Summary

In a statistically controlled double-blind trial of beclamide in 13 patients suffering from uncontrolled major or temporal lobe epilepsy it was shown that that drug, in a dosage of 3 g. daily, was significantly more efficient than an inert tablet, reducing the number of seizures to 75% of their previous frequency without any noteworthy side-effects. Control (inert) tablets were shown not to have any psychological placebo effect. Little improvement occurred on increasing the dosage of beclamide from 3 g. to 4 g. a day, but this increased dosage was given for a relatively short period and the evidence on this point is inconclusive.

It is concluded that beclamide has a significant anti-convulsant effect, but in view of the high cost of this remedy it should be used only in epileptic patients who have failed to respond to other remedies. It appears that the drug may safely be given in combination with other anticonvulsants.

We thank Dr. H. G. Miller for allowing us to include in the trial patients who were under his care; Miss Garnett, chief pharmacist, Royal Victorial Infirmary, for her co-operation in arranging the double-blind controlled trial; and Dr. S. Phillips and Rona Laboratories Ltd. for supplying the beclamide and identical control tablets.

REFERENCES

- Hawkes, C. D. (1952). *Arch. Neurol. Psychiat. (Chicago)*, **67**, 815.
 Hoenig, J., Crotty, I. M., and Chisholm-Batten, W. R. (1956). *J. ment. Sci.*, **102**, 105.
 Merlis, S., and Martin, D. W. (1956). *Psychiat. Quart.*, **30**, 387.
 Quenouille, M. H. (1950). *Introductory Statistics*, p. 164. Butterworth-Springer, London.
 Robinson, L. R. (1957). *Brit. med. J.*, **1**, 1099.
 Sharpe, D. S., Dutton, G., and Mirrey, J. R. (1958). *Ibid.*, **1**, 1044.

RENAL FAILURE IN HYPERCALCAEMIC SARCOIDOSIS

BY

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Hypercalcaemic sarcoidosis is associated in many cases with renal failure. Sarcoid granulomatous infiltration of the kidneys is not uncommon, but the lesion is usually focal and not extensive. Berger and Relman (1955) reported a case of sarcoidosis and renal insufficiency showing granulomatous infiltration of the kidneys without nephrocalcinosis or associated renal disease. Other diseases, such as pyelonephritis (Dent *et al.*, 1953) and renal tuberculosis (Longcope and Freiman, 1952), may be present to account for renal insufficiency in patients with disseminated sarcoidosis. Klatzkin and Gordon (1953) suggested that renal failure in sarcoidosis may be due to hypercalcaemia and nephrocalcinosis. The association of nephrocalcinosis and renal failure in hypercalcaemic sarcoidosis has been reported (Longcope and Freiman, 1952; Shulman *et al.*, 1952; Davidson *et al.*, 1954; Scholz and Keating, 1956). In addition, steroid therapy has been followed by reduction of the hypercalcaemia and improvement in renal

function (Shulman *et al.*, 1952; Dent *et al.*, 1953; Gleckler, 1956; Phillips and Fitzpatrick, 1956; Scholz *et al.*, 1957). We report a case of hypercalcaemic sarcoidosis with renal failure. Steroid therapy resulted in improvement in renal function, although serial renal biopsies showed persistence of nephrocalcinosis.

Case Report

A 36-year-old man was admitted to hospital on April 21, 1958. He complained of weakness, polyuria, polydipsia, insomnia, and exertional dyspnoea, gradually increasing over two years. The past medical history revealed that in 1947 he developed a polyarthritis which responded poorly to salicylates. In 1953 a pulmonary lesion was detected by x-ray examination, and on the basis of follow-up radiological and sputum studies a diagnosis of sarcoidosis was made. He had no history of excessive intake of milk, alkalis, or vitamin D.

The physical examination revealed an asthenic, sallow man. There were no skin lesions. Band keratitis was absent. The blood pressure was 140/90 mm. Hg; pulse rate 80 a minute; temperature 98.6° F. (37° C.); respirations 22 a minute. There was enlargement of the spleen to 4 cm. below the left costal margin.

Laboratory examination showed a blood haemoglobin of 10.5 g./100 ml., and white-cell count of 5,000/c.mm., with a normal cell distribution. The sedimentation rate was 20 mm./hour (normal 2-6 mm./hour). Red-cell indices showed a normochromic normocytic anaemia, and the direct Coombs test was negative. The specific gravity of the urine was 1.010 and the daily urine volumes averaged 2,800 ml. Water deprivation did not correct the isosthenuric polyuria. There was no proteinuria, cylinduria, haematuria, or pyuria. Urine was sterile on culture. Mantoux reaction 1:1,000 was negative. X-ray examination of the chest revealed diffuse fibrosis scattered throughout both pulmonary fields. X-ray studies of the hands, feet, and spine showed no abnormality. A plain x-ray film of the abdomen disclosed a small calculus in the lower pole of the right kidney. An intravenous pyelogram showed poor dye excretion by both kidneys. Renal tomography did not demonstrate calcinosis. The kidneys appeared normal in size and position. An electrocardiogram was normal. The blood urea was 93 mg./100 ml. Serum calcium was 13.2 mg./100 ml.; serum phosphorus, 4 mg./100 ml.; serum alkaline phosphatase, 8 King-Armstrong units; total protein, 7.7 g./100 ml. (serum albumin 4.3 g., serum globulin 3.4 g.); electrophoretic pattern showed an increase in gamma-globulin; serum bilirubin, 0.2 mg./100 ml.; thymol turbidity, 0.5 unit; zinc sulphate, 5.8 units; blood cholesterol, 58 mg./100 ml.

A left aspiration renal biopsy (Fig. 1) was performed by one of us (D.J.D.) with a Franklin modification of the

FIG. 1.—Renal biopsy before commencement of cortisone. Nephrocalcinosis with increase in interstitial connective tissue and cellular infiltration. (Haematoxylin and eosin. $\times 103$.)

Vim-Silverman needle. The tissue contained 22 glomeruli. Nephrocalcinosis was present; five glomeruli were fibrosed, and the others appeared normal. There were patches of fibrous tissue with inflammatory cell infiltration which could be related to the calcinosis or represent the stigmata of chronic pyelonephritis. No sarcoid granulomatous infiltration was seen.

The patient was treated with cortisone, 300 mg. the first day, 200 mg. the second day, and 100 mg. the third and subsequent days. One month after treatment the blood urea was 42 mg./100 ml., and the serum calcium 11.2 mg./100 ml. (Fig. 2). The urine had a specific gravity of 1.018. There was no polyuria. A water-concentration test demonstrated normal renal concentrating ability. A left aspiration renal biopsy was then repeated. The tissue contained 10 glomeruli (Fig. 3). There was no change in the histological features or in the severity of the nephrocalcinosis.

FIG. 2.—Levels of serum calcium and blood urea after treatment with cortisone.

FIG. 3.—Serial renal biopsy performed four weeks after commencement of cortisone. There is no change in the histological severity of nephrocalcinosis. (Haematoxylin and eosin. $\times 75$.)

Discussion

Hypercalcaemia occurs in 20% of cases of sarcoidosis (Longcope and Freiman, 1952), but the mechanism is uncertain. Recent studies have demonstrated a disturbance of metabolism in sarcoidosis characterized by an excessive alimentary absorption of calcium (Henneman *et al.*, 1954; Anderson *et al.*, 1954; Scholz *et al.*, 1957). Increased absorption of calcium from the gut may be due to an abnormal sensitivity to endogenous vitamin D (Anderson *et al.*, 1954) or to excessive production of a vitamin-D-like substance (Henneman *et al.*, 1954). Cortisone has been shown to correct this disturbance of calcium metabolism. Following cortisone administration there is increased faecal excretion of calcium associated with a decrease in its urinary excretion and a return of the serum level to normal limits (Anderson *et al.*, 1954; Henneman *et al.*, 1956; Scholz *et al.*, 1957).

The effect of hypercalcaemia on the kidney is the production of nephrocalcinosis and renal insufficiency. Both the duration and the severity of the hypercalcaemia determine the presence and degree of renal calcinosis. This patient had a serum calcium level of 13.2 mg./100 ml. Evidence of renal insufficiency was present, with a blood urea of 93 mg./100 ml. Renal biopsy showed nephrocalcinosis with areas of interstitial fibrosis.

The renal failure that follows nephrocalcinosis differs from that due to the more common types of renal disease (Elsom *et al.*, 1936). Proteinuria, haematuria, cylinduria, and hypertension are unusual in nephrocalcinosis. More commonly found are inordinate weakness, polyuria, polydipsia, and azotaemia. This patient complained of weakness, anorexia, and polyuria. These symptoms may be explained either by hypercalcaemia or by renal insufficiency. Changes of chronic pyelonephritis may be observed in the kidneys at necropsy in patients with nephrocalcinosis. Biopsy of the renal tissue of this patient showed a number of obliterated and fibrosed glomeruli, with areas of fibrous tissue and inflammatory cell infiltration. Whether these changes are a consequence of calcinosis or evidence of chronic pyelonephritis cannot be determined from renal biopsy tissue.

Renal insufficiency in cases of sarcoidosis is commonly ascribed to hypercalcaemia with nephrocalcinosis, without, however, adequate biochemical, radiological, or histological evidence. In a case of sarcoidosis with renal failure and hypercalcaemia, Longcope and Freiman (1952) described the renal lesion found at necropsy as pyelonephritis secondary to nephrolithiasis and nephrocalcinosis. Davidson *et al.* (1954) reported seven cases of nephrocalcinosis with hypercalcaemia due to sarcoidosis. In two cases renal insufficiency was present and nephrocalcinosis was confirmed at necropsy. Shulman *et al.* (1952) found three cases of renal insufficiency with hypercalcaemia in sarcoidosis. In one case nephrocalcinosis was present at necropsy. In the present case radiological examination of the kidneys, including tomography, failed to reveal calcinosis, which was, however, demonstrated by means of aspiration renal biopsy.

Steroid administration in hypercalcaemic sarcoidosis has been shown to result in improved renal function (Shulman *et al.*, 1952; Dent *et al.*, 1953; Gleckler, 1956; Phillips and Fitzpatrick, 1956; Scholz *et al.*, 1957). Phillips and Fitzpatrick (1956) postulated renal calcinosis in those patients in whom improvement was

slow and imperfect after correction of the hypercalcaemia by cortisone. The present case report shows that, in spite of established renal calcinosis, marked and rapid improvement in renal function followed the use of cortisone. There was no change in the degree of renal calcinosis as determined by serial renal biopsy after one month of cortisone therapy, although renal function had returned to normal. The mechanism is therefore unlikely to be the removal of precipitated calcium from the kidney, although this may well be the end-result of continued steroid administration. We suggest that cortisone exerts its beneficial effect on the renal failure of hypercalcaemic sarcoidosis principally by correcting the hypercalcaemia itself.

Summary

A case is reported of sarcoidosis with hypercalcaemia, nephrocalcinosis, nephrolithiasis, and renal failure. Treatment with cortisone resulted in lowering of the serum calcium level to normal and improvement in renal function within one month, although serial renal biopsies showed no change in the degree of nephrocalcinosis during this time.

It is suggested that renal failure in hypercalcaemic sarcoidosis is not necessarily a reflection of irreversible nephron destruction by calcinosis, but that it may result from the high level of circulating calcium itself adversely affecting renal function. Also, the presence of nephrocalcinosis does not necessarily imply that the response to steroid therapy will be unsatisfactory.

We thank Dr. W. Freeborn, general medical superintendent of the Royal North Shore Hospital of Sydney, for allowing us to publish details of this case, and Dr. C. Graham for giving the histopathological report.

REFERENCES

- Anderson, J., Harper, C., Dent, C. H., and Philpot, G. R. (1954). *Lancet*, **2**, 720.
 Berger, K. W., and Relman, A. S. (1955). *New Engl. J. Med.*, **252**, 44.
 Davidson, C. N., Dennis, J. M., McNinch, E. R., Willson, J. K. V., and Brown, W. H. (1954). *Radiology*, **62**, 203.
 Dent, C. E., Flynn, F. V., and Nabarro, J. D. N. (1953). *Brit. med. J.*, **2**, 808.
 Elsom, K. A., Wood, F. C., and Ravdin, I. S. (1936). *Amer. J. med. Sci.*, **191**, 49.
 Gleckler, W. J. (1956). *Ann. intern. Med.*, **44**, 174.
 Henneman, P. H., Carroll, Evelyn L., and Dempsey, Eleanor, F. (1954). *J. clin. Invest.*, **33**, 941.
 ———, Dempsey, Eleanor F., Carroll, Evelyn L., and Albright, F. (1956). *Ibid.*, **35**, 1229.
 Klatskin, G., and Gordon, M. (1953). *Amer. J. Med.*, **15**, 484.
 Longcope, W. T., and Freiman, D. G. (1952). *Medicine (Baltimore)*, **31**, 1.
 Phillips, R. W., and Fitzpatrick, D. P. (1956). *New Engl. J. Med.*, **254**, 1216.
 Scholz, D. A., and Keating, F. R., jun. (1956). *Amer. J. Med.*, **21**, 75.
 ———, Power, M. H., and Dearing, W. H. (1957). *Proc. Mayo Clin.*, **32**, 182.
 Shulman, L. E., Shoenrich, E. H., and Harvey, A. McG. (1952). *Bull. Johns Hopk. Hosp.*, **91**, 371.

The term "biophysics" has hardly yet had time to acquire a fixed or generally accepted meaning. In consequence, the author of *Elements of Biophysics*, James E. Randall, Ph.D. (of Missouri University), explains that he wrote his book "to present to the student of biology and medicine the physical and quantitative concepts of basic importance to these fields." The subjects he discusses include the following: principles of measurement and statistical analysis; mechanics and kinetics; electricity, atomic structure, and radioactivity. The book has 333 pages and is published by Year Book Publishers for \$8.

COR TRIATRIATUM (STENOSIS OF THE COMMON PULMONARY VEIN)

SUCCESSFUL TREATMENT OF A CASE

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In the cor triatriatum the left atrium is divided by a septum into two chambers—postero-superior, which receives the pulmonary veins, and antero-inferior, which opens into the mitral valve and left ventricle. The septum contains one or more apertures which may be large or small, or it may be imperforate, in which case the infant is stillborn or dies in the first few months. Since the septum causes an obstruction at left atrial level, it can simulate the symptoms, radiological appearances, and haemodynamics of mitral stenosis. It is eminently suitable for surgical treatment, yet to date only three successful cases have been reported. A fourth is now presented.

Case Report

A woman aged 28 complained of progressive breathlessness, palpitation, and tiredness for four years. A "leaky valve" had been diagnosed when she was aged 12. Walking a few yards caused severe dyspnoea, but she complained little and was working as a secretary. Orthopnoea, haemoptysis, syncope, or chest pain was not present.

The rhythm was atrial fibrillation; venous pressure was raised to 4 cm. above the sternal angle, and there was an obvious systolic lift to the left of the sternum. The main auscultatory findings were a mitral pansystolic murmur

FIG. 1.—Electrocardiogram showing atrial fibrillation and right ventricular hypertrophy.

(grade 2) and a loud first sound at the mitral (grade 3) and tricuspid area (grade 3). The second sound was closely split, the pulmonary element being loud. There was no diastolic murmur and no opening snap. The blood pressure was 120/85. Other findings were normal. The electrocardiogram showed atrial fibrillation and a strong right ventricular hypertrophy pattern (Fig. 1). The heart was moderately increased in size (Fig. 2), the pulmonary artery prominent, and the left atrium slightly enlarged when viewed