evidence in this differentiation, although the usefulness of this test has been disputed (Milne, 1951 ; Dent, 1953 ; MacGregor and Whitehead, 1954).

Of great interest, however, is the finding in our case of normal or high levels of calcium excretion in the urine. Reviews of published cases of idiopathic hypoparathyroidism (Lachmann, 1941 ; Steinberg and Waldron, 1952) are reticent on the matter of urinary calcium content. The records of most cases contain bare statements that the Sulkowitch test was either "negative" or "faintly positive"—findings which, according to Albright and Reifenstein (1948), indicate blood calcium levels of "below 7.5 mg. per 100 ml." They further admit, however, that certain individuals apparently have a low renal threshold for calcium excretion, and mention, without further details, three patients with hypoparathyroidism who excreted large amounts of calcium in the urine at low levels of serum calcium.

It would appear preferable, where possible, in further studies of cases of hypoparathyroidism to substitute for the Sulkowitch test the more precise assay of daily calcium excretion. It does not seem to us adequate to regulate the calciferol dosage by the Sulkowitch test without periodic checks upon the serum calcium level. In our own case the absence of other urinary abnormality, together with the increase in urinary calcium excretion parallel with elevation of the serum calcium, suggests an abnormality of renal threshold for calcium, an "idiopathic hypercalciuria." There is no evidence of osteoporosis, and the radiological abnormalities typical of hypoparathyroidism suggest that the hypercalciuria is no more than an incidental unassociated abnormality.

Summary

A case of idiopathic hypoparathyroidism presenting with epilepsy is described.

Restoration of normal serum levels of calcium and phosphate was achieved with calciferol in high dosage.

The unusual finding of a high normal daily calcium excretion in the urine before treatment is discussed.

Our thanks are due to Mr. W. M. Nichols for permission to publish this case and for his continued encouragement, to Dr. M. MacLeod for his advice and criticism, and to Mr. Topp for the photographs. We are particularly indebted to Dr. F. A. Macrae, Kyle of Lochalsh, for his unfailing help in the follow-up of the case.

REFERENCES

Albright, F., and Ellsworth, R. (1929). *J. clin. Invest.*, **7**, 183.
—— and Reifenstein, E. C. (1948). *The Parathyroid Glands and Metabolic Bone Disease.* Williams and Wilkins, Baltimore.
Blohm, R. W., Wurl, O. A., Gillespie, J. O., and Escamilla, R. F. (1953). *J. clin. Endocr.*, **13**, 519.
Dent, C. E. (1953). *Proc. roy. Soc. Med.*, **46**, 291.
Eaton, L. M., and Haines, S. F. (1939). *Proc. Mayo Clin.*, **14**, 48.
Lachmann, A. (1941). *Acta med. scand.*, Suppl. 121.
MacGregor, M. E., and Whitehead, T. P. (1954). *Arch. Dis. Childh.*, **29**, 398.
McLean, F. C. (1941). *J. Amer. med. Ass.*, **117**, 609.
Milne, M. D. (1951). *Clin. Sci.*, **10**, 471.
Nordin, B. E. C., and Fraser, R. (1954). Ibid., **13**, 477.
—— —— (1956). In *Ciba Foundation Symposium on Bone Structure and Metabolism*, p. 222. Churchill, London.
Steinberg, H., and Waldron, B. R. (1952). *Medicine (Baltimore)*, **31**, 133.

The Medical Directory for 1959, the 115th annual issue, is now available from Messrs. J. & A. Churchill Ltd., 104 Gloucester Place, London, W.1 (2 parts ; 4 guineas). It contains 91,206 names, an increase of nearly 2,000 over the previous issue.

SERUM HAPTOGLOBINS IN HEPATOBILIARY DISEASE

BY

J. A. OWEN,*† M.D., Ph.D., B.Sc.

IAN R. MACKAY,* M.D., M.R.C.P., M.R.A.C.P.

AND

CATHERINE GOT*

From the Department of Biochemistry, University of Melbourne, and the Clinical Research Unit of the Royal Melbourne Hospital and the Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia

Haptoglobins are globulins which combine with haemoglobin (Polonovski and Jayle, 1940). We have measured serum haptoglobins in 64 patients with hepatobiliary disease and have found that levels are low in parenchymatous liver disease and high in biliary obstruction. We have assessed the measurement of serum haptoglobins as an index of hepatic function in hepatitis and cirrhosis, and as an aid in the differential diagnosis of the jaundiced patient.

Material and Methods

A range of normal values was obtained by analysing sera from 50 healthy blood donors. The 64 patients with hepatobiliary disease were classified as follows: (1) Acute infective hepatitis. (2) Active chronic hepatitis: hepatitis and cirrhosis of uncertain aetiology, including cases of post-hepatitic and post-necrotic cirrhosis. (3) Lupoid hepatitis: active chronic hepatitis and a positive L.E. cell test (Mackay *et al.*, 1956). (4) Nutritional cirrhosis (Laennec's cirrhosis, alcoholic cirrhosis): all patients in this group admitted to a high intake of alcohol. (5) Extrahepatic biliary obstruction due to gallstones, neoplasm of the biliary tract or pancreas, or surgical damage to the common bile duct. None of these patients had biliary cirrhosis. (6) Miscellaneous (see Table I).

Serum haptoglobins were measured by determining the amount of haemoglobin which must be added to serum to saturate the haptoglobins present. Haemoglobin solutions of different concentrations were prepared from washed human erythrocytes lysed with water. 0.1 ml. of each solution was added to 0.2 ml. of the serum to be analysed, giving serum haemoglobin concentrations varying from 0 to 400 mg. per 100 ml. The mixtures were analysed by paper electrophoresis (phosphate buffer 0.025 M, *p*H 6.5, temperature 3–5° C., potential gradient 10 v. per cm., duration four hours). Under these conditions the haemoglobin-haptoglobin complex migrates towards the anode while haemoglobin remains at the origin. After electrophoresis the strips were stained with a dianisidine reagent (Owen *et al.*, 1958) and the minimal amount of added haemoglobin which produced a zone of free haemoglobin was noted. Results, in mg. of bound haemoglobin per 100 ml. of serum, were expressed as the range between the amount of added haemoglobin which just failed to produce a zone of free haemoglobin on the paper strip and the amount which was just sufficient for this (Fig. 1).

*Working with the aid of a grant from the National Health and Medical Research Council of Australia.

†Now at the Biochemistry Laboratory, St. Vincent's Hospital, Melbourne.

Serum glutamic oxalacetic transaminase was determined by the method of Reitman and Frankel (1957), serum albumin was separated as described by Hawk *et al.* (1937) and measured by the biuret method of Gornall *et al.* (1949), and the serum bilirubin method was that of Malloy and Evelyn (1937).

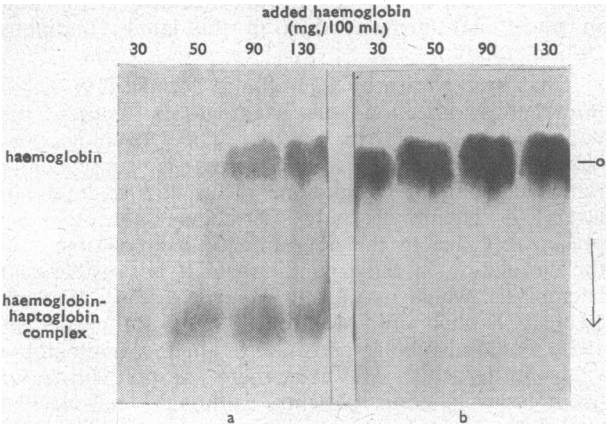

FIG. 1.—Electrophoretic determination of haptoglobins (strips stained with dianisidine reagent). O indicates the origin; the arrow indicates direction of migration. Haptoglobin values: (*a*) 50–90 mg. per 100 ml.; (*b*) 0–30 mg. per 100 ml. In strip (*a*) 90 mg. per 100 ml. of added haemoglobin has saturated the serum haptoglobin as shown by the presence of free haemoglobin. In strip (*b*) 30 mg. per 100 ml. of added haemoglobin was sufficient for this.

Results

Results of haptoglobin determinations for all subjects are shown in Table I. The mean value in the normal subjects was 84 mg. per 100 ml., which agrees with that obtained by Laurell and Nyman (1957) using a similar method, and with that obtained by Jayle and Boussier (1955) and by Nyman (1958a) using a method based on the peroxidase activity of the haemoglobin-haptoglobin complex.

TABLE I.—*Serum Haptoglobin Levels in Normal Subjects and in Hepatobiliary Disease*

Condition	Total No. of Cases	Case Distribution for Different Ranges of Serum Haptoglobin Level (as Haemoglobin in mg./100 ml.). (Figures Indicate Number of Patients)							Mean Haptoglobin Level
		0–15	15–30	30–50	50–90	90–130	130–200	>200	
Normal subjects	50	—	—	7	20	19	4	—	84
Acute infective hepatitis	5	—	2	1	2	—	—	—	45
Active chronic ,,	16	5	3	2	3	1	2	—	42
Lupoid hepatitis	10	5	2	1	2	—	—	—	26
Nutritional cirrhosis	13	2	1	3	2	5	—	—	65
Extrahepatic biliary obstruction	12	—	—	—	1	3	4	4*	185
Miscellaneous:									
Metastatic carcinoma of liver	2	—	—	—	—	—	2	—	—
Primary biliary cirrhosis	1	—	—	—	—	1	—	—	—
Obstructive ,, ,,	2	—	2	—	—	—	—	—	—
Indeterminate cirrhosis	1	—	—	—	1	—	—	—	—
Obstructive hepatic necrosis	1	1	—	—	—	—	—	—	—
Haemochromatosis	1	—	—	1	—	—	—	—	—

* Values were, respectively, 200–250, 300–400, 300–400, and 400–500 mg./100 ml.

Acute Infective Hepatitis.—In the five patients, serum haptoglobin levels were either low-normal or low.

Active Chronic Hepatitis and Lupoid Hepatitis.—Of 26 cases studied, 18 had serum haptoglobins in the range of 0–50 mg. per 100 ml., and 15 had values below 30 mg. per 100 ml. In the few cases having haptoglobin values within the normal range, liver function was good, whereas low values were obtained in patients with more severe liver involvement. Four critically ill patients in this group had no demonstrable serum haptoglobins.

Nutritional Cirrhosis.—Of 13 cases, three had low levels (<30 mg. per 100 ml.) whilst the remainder had normal levels.

Extrahepatic Biliary Obstruction.—In this group haptoglobin levels were either normal or high; four patients had considerably elevated levels (Table I, footnote).

Miscellaneous.—In two patients with metastatic carcinomatosis of the liver, haptoglobin values were high-normal; in two patients with obstructive biliary cirrhosis values were low. Haptoglobin values in other liver conditions are presented in Table I.

In certain patients with chronic hepatitis, serum haptoglobins have been measured at intervals; the results (Table II) indicate that changes in serum haptoglobin level tended to parallel changes in clinical status.

TABLE II.—*Serial Serum Haptoglobin Levels in Liver Disease*

Case	Diagnosis*	Period of Observation (Months)	Haptoglobin Level (as Hb in mg./100 ml.)	Clinical Course
DEL	LH	0	0–15	Improved with cortisone
		7	50–70	
EGL	ACH	0	0–15	,, ,,
		10	90–130	
MAG	LH	0	50–70	,, ,,
		9	110–150	
		11	130–150	
TIN	LH	0	50–90	,, ,,
			90–130	
BUG	NC	0	15–30	No response to medical treatment, including prednisolone
		4	0–15	
SAV	ACH	0	0–15	Compensated cirrhosis; no change
		12	0–15	
GRL	NC	0	30–50	Deterioration
		1	0	

* LH = Lupoid hepatitis. ACH = Active chronic hepatitis. NC = Nutritional cirrhosis.

In 32 patients (excluding the miscellaneous group) jaundice was present (serum bilirubin >2 mg. per 100 ml.). In 14 of these jaundice was due to acute infective hepatitis, active chronic hepatitis, or lupoid hepatitis; the mean haptoglobin level in this group was 35 mg. per 100 ml., and all but one had values below 90 mg. per 100 ml. (Table III). Jaundice was due to biliary obstruction in 12 cases; the mean haptoglobin level in this group was 185 mg. per 100 ml., and all but one had values above 90 mg. per 100 ml. In cases of nutritional cirrhosis with jaundice, values were intermediate.

In certain patients with hepatitis and cirrhosis the serum haptoglobin level was compared with the serum

TABLE III.—*Distribution of Serum Haptoglobin Levels in 32 Patients with Jaundice*

Condition	Total No. of Cases	Case Distribution for Different Ranges of Serum Haptoglobin Level (as Hb in mg./100 ml.)			
		0–50	50–90	90–130	>130
Acute infective hepatitis, active chronic hepatitis, lupoid hepatitis	14	8	5	–	1
Extrahepatic biliary obstruction	12	–	1	3	8
Nutritional cirrhosis	6	2	–	4	–

albumin level (Fig. 2), and with the level of serum glutamic oxalacetic transaminase (Fig. 3). The data suggest that low haptoglobin levels were associated with advanced parenchymal damage as indicated by low serum albumin levels (Fig. 2), and in a less consistent manner with active necrosis of the liver, as indicated by high transaminase values (Fig. 3).

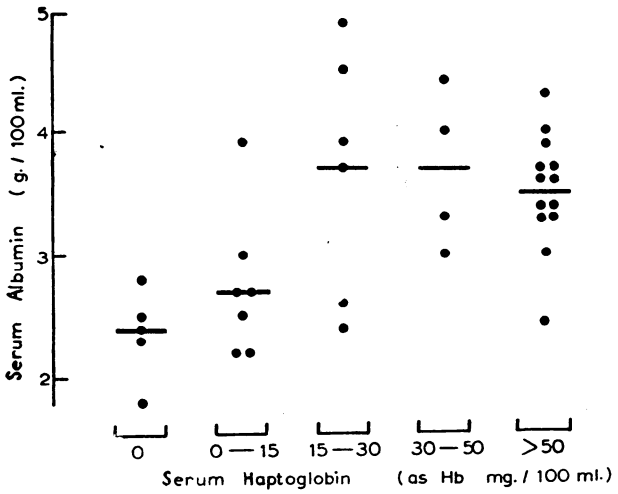

FIG. 2.—Comparison of serum albumin level with serum haptoglobin level. Horizontal lines indicate mean values for each group. Low serum albumin levels are associated with low levels of serum haptoglobin.

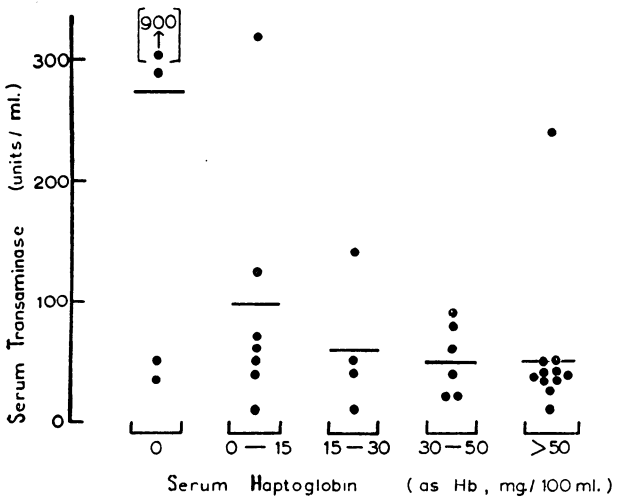

FIG. 3.—Comparison of serum transaminase activity with serum haptoglobin level. Horizontal lines indicate mean values in each group. There is some correlation of low serum haptoglobin levels with raised transaminase levels.

Discussion

Low haptoglobin levels in serum have been found in haemolytic anaemia (Polonovski, 1945; Allison and ap Rees, 1957; Nosslin and Nyman, 1958) and in pernicious anaemia (Nyman, 1957). High levels have been reported in inflammatory and neoplastic disorders by Jayle and Boussier (1955). There are also brief references to low haptoglobin values being found in hepatocellular failure (Jayle and Boussier, 1955; Nyman, 1958b). Our results confirm the latter finding and further indicate that determination of serum haptoglobins may be of value in the following clinical situations: firstly, in assessing the degree and progress of hepatocellular damage in patients with hepatitis and cirrhosis; and, secondly, in the differential diagnosis of jaundice, wherein low levels suggest parenchymal damage and high levels suggest biliary obstruction. Nutritional cirrhosis was less often associated with low haptoglobin values than was active chronic hepatitis or lupoid hepatitis, and this corresponds with our experience that there is less disturbance of liver function in nutritional cirrhosis than in the latter conditions (Wood, 1959).

It has been shown by Laurell and Nyman (1957) that intravenous injection of haemoglobin causes the haptoglobin level to fall. The haemoglobin–haptoglobin complex which forms is subsequently removed from the circulation. Thus, low haptoglobin levels in haemolytic and pernicious anaemia are presumably due to the liberation of haemoglobin into the circulation in these conditions. It is possible that haemolysis, which may occur in liver disease (Watson, 1939; Chaplin and Mollison, 1953; Raffensperger, 1958), could also be responsible for the low haptoglobin values in hepatitis. However, there was no evidence of haemolysis in our patients, although cell-survival studies were not done.

It should be noted that with the method used any haemoglobin already present in the serum as a result of *in vitro* haemolysis reduces the result. However, this was not the cause of the low values found in hepatocellular disease, since sera with visible haemolysis were not analysed, whilst doubtful specimens were analysed without the addition of haemoglobin and those containing appreciable amounts of haemoglobin were discarded.

Smithies (1955) has shown that persons can be divided into three distinct groups on the basis of the electrophoretic haptoglobin pattern, and Nyman (1958a) has reported that mean haptoglobin values in normal persons depend somewhat on the haptoglobin type. We did not take into account the haptoglobin type of our patients, since determination of this requires starch-gel electrophoresis, which is not, as yet, a procedure suitable for the average hospital laboratory. We do not think, however, that this omission has seriously influenced our assessment of serum haptoglobin analysis.

We believe that low haptoglobin levels in liver disease are the result of hepatocellular failure. Low levels of plasma albumin in liver disease have been attributed directly to a reduced capacity of the damaged liver to synthesize albumin, and this may also apply to haptoglobins. At present we can offer no explanation for the abnormally high values found in patients with obstructive jaundice.

Summary

Serum haptoglobins have been estimated by a simple paper electrophoretic method in 50 normal persons and in 64 patients with hepatobiliary disease.

Haptoglobin values were low in hepatocellular failure and high in biliary obstruction and secondary carcinomatosis.

Measurement of the serum haptoglobin level is of value in assessing the degree of hepatocellular damage.

The test is useful in the differential diagnosis of jaundice.

Members of the honorary medical staff of the Royal Melbourne Hospital kindly permitted access to their cases.

We are indebted to Dr. Sara Weiden and Miss Beryl Splatt for biochemical data, and to Miss Hania Ayzner for technical assistance.

REFERENCES

Allison, A. C., and ap Rees, W. (1957). *Brit. med. J.*, **2**, 1137.
Chaplin, H., jun., and Mollison, P. L. (1953). *Clin. Sci.*, **12**, 351.
Gornall, A. G., Bardawill, C. J., and David, M. M. (1949). *J. biol. Chem.*, **177**, 751.
Hawk, P. B., Bergeim, O., Oser, B. L., and Cole, A. G. (1937). *Practical Physiological Chemistry*, 11th ed. Blakiston, Philadelphia.
Jayle, M. F., and Boussier, G. (1955). *Expos. ann. Biochim. méd.*, **17**, 157. Quoted by Laurell and Nyman (1957).
Laurell, C-B., and Nyman, M. (1957). *Blood*, **12**, 493.
Mackay, I. R., Taft, L. I., and Cowling, D. C. (1956). *Lancet*, **2**, 1323.
Malloy, H. T., and Evelyn, K. A. (1937). *J. biol. Chem.*, **119**, 481.
Nosslin, B. F., and Nyman, M. (1958). *Lancet*, **1**, 1000.
Nyman, M. (1957). *Scand. J. clin. Lab. Invest.*, **9**, 168.
—— (1958a). *Clin. chim. Acta*, **3**, 111.
—— (1958b). Unpublished data, quoted by Nosslin and Nyman (1958).
Owen, J. A., Silberman, H. J., and Got, C. (1958). *Nature (Lond.)*, **182**, 1373.
Polonovski, M. (1945). *Schweiz. med. Wschr.*, 75, 859.
—— and Jayle, M. F. (1940). *C.R. Acad. Sci. (Paris)*, **211**, 517.
Raffensperger, E. C. (1958). *Ann. intern. Med.*, **48**, 1243.
Reitman, S., and Frankel, S. (1957). *Amer. J. clin. Path.*, **28**, 56.
Smithies, O. (1955). *Biochem. J.*, **61**, 629.
Watson, C. J. (1939). *Ann. intern. Med.*, **12**, 1782.
Wood, I. J. (1959). Submitted for publication.

Medical Memoranda

Retention of Islets of Sensation in Cervical Cord Injury

The following two cases are reported because of their interest and because I have failed to find a note of similar cases.

CASE 1

At midday on December 6, 1947, a farmer aged 52 was out hunting. While walking his horse on the hard road from one draw to another it suddenly pecked and he was thrown to the ground. He immediately became helpless and was admitted to hospital. He arrived at 1.5 p.m. and I saw him soon afterwards. He was conscious, co-operative, and sensible, and his only complaint was that he had lost the use of his limbs. It was difficult to know exactly what had happened, but from the appearance of his hard hat it was assumed that he had landed on the back of his head.

On examination there was no sensation in his body or in the arms or legs, and there was a total quadriplegia. The reflexes in the legs were brisk and an ankle clonus was present. The plantar responses were extensor, and it was noticed that touch sensation was still present in the soles of both feet. An *x*-ray examination did not help in determining the anatomical lesion. At 3.30 p.m. the area of loss of sensation had diminished and was now from below the first ribs and below the insertion of the deltoid muscles. Sling traction was applied, but this caused so much discomfort that after some hours it was replaced by skeletal traction by calliper, and this made the patient much more comfortable. His condition, however, gradually deteriorated and he died at 7 p.m. on December 8.

A post-mortem examination was made by Dr. Ian Mackenzie. It was found that, although there was no fracture, the body of the fourth cervical vertebra could be moved on the body of the fifth because there was some tearing of the anterior longitudinal ligament. In the cervical region there was some extradural haemorrhage and the cord appeared to be congested. Section of the cord showed some blood in the central canal. There was nothing otherwise significant in the examination.

CASE 2

At 8 p.m. on April 3, 1955, a miner aged 55 stepped on the colliery belt, which gave way and he fell on the pans. He immediately became helpless and was admitted to hospital. He arrived at 10.30 p.m. and I saw him soon after.

On examination there was a quadriplegia and an area of anaesthesia below a line from the left axilla to the right anterior spine of the pelvis. There was also anaesthesia on the inner surfaces of both arms and the whole of the forearms. The reflexes were exaggerated and the plantar responses were extensor. When ascertaining the nature of the plantar responses it was noted that epicritic and protopathic sensation was still present in the soles of both feet. An *x*-ray examination did not help in deciding on the anatomical lesion. Sling traction was applied and for a day or two the patient, who was quite co-operative, appeared to be holding his own, but on April 7 signs developed at both bases and he deteriorated, dying on April 9.

A post-mortem examination was made by Dr. E. W. N. Trounson, the material findings being as follows: The anterior longitudinal ligament was ruptured between the sixth and seventh cervical vertebrae and there was a horizontal tear in the lower part of the intervertebral disk. The vertebral bodies above were hyperextended. External examination of the cord showed barely detectable contusions in the lower cervical region. The lungs were congested and grossly oedematous, with widespread ill-defined pneumonic consolidation at both bases. There was also fairly well marked dust pigmentation with focal emphysema. Dr. Trounson attributed death to hypostatic pneumonia and contusion of the spinal cord. The cord was subsequently examined microscopically, and this showed some tiny haemorrhages within its substance.

COMMENT

When I first saw Case 1 my impression was that the patient had probably sustained a contusion of the cord from which he was possibly going to recover, but I had never before found such a large anaesthetic area containing islands of sensation in the soles of the feet. As I knew that Mr. Leslie Morris, of Leicester, had a large experience of cord injuries in miners, I discussed the case with him over the telephone and he was so interested that he came to see the patient and confirmed my findings. When the second patient developed signs in the chest I asked Dr. Wakes Miller to see him, and he also was most interested in the fact that these islands of sensation had persisted.

Both patients were men of approximately the same age with similar lesions. Both had sustained hyperextension injuries in the cervical region with tears of the anterior longitudinal ligament and consequent damage to the cervical cord. In both patients the fibres conveying sensation from the soles of the feet had escaped damage. These, I understand, run on the surface of the cord posteriorly in this region. It is not difficult, therefore, to understand that they would be the last to sustain damage by hyperextension.

These two cases may have exhibited a rare phenomenon, but I cannot help feeling that retention of sensation in the soles of the feet may persist in cervical cord injuries much more often and is overlooked when the loss-of-sensation area is mapped out. It was not until I had noted it in the first case that I looked for it in others.

D. S. PRACY, F.R.C.S.Ed.,
Formerly Surgeon, Nuneaton and Coventry and Warwickshire Hospitals.