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THE AETIOLOGY OF ERYTHEMA NODOSUM

BY

C. BRUCE PERRY, M.D., F.R.C.P.

Professor of Medicine, University of Bristol

Its Relation to Rheumatism and Heart Disease

The aetiology of erythema nodosum has for long been the subject of discussion and argument. The earliest view that I have been able to trace as to the nature of this common and clear-cut eruption is the one expressed by Bouillaud (1840) in his classical treatise on acute rheumatism. There he states that in view of the frequent occurrence of limb pains with erythema nodosum he considered that it is probably "rheumatic" in nature. Trousseau (1869) in his lectures on clinical medicine endorsed this opinion. However, in 1883 Sir Thomas Barlow paid more critical attention to these pains which occur with erythema nodosum, and, realizing that the development of heart lesions is the most certain criterion of acute rheumatism, stated 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."

Perhaps stimulated by this criticism of Barlow's, Stephen Mackenzie in 1886 attempted to show this association with heart disease, and in fact claimed to have done so. However, the method by which Mackenzie obtained his information and the interpretation which he gave to it are open to grave criticism. It appears fairly certain from Mackenzie's paper that he examined very few of the patients himself. He analysed 108 cases collected from four London hospitals, presumably by registrars, and 19 of these were considered to present signs of heart disease. It should be remembered that at this time any cardiac murmur was accepted as undoubted evidence of heart disease, and from the description given of these cases it is doubtful if many really had rheumatic heart disease. Mackenzie suggested that his findings "justify the inference that erythema nodosum is frequently, if not generally, an expression of rheumatism even when no other definitely rheumatic symptoms are present."

This view was generally accepted in this country, and until comparatively recently has been repeated in most textbooks. From time to time doubt has been thrown on its validity, notably by Gosse (1913), Miller (1921), Walker (1927), and Symes (1928) in this country, Keil (1937) in America, and Feer (1926) and Landau (1927) on the Continent. Both Gosse and Symes point out that, apart from the fact that true carditis is rarely found in erythema nodosum, there are other striking differences between the two diseases. In acute rheumatism males and females are about equally affected, whereas erythema nodosum is far more frequently seen in females. Further, salicylates, which have such a marked effect on the fever and arthritis of acute rheumatism, do not in any way modify the course of erythema nodosum. In addition these observers point out that with a disease so common as acute rheumatism it is hardly surprising that an occasional case of erythema nodosum is seen with pre-existing rheumatic heart disease. Despite these

objections the rheumatic theory has been extremely popular, and has been supported by several observers, including Holmes (1937) and de Meuron (1919). The case described by the latter is of considerable interest in view of the crucial point made by Barlow of the initiation of heart disease in an attack of erythema nodosum. A child aged 8½ developed almost certain carditis while under treatment for erythema nodosum, but the patient finally made a complete recovery. However, Wallgren (1938a, 1938b), who has perhaps done more than anyone to establish the relationship between erythema nodosum and tuberculosis, has described cases showing clearly that this association demanded by Barlow and described by de Meuron is not necessarily proof that the erythema nodosum is rheumatic in origin.

For instance, a child aged 10 developed chorea and carditis and recovered with a permanent cardiac lesion. Fifteen months later she was readmitted to hospital, and changes in the electrocardiogram provided evidence of a recurrence of the carditis. The tuberculin reaction was negative, but a week later the temperature, which had been subnormal, became elevated, and a fresh Mantoux reaction was strongly positive and skiagrams showed enlarged hilar glands on one side with a primary focus in the corresponding lung, and she developed erythema nodosum.

It is clear that in this case a child with smouldering rheumatic heart disease developed primary tuberculosis and at the same time erythema nodosum. Despite such possibilities Wallgren has been led to believe that very occasionally erythema nodosum may be due to acute rheumatism, and has described a case in which a child seven days after the onset of erythema nodosum developed arthritis and subsequent carditis which ran a prolonged course.

Question of Specificity

The next phase in the study of the disease was the recognition of small epidemics. This gave rise to the theory, particularly championed by Lendon (1905, 1925), that erythema nodosum is a specific infectious disease. This conception of a specific disease has been supported by Symes (1921), Walker (1927), and others, and recently Keil (1939) has stated his belief in this view. Claims to have isolated a specific causal organism have been made on two occasions—by Rosenow (1915) and by Moon and Strauss (1932)—but these findings have never been confirmed.

Further studies of erythema nodosum soon revealed the fact that it is not infrequent for the eruption to be followed some months later by evidence of tuberculosis such as a pleural effusion or tuberculous meningitis. Those who regard erythema nodosum as a distinct disease *sui generis*, realizing this association, suggest that it predisposes to subsequent tuberculous infection. However, the work of the Scandinavian school of paediatrics, particularly that of Ernberg (1932, 1933) and Wallgren (1926a, 1926b, 1938b), has made it clear that this is not the correct explanation. They have shown that in Scandinavia the vast majority of children with erythema nodosum have strongly positive tuberculin reactions. The conclusion that this finding indicates that there is an intimate association between tubercle and erythema nodosum has been criticized on the grounds that the majority of all patients have a positive tuberculin reaction.

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However, the Scandinavian investigators were dealing with children in whom the expected incidence of a positive tuberculin reaction is much lower. In some cases a tuberculin test performed as the nodes are fading not only gives a positive reaction but results in fever and a recrudescence of the eruption (Arnaud, 1939). "These cases are so sensitive to tuberculin that a minimal dose must be used lest severe necrotic reactions are produced. In addition to this very marked tuberculin sensitivity, many cases present radiological evidence of enlargement of the hilar glands and, in a smaller number, shadows of the primary tuberculous lesion—the Ghon focus—may be seen. Finally, Wallgren (1931) and others have been able to demonstrate tubercle bacilli in the resting gastric juice. Thus the close association with recent primary tuberculous infection is firmly established. Pollak (1912) had previously reported similar findings in Austria, and these have been confirmed by many others, including Collis (1932, 1933), Forman and Whitwell (1934), Ford (1936), and Thompson (1938) in this country, Faerber and Boddin (1924) in Germany, Tsukkerman and Rybak (1937) in Russia, Dickey (1930, 1932) in the United States, and the Rascovskys (1938) in the Argentine.

Several investigations have clearly shown that the occasional epidemics of erythema nodosum seen in schools and institutions are in the vast majority of cases due to recent simultaneous infection with the tubercle bacillus. Thus there is no need to postulate a specific infection. Usually, as in the epidemics described by Begg (1932), Landau (1932), and Brandon, Hardman, and Birks (1938), the infection has occurred as the result of the presence of an unsuspected open case of pulmonary tuberculosis in the community. Törnell (1936) has described a local epidemic due to the consumption of milk infected with tubercle bacilli. Stimulated by these findings, many attempts have naturally been made to demonstrate tubercle bacilli in the actual nodes and in the circulating blood. A very few of these have been successful, such as those reported by Hildebrandt (1907), Aguirre and Cervini (1936), and Wallgren and Gnosspeliuss (1940). These few successes are probably to be explained by the assumption that the cultures were made at a time when there was a tuberculous bacillaemia—a condition which is believed to occur very occasionally in many, if not in all, patients with a primary tuberculous complex.

Tuberculous Theory

As a result of these investigations the theory was put forward that erythema nodosum occurs during the primary tuberculous infection at the time the patient first develops hypersensitivity to tuberculin. Wallgren showed that the eruption coincides with sudden development of this hypersensitivity by tuberculin tests performed in the stage of the preceding fever, when they are negative, and in the same child immediately after the eruption, when they are strongly positive. Observations such as that made by Punch (1941) confirm these views. He found that in a number of student nurses undergoing regular tuberculin-testing the change from a negative to a positive tuberculin reaction was marked by the development of erythema nodosum. Wallgren has also demonstrated that when a second attack of erythema nodosum occurs after such illnesses as measles it may be due to the fact that the infection temporarily depresses or even abolishes tuberculin sensitivity, which returns suddenly two or three weeks later when the second attack of erythema nodosum occurs. This view of the aetiology of the disease has gained wide acceptance in Scandinavia and on the Continent generally; also in the United States. In this country it has made slow headway against the rheumatic theory.

Even Wallgren (1926b) himself has had to admit that every patient with erythema nodosum does not show a positive tuberculin reaction, and has reported 3 cases with negative reactions in a series of 135 patients and 5% in a larger series of 800 cases (Wallgren, 1938b). Similar findings are reported by Landorf (1935), who found 24 such cases in a series of 650, and by Ernberg and Gabinus (1938), who describe a group of 34 cases occurring in Stockholm in six months, of which 20 were tuberculin-negative. All of the latter were seen in a short period of just under two months. Further evidence that all cases of erythema nodosum cannot be explained on the tuberculous theory is provided by the occurrence of the eruption in patients known to have been infected with tubercle years

before and who show evidence of this old infection in the form of calcified hilar glands (Lemming, 1935). It thus became clear that even if many cases of erythema nodosum were causally related to tuberculosis this could not be the explanation of all.

An Alternative "Rheumatic" Theory

Collis (1932) shed new light on the problem by showing that in some of the tuberculin-negative cases the patients exhibited at the time of the eruption very marked skin sensitivity to streptococcal nucleoprotein. This has been confirmed by Coburn and Moore (1936), who were able to show exacerbations of the disease following intracutaneous injections of nucleoprotein of haemolytic streptococci, exactly as may happen after tuberculin tests in the supposedly tuberculous cases. These observations fall into line with the occasional development of erythema nodosum after haemolytic streptococcal infections such as scarlet fever (Moro, 1935; M6ritz, 1934). Actually this appears to be a very rare occurrence, and Dr. Peters (1944), medical superintendent of the fever hospital at Bristol, has seen only one example in the last 2,346 cases of scarlet fever. It must be remembered that Wallgren (1938a) has demonstrated clearly that many of the cases which apparently follow a sore throat are associated with a change in tuberculin sensitivity. However, this streptococcal theory offers an alternative explanation of the apparently "rheumatic" cases. It is well known that relapses of acute rheumatism are often preceded by an acute haemolytic streptococcal pharyngitis. It is surely possible that the same infection may both produce erythema nodosum and initiate an attack of acute rheumatism without the two latter conditions being more closely related. One occasionally finds cases of acute rheumatism which show in addition some evidence of acute nephritis. Here the explanation would appear to be similar—that the streptococcal infection gives rise to two different sequelae. In the patient described by Wallgren as the one "rheumatic case" seen in 800 attacks of erythema nodosum the rash developed seven days before any manifestation of acute rheumatism was present.

"Valley Fever"

For many years there has been recognized in certain parts of California and Arizona a chronic granuloma-forming disease which has a particularly high incidence in the San Joaquin Valley. The granulomas may involve any part of the body, and the clinical and histological picture closely resembles that of tuberculosis. The causal organism is a fungus, the *Coccidioides immitis*. In the same areas occurs an acute and relatively mild disease with respiratory symptoms, fever, malaise, and sweating, known as "valley fever." In 1937 Dickson proved that this "valley fever" was the early stage of coccidioidomycosis. The vast majority of the patients afflicted with valley fever make a fairly rapid and complete recovery. In a small number, however, the granulomatous lesions develop years afterwards. In the acute stage radiology reveals enlargement of the hilar glands on one or both sides, and, rarely, pulmonary cavitation or pleural effusion occurs as a sequel. About 5% of the patients with valley fever show typical erythema nodosum, known locally as "the bumps." Further, patients with this disease develop marked and lasting skin sensitivity to coccidioidin, and mass skin-test surveys have shown that there must be many subclinical primary infections (Smith, 1940; Goldstein and Louie, 1943; Goldstein and McDonald, 1944). Thus we have a disease closely similar in all stages to tuberculosis, characterized by a relatively mild primary stage, with subsequent blood dissemination, and, in some patients only, the development of more serious granulomas; and a disease which in certain people gives rise to erythema nodosum.

Association with Sarcoidosis

Erythema nodosum is occasionally met with as an episode in the prolonged clinical histories of some cases of sarcoidosis. Reports of large numbers of patients with this condition are uncommon, and it is difficult to determine with any certainty how often this happens. Kerley (1942, 1943) has drawn attention to the x-ray findings in 37 adults with erythema nodosum. These cases were mainly drawn from the Services, and their ages ranged from 18 to 33. In 28 there was radiological evidence of pulmonary pathology. These changes were of two

main types—glandular enlargement, usually bilateral, and a coarse reticular striation in the lungs very much like the picture of early silicosis. Kerley believes that the latter indicates some lymphatic obstruction. In 17 these changes occurred together, in 8 enlarged glands only were found, and in 3 the pulmonary changes appeared alone. Two patients subsequently developed pleural effusion, and in one this was bilateral—an unusual occurrence with tuberculous effusion. The x-ray changes which Kerley describes are reminiscent of those found in

nodosum, and in four of his cases was able to demonstrate calcified hilar glands, thus proving that the primary tuberculous infection had occurred years before and could not be related to the erythema nodosum.

Sulphonamide Rash

The use of the various sulphonamides is not infrequently complicated by rashes of diverse types, including occasionally an eruption indistinguishable clinically and histologically from

FIG. 1.—Skiagram of a girl aged 11 taken two days after the onset of erythema nodosum, showing enlarged right hilar glands.

FIG. 3.—Skiagram of a girl aged 6 taken two months after an attack of erythema nodosum, showing enlargement of the right hilar glands and a "flare" spreading out to and involving the primary focus.

FIG. 2.—Skiagram of a boy aged 8 taken six months after an attack of erythema nodosum, showing enlarged right hilar glands and a primary focus in the right lung.

FIG. 4.—Skiagram of a girl aged 11 taken three weeks after an attack of erythema nodosum, showing a picture like that of "epituberculosis."

coccidioidomycosis, but no fungi were present in the sputum of any of the cases. Tuberculin reactions were not done as a routine. Kerley considers that the pulmonary shadows are very much like those seen in sarcoidosis, and in two of the cases skin lesions excised after the acute rash had subsided showed the histological characteristics of sarcoid. In addition to changes in the mediastinal glands, five showed enlarged glands in the neck, and one in the axilla. Kerley is extremely doubtful of the validity of the tuberculous theory of erythema

erythema nodosum. The only difference is that the eruption fades away rapidly when the drug is stopped (Haviland and Long, 1940; Combes and Cañizares, 1941; Jersild and Iversen, 1942). Sulphathiazole is the member of the sulphonamide group which most often causes erythema nodosum, but there is at least one case reported due to sulphanilamide (Loveman and Simon, 1940). It is generally considered that these rashes are due to sensitization, and Shaffer, Lentz, and McGuire (1943), from a study of sulphathiazole sensitivity, report that

passive transfer tests with the Prausnitz-Küstner technique give positive delayed reactions to sulphathiazole similar to the tuberculin reaction as well as the early wheal type of reaction.

Occasionally erythema nodosum has been reported complicating various other infections, such as in the case of gonorrhoeal septicaemia of Bakst, Foley, and Lamb (1935). However, such cases are so infrequent as to make it impossible to draw any definite conclusion from them.

Series of Cases showing Aetiological Diversity

In view of the diversity of conditions which may apparently cause this eruption it was decided to study a series of cases in an attempt to determine the aetiology in each. In all, 112 cases were investigated. Of these, 38 were males and 74 females. This confirms the well-known preponderance of females. The cases were tuberculin-tested by the Mantoux reaction. Only the reaction to 0.01 mg. of old tuberculin was tested in view of the fact that if the theory already described is correct and the case is tuberculous in origin the patient must be extremely sensitive to tuberculin. Any patient not reacting to this dose of tuberculin was regarded as giving a negative tuberculin reaction for the purpose of this study. A few cases were also tested with streptococcal nucleoprotein, kindly provided by Collis, but insufficient material was available to test all. In addition all cases were x-rayed and have been followed up to the present time. Of these, 61 gave a strongly positive Mantoux reaction and 51 a negative reaction to 0.01 mg. of tuberculin. In 21 of the 61 the x rays showed enlarged hilar shadows on one side (Fig. 1); some of these also showed a shadow of the primary lesion (Figs. 2 and 3), and others a picture similar to that of epituberculosis (Fig. 4). One case had a typical tuberculous cervical adenitis, and one patient died later of tuberculous peritonitis. Four cases subsequently developed a pleural effusion, and two of these showed normal skiagrams at the time of the eruption.

For instance, a nurse aged 23 developed erythema nodosum on March 1. Her Mantoux reaction was strongly positive, but a skiagram of the chest showed no abnormality. Her sister, also a nurse, had had erythema nodosum some years ago and subsequently developed a pleural effusion. This patient was kept in bed for six weeks, when her temperature and erythrocyte sedimentation rate were normal. She was discharged to continue rest at home. Fourteen weeks after the onset she developed a pleural effusion. This cleared up with further rest, and subsequent skiagrams show no sign of any lung lesion.

A further case with a normal skiagram subsequently developed miliary tuberculosis. This patient was a boy aged 2 years and 2 months who developed erythema nodosum in Feb., 1941. He had a strongly positive tuberculin reaction, but x rays showed no abnormality in his chest. A month later he was not so well, and was admitted to hospital. He did not improve, and in May skiagrams showed miliary tuberculosis of the lungs. He improved for a time but developed pertussis. After this he went steadily downhill and died of tuberculous meningitis eleven months after the onset. Post-mortem examination revealed generalized tuberculosis with caseous cervical, hilar, and mesenteric glands. He thus appeared to have suffered at least three "primary" infections. A brother died of pulmonary tuberculosis a month before the patient was taken ill.

All these cases were considered to be definitely tuberculous, making a total of 32 in this category. Those with strongly positive Mantoux reactions but no other evidence of tuberculosis were regarded as probably tuberculous, and numbered 28. It must be remembered that by no means all enlarged hilar glands produce definitely enlarged hilar shadows. Two of the cases later developing pleural effusion, the patient dying of tuberculous peritonitis, and the boy developing miliary tuberculosis—all of whom had normal chest skiagrams at the time of the eruption—would have fallen into this group but for subsequent events. Seventeen cases were tested with Collis's streptococcal nucleoprotein; 15 gave a positive reaction, but one was also positive to tuberculin and has been classified as doubtful, and 2 were negative both to tuberculin and to streptococcal nucleoprotein. Thus of the total 112, 32 (28%) were certainly tuberculous, 28 (25%) were probably tuberculous, and 51 (45%) were definitely not tuberculous.

However, when these cases are analysed further into age groups two striking facts emerge. The sex incidence (Table I), which in the total group was roughly 2 females to 1 male, becomes much

TABLE I.—Age and Sex Incidence

Age	Males	Females	Total
0-15 years	36	31	67
Over 15 years	2	43	45
All ages	38	74	112

TABLE II.—Relationship to Tuberculosis

Age	Certainly Tuberculous	Probably Tuberculous	Not Tuberculous	Doubtful	Total
	Mantoux +ve, X-ray +ve, and/or Subsequent Tuberculous Illness	Mantoux +ve. No other Evidence of Tuberculosis	Mantoux -ve	Mantoux +ve; Streptococcal Nucleoprotein +ve	
0-15	29 (43%)	20 (29%)	17 (25%)	1	67
Over 15	3 (6%)	8 (17%)	34 (76%)	—	45
All ages	32 (28%)	28 (25%)	51 (45%)	1	112

altered. Under 15 there were 36 boys and 31 girls, whereas over this age there were 43 females and only 2 males. There were 67 cases under the age of 15, and of these 29 (43%) were definitely tuberculous and 20 (29%) probably tuberculous, whereas of the 45 patients over 15 only 3 (6%) were definitely tuberculous and 8 (17%) probably tuberculous. So that in 72% of cases of erythema nodosum in children of school age or under the eruption probably marked the development of primary tuberculosis. The importance of this in treatment and tuberculous-case finding is so obvious as to need no comment.

Turning now to the relationship to acute rheumatism, 10 of the 112 cases had had this condition previously; in four of them the heart was normal at the time of the erythema nodosum. In only two of these was there any evidence of a rheumatic relapse. In both the rheumatism appeared to follow the erythema nodosum and not to occur simultaneously. This supports the theory, already put forward, that while the two diseases both follow a streptococcal infection they are not necessarily the same. Five, including the two having a rheumatic relapse, gave negative tuberculin reactions, and four of these were sensitive to streptococcal nucleoprotein. Of the remaining 5, two were certainly tuberculous, as judged by skiagrams and Mantoux findings. The other three had positive tuberculin reactions but no other evidence of tuberculosis. None of them showed any relapse. One boy with a strongly positive Mantoux reaction developed acute rheumatism and carditis two years after his erythema nodosum. There was no recurrence of the erythema.

These cases thus offer little support to the theory that erythema nodosum is a manifestation of acute rheumatism. In fact, it is comparatively rare in rheumatic patients, since these 10 were the only ones found in over 1,000 patients with acute rheumatism.

A family history of erythema nodosum was elicited in 10 cases. In one family three children with erythema nodosum which was definitely tuberculous led to the discovery of a tuberculous father. A history of a previous attack was given by 13 patients. All of these were females and all were tuberculin-negative, but the only four cases tested were sensitive to streptococcal nucleoprotein.

Eleven patients gave a clear-cut history of an acute pharyngitis preceding the erythema nodosum. Of these, four had had previous attacks, and all but two had a negative tuberculin reaction.

Conclusions

These findings thus agree with those of other workers, and we are forced to conclude that, as Arborelius (1928), Spink (1937), and others have claimed, erythema nodosum must be regarded as the result of a non-specific reaction to a variety of infections or toxic agents and that it is not a specific disease. However, it is clear that these agents can and do give rise to the syndrome only in patients predisposed by their constitutional make-up, since everyone who suffers a primary tuberculous infection—and that is probably all of us by the time we are 30—develops hypersensitivity to tuberculin, yet only a small proportion show erythema nodosum. In the recent Prophit Trust survey carried out by this College Daniels (1944) found that in 5 of 284 nurses developing a positive tuberculin reaction the change was marked by the occurrence of erythema nodosum. Similarly with coccidioidomycosis, only about 5% of the patients develop erythema nodosum although all become sensitive to coccidioidin. The frequency with which other members of the family suffer from erythema nodosum probably offers the clue to this part of the problem and shows that the diathesis is partly, at any rate, inherited. The sex difference in the incidence of the eruption after the age of puberty suggests that endocrine factors also contribute to this predisposition.

Sir Thomas Lewis (1944) has recently drawn attention to the way in which the great importance attached to diagnosis in

present-day medical practice tends to limit investigation to assigning a name to a clinical picture. "These names applied to disease," he says, "come to assume the importance of specific entities, whereas they are for the most part no more than insecure and therefore temporary conceptions." Further, with the development of the science of bacteriology we have tended to take the view that one disease is likely to have one cause. This review of the aetiology of erythema nodosum shows how false this conception is and how necessary it is to search beyond a mere diagnosis if we are to understand a disease or syndrome. Erythema nodosum presents a clinical picture as clear-cut as many other so-called diseases, yet, as we have seen, it may be produced by several different and quite unrelated infections. Further studies may well show that the same holds true for many disorders at present accepted as specific diseases.

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Physiotherapy is a profession in which the blind practitioner excels. Indeed, absence of sight seems to be an asset rather than a handicap in this work, allowing undisturbed concentration and providing an exceptional sense of touch. For many years the National Institute for the Blind (224, Great Portland Street, London, W.1) has been paying special attention to the training of suitable blind men and women for this profession, and the annual report for 1943-4 refers encouragingly to those who have qualified. During the war they have been giving valuable service both in military hospitals and in private practice. In the past year all previous records were broken at the Institute's evening clinic and the Eichholz Clinic.

STUDIES ON HEPATIC DYSFUNCTION

III. CARBON TETRACHLORIDE POISONING: SULPHUR METABOLISM

BY

J. BEATTIE, M.D., D.Sc.

Bernhard Baron Research Professor, R.C.S.

P. H. HERBERT, B.A.

Leaverhulme Scholar, R.C.S.

C. WECHTEL, M.D.

Capt., U.S. Army Medical Corps

AND

C. W. STEELE, M.D.

Major, U.S. Army Medical Corps

(From a U.S. Military Hospital, E.T.O., and the Bernhard Baron Research Laboratories, Royal College of Surgeons of England)

In a previous article (Beattie *et al.*, 1944) we described a case of carbon tetrachloride poisoning in which the predominating clinical findings were those of acute hepatic dysfunction. Administration of methionine and casein digest intravenously was followed by a rapid recovery, and a slight relapse which occurred about 26 hours later showed a similar rapid response to methionine given orally.

In addition to the routine investigations an attempt was made to follow the mode of action of the methionine by estimating the nitrogen and sulphur balance of the patient and by determining the partition of the urinary sulphur between the oxidized (total sulphate) and unoxidized (neutral) fractions. It was this last determination which yielded the most interesting results. We had expected to find either that the methionine sulphur would be retained in the body or that it would be excreted as sulphate. In fact, we found that the major part of it was excreted in the neutral sulphur fraction. We therefore concluded tentatively that the effect of the carbon tetrachloride had been to interfere with the normal metabolism of methionine by the liver and that this was the intimate cause of the liver disturbance.

Such a conclusion assumes that a normal person would not have excreted such a large quantity of neutral sulphur following a similar dose of methionine. It also presupposes that our patient would have metabolized the methionine normally had he not previously ingested carbon tetrachloride. With regard to the first supposition we had only indirect evidence available at the time. Subsequent work on normal individuals has shown, however, that, although the excretion of neutral sulphur is somewhat higher than is suggested by the work of other investigators on orally administered methionine, the greater part of the sulphur contained in 10 g. of methionine administered intravenously is excreted as sulphate within 24 hours.

The second point could only be determined by investigating the metabolism of methionine in our patient under normal conditions and comparing the findings with those previously obtained when he was suffering from the toxic effects of the carbon tetrachloride. Accordingly it was decided at the time of the original incident to readmit the patient for investigation after six months had elapsed, at which time he might be assumed free from any residual liver damage. This has now been done, and the results obtained will be presented in this communication.

The patient was readmitted on April 1, 1944. In the interval he had been on full duty with his squadron, had made more than 40 operational flights over enemy-occupied territory, often at high altitudes, and had remained in excellent health throughout. Physical examination on readmission revealed no abnormalities. His liver was not palpable during normal respiration, and when felt on deep inspiration was not tender. The serum bilirubin level was 0.8 mg. per 100 c.cm. Various tests of kidney function which were performed gave values within the normal range.

The diet of the patient was planned so as to give a daily protein intake of about 100 g. All urine was collected, and the output of nitrogen, creatine, creatinine, total sulphur, and total sulphate was determined. On the second day in hospital he was infused with a solution containing 10 g. of methionine.