of very high altitudes (and consequently low pressures) are carefully analysed as regards pulse, body temperature, breathing capacity, fatigue, and general sensations, etc.