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.

REFERENCES

- Aguirre, R. C., and Cervini, P. R. (1936). *Presse méd.*, **44**, 110.
 Arborelius, M. (1928). *Acta med. scand.*, **68**, 151.
 Arnaud, J. (1939). *Rev. Tuberc.*, **5**, 65.
 Bakst, H. J., Foley, J. A., and Lamb, M. E. (1935). *Ann. intern. Med.*, **9**, 790.
 Barlow, T. (1883). *British Medical Journal*, **2**, 509.
 Begg, N. D. (1932). *Brit. J. Child. Dis.*, **29**, 193.
 Bouillaud, J. B. (1840). *Traité clinique du Rhumatisme articulaire*, Paris.
 Brandon, K. F., Hardman, R. P., and Birks, W. H. (1938). *Canad. publ. Hlth. J.*, **29**, 533.
 Coburn, A. F., and Moore, L. V. (1936). *J. clin. Invest.*, **15**, 509.
 Collis, W. R. F. (1932). *Quart. J. Med.*, **25**, 141.
 — (1933). *British Medical Journal*, **2**, 1162.
 Combes, F. C., and Cañizares, O. (1941). *Arch. Derm. Syph.*, Chicago, **44**, 236.
 Daniels, M. (1944). *Lancet*, **2**, 165, 201, 244.
 Dickey, L. B. (1930). *Amer. J. med. Sci.*, **180**, 489.
 — (1932). *Amer. Rev. Tuberc.*, **26**, 614.
 Dickson, E. C. (1937). *Calif. West. Med.*, **47**, 151.
 Ernberg, H. (1932). *Nord. med. Tidskr.*, **4**, 230.
 — (1933). *Amer. J. Dis. Child.*, **46**, 1297.
 — and Gabinus, O. (1938). *Nord. med. Tidskr.*, **15**, 300.
 Feerber, E., and Boddin, M. (1924). *Jhr. Kinderheilk.*, **106**, 293.
 Feer, E. (1926). *Schweiz. med. Wschr.*, **56**, 682.
 Ford, F. J. (1936). *Glas. med. J.*, **126**, 133. (*Trans. roy. med.-chir. Soc. Glas.*, **30**, 133.)
 Forman, L., and Whitwell, G. P. B. (1934). *Guy's Hosp. Rep.*, **48**, 213.
 Goldstein, D. M., and Louie, S. (1943). *War Med.*, **4**, 299.
 — and McDonald, J. B. (1944). *J. Amer. med. Ass.*, **124**, 557.
 Gosse, A. H. (1913). *Practitioner*, **91**, 240.
 Haviland, J. W., and Long, P. H. (1940). *Johns Hopk. Hosp. Bull.*, **66**, 313.
 Hildebrandt, W. (1907). *Munch. med. Wschr.*, **54**, 310.
 Holmes, A. H. (1937). *Practitioner*, **138**, 181.
 Jersild, T., and Iversen, K. (1942). *Acta med. scand.*, **111**, 105.
 Keil, H. (1937). *Ann. intern. Med.*, **10**, 1686.
 — (1939). *J. Amer. med. Ass.*, **112**, 763.
 Kerley, P. (1942). *Brit. J. Radiol.*, **15**, 155.
 — (1943). *Ibid.*, **16**, 199.
 Landau, A. (1927). *Acta paediatr.*, Stockh., **6**, 402.
 — (1932). *Arch. Dis. Childh.*, **7**, 77.
 Landorf, N. (1935). *Rev. frang. Pédiat.*, **11**, 157.
 Lemming, R. (1935). *Hygiea, Stockh.*, **97**, 60.
 Lendon, A. A. (1905). *Nodal Fever*, Baillière, Tindall and Cox, London.
 — (1925). *British Medical Journal*, **1**, 651.
 Lewis, T. (1944). *Lancet*, **1**, 619.
 Loveman, A. B., and Simon, F. (1940). *J. Allergy*, **12**, 28.
 Mackenzie, S. (1886). *Clin. Soc. Trans.*, **19**, 215.
 Meuron, de (1919). *Arch. Méd. Enf.*, **22**, 428.
 Miller, R. (1921). *British Medical Journal*, **2**, 863.
 Moon, V. H., and Strauss, A. (1932). *Arch. Derm. Syph.*, Chicago, **26**, 78.
 Moritz, D. v. (1934). *Arch. Kinderheilk.*, **103**, 227.
 Moro, E. (1935). *Z. Kinderheilk.*, **57**, 321.
 Peters, B. A. (1944). Personal communication.
 Pollak, R. (1912). *Wien. klin. Wschr.*, **25**, 1223.
 PUNCH, A. L. (1941). *Lancet*, **1**, 10.
 Rascovsky, L., and Rascovsky, A. (1938). *Arch. argent. Ped.*, **9**, 625.
 Rosenow, E. C. (1915). *J. infect. Dis.*, **16**, 367.
 Shaffer, B., Lentz, J. W., and McGuire, J. A. (1943). *J. Amer. med. Ass.*, **123**, 17.
 Smith, C. E. (1940). *Amer. J. publ. Hlth.*, **30**, 600.
 Spink, W. W. (1937). *Arch. intern. Med.*, **59**, 65.
 Symes, J. O. (1921). *British Medical Journal*, **2**, 741.
 — (1928). *Bristol med.-chir. J.*, **45**, 233.
 Thompson, B. C. (1938). *Newcastle med. J.*, **18**, 24.
 Törnell, E. (1936). *Nord. med. Tidskr.*, **12**, 1865.
 Trousseau, A. (1869). *Lectures in Clinical Medicine*, Lect. viii, **2**, 239. New Sydenham Society, London.
 Tsukerman, N. A., and Rybak, P. T. (1937). *Probl. Tuberc.*, No. 10, p. 75.
 Walker, G. F. (1927). *Brit. J. Derm. Syph.*, **39**, 241.
 Wallgren, A. (1926a). *Acta paediatr.*, Stockh., **5**, 225.
 — (1926b). *Acta med. scand. Suppl.*, **16**, 363.
 — (1931). *Amer. J. Dis. Child.*, **41**, 816.
 — (1938a). *Ibid.*, **55**, 897.
 — (1938b). *Lancet*, **1**, 359.
 — and Gnosspelius, A. (1940). *Acta med. scand.*, **103**, 341.

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.

This amount of methionine contains as much sulphur as was present in the original methionine-casein digest infusion. It was given at the same rate. There was no reaction.

In Table I the urinary output of total sulphur and total sulphate during the original incident is given in rather more detail than in our previous communication. The figures for

TABLE I

1st Admission					2nd Admission				
Period	Time in Hours	Excretion of Sulphur in Grammes			Period	Time in Hours	Excretion of Sulphur in Grammes		
		Total Sulphur	Total Sulphate	Neutral Sulphur			Total Sulphur	Total Sulphate	Neutral Sulphur
I	3½	0.062	0.041	0.021	I	—	—	—	—
II	3½	0.410	0.250	0.160	II	4	0.626	0.373	0.253
III	12	0.532	0.380	0.142	III	13½	2.113	1.696	0.417
IV	24	2.650	1.300	1.350	IV	24	1.747	1.269	0.478
V	24	1.010	0.770	0.240	V	24	1.218	0.850	0.368
VI	24	1.080	0.980	0.100	VI	24	1.143	0.856	0.287

comparable periods during the second admission are also included. In order to make comparison easy the same figures are given in the form of a histogram (see Fig.). The infusion in each case was started at the beginning of Period II, and extended over 3 hours.

Urinary sulphur excretion. Neutral sulphur is indicated by hatched areas, sulphate sulphur by clear areas. Periods are as described in text. The vertical scale is proportional to the hourly excretion of each urinary sulphur component.

Before direct comparison is made between the two sets of figures there are several points which require discussion. First, the normal excretion of neutral sulphur on the last four days of the original experiment never exceeded 100 mg. (Period V on the graph is misleading, as the patient received more methionine by mouth on that day.) On the last two days of the second admission (Periods V and VI) it was 368 and 287 mg. We believe that this apparent discrepancy is due to a difference in the methods of total sulphur determination used on the two occasions. On the first occasion oxidation was with nitric and perchloric acids (Pirie, 1932); on the second occasion oxidation by fusion with sodium peroxide (Folin, 1905) was used. We have found the latter method to give higher figures than the former with certain urines. This is particularly marked in periods following methionine administration. It should be borne in mind during the subsequent discussion that the tendency is therefore to obtain slightly higher figures for neutral sulphur during the second investigation.

Secondly, the neutral sulphur excretion is definitely increased after the second infusion, and this increase cannot be accounted for as a simple spill-over of methionine in the urine. Results we have obtained by the direct analysis of methionine in urine strongly suggest that not more than 1.5 g. of methionine is lost in this way even when 10 g. is given in as short a period as 45 minutes. As our patient received his methionine over the comparatively long period of 3 hours we are forced to conclude that about twice as much excess neutral sulphur is excreted as can be accounted for as methionine. The apparent discrepancy between our findings and those of Medes (1937), who concluded that there was no significant rise in the neutral sulphur after giving 3.2 g. methionine by mouth, may be due

to the difference in dosage, route of administration, or possibly methods of determining total sulphur.

The third point requiring consideration concerns the very definite lag in the excretion of neutral sulphur after the first infusion. There was no rise during the 12 hours following the infusion (Period III), but during the subsequent 24 hours (Period IV) the greater part of the methionine sulphur was excreted as neutral sulphur. There are two possible explanations of this lag in the excretion of neutral sulphur. The methionine might have been retained, presumably in the liver, for a period of at least 12 hours, during which time it was performing some unusual function. At the end of this time excretion of the breakdown products as neutral sulphur began. It is of interest to note that it was precisely during this 12-hour period that the liver was retracting rapidly and the clinical condition of the patient undergoing marked improvement, as we have reported previously. The other explanation is that put forward by Stewart and O'Brien (1944). They suggested that the toxic effect of carbon tetrachloride on the kidney produced some degree of retention during the early period, and that during a subsequent diuresis the accumulated metabolic products were washed out in the following 24 hours. If there had been kidney damage during the earlier period some evidence of this should have been present. In fact, the secretion rate was normal (53 ml./hour for a night specimen), the concentration of sulphate was normal, and the level of non-protein nitrogen in the blood was not suggestive of retention. The evidence, incomplete though it is, is more suggestive of normal than of abnormal function. The major point in our thesis, however, was that the absolute amount of neutral sulphur excreted was abnormally high. It seems unlikely that kidney damage, by causing retention of methionine within the body, could diminish the rate of oxidation of methionine sulphur by the liver. One would have expected that the liver, having the methionine available for a longer period than usual, would have been more rather than less successful in its endeavour to oxidize the methionine sulphur. However, in order to avoid this point we propose to compare our findings on the two occasions over the whole period of about 40 hours from the beginning of the infusion.

In Table II the average hourly excretion of total sulphate and sulphur is given for the pre-transfusion period, for the subsequent period of about 40 hours, and for the two following

TABLE II

1st Admission					2nd Admission				
Period	Time in Hours	Average Hourly Excretion			Period	Time in Hours	Average Hourly Excretion		
		Total Sulphur	Total Sulphate	Neutral Sulphur			Total Sulphur	Total Sulphate	Neutral Sulphur
I	3½	0.0177	0.0117	0.0060	I	—	—	—	
II-IV	39½	0.0910	0.0489	0.0418	II-IV	41½	0.1081	0.0805	0.0277
V	24	0.0421	0.0321	0.0100	V	24	0.0508	0.0354	0.0153
VI	24	0.0450	0.0408	0.0047	VI	24	0.0476	0.0357	0.0120

periods of 24 hours each. It is clear from an examination of this table, together with the accompanying diagram, that after the first infusion there was a marked rise in the neutral sulphur excretion and a much smaller rise in the sulphate excretion. After the second infusion these findings were reversed —by far the greater rise occurring in the sulphate excretion. In order to determine quantitatively the way in which the methionine sulphur was excreted it is necessary to assess the rate at which the two sulphur fractions would have been excreted had no extra methionine been given. Unfortunately it is not possible to determine the basal rate of sulphate excretion on either occasion. With regard to the first occasion, the picture is complicated by the fact that the patient had been starved for 24 hours previous to the infusion and subsequently received further methionine by mouth. On the second occasion it was intended that the patient's intake of sulphur in the food should be maintained at a steady known level, but in fact this was impracticable at the time he was readmitted to hospital. However, we have been primarily concerned with the excretion of neutral sulphur, which is relatively unaffected by dietary factors. From Table I it is seen that basal neutral sulphur excretion during the first investigation

was not greater than 0.006 g./hour (the excretion of 0.01 in Period V is probably due to the fact that the patient was given further methionine on this day) and during the second investigation was not less than 0.012 g./hour. Calculating from these figures, we can determine the percentage of methionine sulphur recovered as neutral sulphur after the two infusions. These figures are given in Table III.

TABLE III

	Excretion of Neutral Sulphur in g./hour			Time in Hours	Total Excess Neutral Sulphur	Methionine Sulphur recovered as Neutral Sulphur
	Basal Rate	Total Rate	Difference			
1st admission	0.006	0.0418	0.0358	39½	1.412	66% (minimum)
2nd admission	0.012	0.0277	0.0157	41½	0.620	29% (maximum)

We have no evidence as to the compound or compounds which constituted this excess neutral sulphur on the first occasion. We have given above our reasons for believing that not more than 0.322 g. was present as methionine on either occasion, and that it was probably less after the first infusion. On the second occasion we determined the urinary amino-nitrogen output using the ninhydrin method (van Slyke *et al.*, 1943). These figures, together with the total nitrogen output, are given in Table IV. It will be seen that for the pre-transfusion period and the two final 24-hour periods the

TABLE IV

Urinary Nitrogen Excretion: 2nd Admission

Period	Time in Hours	Urine Volume (ml.)	Total Nitrogen (g.)	Amino-nitrogen -Nitrogen (mg./litre)	Total Amino-nitrogen -Nitrogen (g.)
I	—	—	—	88.5	—
II	4	590	15.6	196.4	0.116
III	13½	1,440	18.4	149.8	0.216
IV	24	2,180	17.1	106.2	0.232
V	24	2,075	14.7	77.9	0.162
VI	24	1,510	—	99.1	0.150

concentration of amino-nitrogen averaged 88 mg./litre urine. If we assume that the basal excretion rate in the post-transfusion period approximated to this figure, we find an excretion of excess amino-nitrogen=0.194 g., which would be sufficient to account for 0.443 g. sulphur in the form of an amino-acid containing equivalent weights of nitrogen and sulphur. If we subtract 0.322 g. sulphur (the maximum amount attributed to the methionine present in the urine) from 0.620 (the total excess neutral sulphur) we find 0.298 g. neutral sulphur not accounted for. It is clear, therefore, that this excess sulphur could be accounted for as an amino-acid. In view of the many uncontrolled factors influencing the excretion of amino-nitrogen, these figures cannot be regarded as more than suggestive.

Summary

A case of acute carbon tetrachloride poisoning reported previously has been reinvestigated six months after the original incident.

The patient showed no signs of impaired liver or kidney function.

The excretion of neutral sulphur after an infusion of methionine was markedly different from that observed after a similar infusion given at the time of the original incident.

The possible significance of this finding has been discussed.

REFERENCES

- Beattie, J., Herbert, P. H., Wechtel, C., and Steele, C. W. (1944). *British Medical Journal*, **1**, 209.
 Folin, O. (1905). *J. biol. Chem.*, **1**, 131.
 Medes, G. (1937). *Biochem. J.*, **31**, 1330.
 Pirie, N. W. (1932). *Ibid.*, **26**, 2041.
 Stewart, A., and O'Brien, J. R. P. (1944). *British Medical Journal*, **1**, 336.
 van Slyke, D. D., MacFadyen, D. A., and Hamilton, P. B. (1943). *J. biol. Chem.*, **150**, 251.

Recently we published a note on the aims of the medical society founded by the L.C.C. medical staff. Nearly 300 of the Council's medical staff applied for foundation membership, including doctors now in the Services. Sir Allen Daley is the president and Mr. G. F. Stebbing has been nominated as chairman. Full membership is open to whole-time L.C.C. medical officers; associate membership is open to medical practitioners attached to the L.C.C. medical service; and honorary membership is open, among others, to the medical members of the Council. The inaugural meeting is to be held at the County Hall on Thursday, Jan. 11, at 4.30 p.m. The acting hon. secretary is Dr. Eli Davis, St. Andrew's Hospital, Bow, E.3.

A CRITIQUE OF GASTROSCOPY

BY

NORMAN C. TANNER, F.R.C.S.

Surgical Specialist, L.C.C. St. James' Hospital

Now, just over a decade since the introduction of the flexible gastroscope and safer gastroscopy, it is well worth while that users of the instrument should review their cases and consider how this method compares with other means of examination. Although most reports by experienced users are enthusiastic, different clinics give conflicting views as to the extent of its value; but this is to be expected when one considers how the nature of the gastric disease encountered in an urban municipal hospital varies from that encountered, for example, in a clinic catering for private well-to-do patients or the patients of a military hospital. In the clinic at St. James' Hospital the percentage of dyspeptics who eventually prove to have a chronic gastric ulcer is so high that one feels that the instrument has become indispensable.

It is easy but often unwise to develop a predilection for a particular mode of examination or therapy, and so, in order to discover if my partiality is warranted, I have recently reviewed the gastroscopic examinations carried out personally from the beginning of this war until December, 1943, at this clinic.

In the first 950 cases the Schindler instrument was used, and thereafter the Hermon Taylor model. I do not propose to discuss the relative merits of the instruments beyond confirming the advantages originally claimed by Mr. Hermon Taylor, though I would suggest it requires a little more skill in the passage and is less suitable for mild degrees of kyphosis. It has an advantage I believe not originally claimed—namely, that introduction through deformed or distorted stomachs is often possible under vision. It cannot be said to have entirely abolished the "blind" area, but it has done much to diminish it.

In the period under review the number of gastroscopic examinations was 2,200, and these were made on 1,730 patients. The 470 repeat examinations were mainly to follow the progress of the ulcers while under medical treatment, to confirm healing, to observe relapses, and, less frequently, to confirm doubtful diagnoses, particularly that of carcinoma.

Examination of the 1,730 patients showed, or subsequently showed, the following conditions:

Gastric ulcer alone	589
Gastric and duodenal ulcer	39
Gastric ulcer and diverticulum	3
Post-operative stomach	77
Gastric carcinoma	101
Gastritis	267
Mucosal tumours	7
Submucosal tumours	8
Gastric diverticulum alone	2
Extragastic tumour	3
Multiple telangiectases of stomach	1
Gastric urticaria	1
Volvulus of stomach	1
Duodenal ulcer	296
Duodenal diverticulum	4
Cirrhosis of liver	3
Functional or extragastric dyspepsia with normal stomach	262
Failed or incomplete examination	66

Gastric Ulcer

Although there has been a tendency to regard the gastroscope as an instrument chiefly for the diagnosis of gastritis and rarities, in our own clinic its main usage is in the diagnosis and observation of gastric ulcer. Of the 631 gastric ulcers no fewer than 159 were diagnosed by gastroscopy alone and had apparently normal radiographs—the latter examinations being carried out by a number of expert radiologists. There are several reasons for the difficulty in the diagnosis of many of these gastric ulcers. In the first place, acute ulcers may be too shallow to retain barium, or, particularly after a haemorrhage, the base may be filled with blood-clot, which prevents the entry of barium to the crater. Again, if one waits till the patient is in good general condition after a haemorrhage before subjecting him to investigation, the ulcer may be healed and the scar be missed radiologically. In such cases gastroscopy may show a well-marked cicatrix, rendering the cause of the bleeding evident; though it is on the whole more