SUMMARY

Increased fibrinolytic activity in the blood of the superficial veins of hemiplegic arms as compared with that in the same veins on the normal side was observed in 20 out of 21 patients studied in whom hemiplegia had been present for up to two years. Possible explanations for this are discussed.

Thanks are due to Professor S. Shuster and Mr. C. Johnston for help with the study, to Miss M. Roberts for technical assistance, and to Mrs. M. Jackson for valuable editorial help.

I. SUDHAKARAN MENON, M.B., B.S.,
Research Fellow, Department of Medicine, the Royal Victoria Infirmary, Newcastle upon Tyne.
H. A. DEWAR, M.D., F.R.C.P.,
Cardiologist and Physician, Department of Medicine, the Royal Victoria Infirmary, Newcastle upon Tyne.

REFERENCES

Brain, Lord (1962). *Diseases of the Nervous System*, 6th ed., p. 768. London.
Ellis, L. B., and Weiss, S. (1936). *Arch. Neurol. Psychiat. (Chic.)*, **36**, 362.
Fearnley, G. R., Balmforth, G., and Fearnley, E. (1957). *Clin. Sci.*, **16**, 645.
Franz, R. C., Kark, A. E., and Hathorn, M. (1961). *Lancet*, **1**, 195.
Hoerner, E. F., Dasco, M. M., McKeown, J., and Case, H. (1954). *Angiology*, **5**, 414.
Kwaan, H. C., Lo, R., and McFadzean, A. J. S. (1957). *Clin. Sci.*, **16**, 241.
LaBan, M. M., and Johnson, E. W. (1965). *Arch. phys. Med.*, **46**, 245.
Lackner, H., and Goosen, C. C. (1959). *Acta haemat. (Basel)*, **22**, 58.
Messer, D. L., Celander, D. R., and Guest, M. M. (1962). *Circulat. Res.*, **11**, 832.
Sherry, S., Lindemeyer, R. I., Fletcher, A. P., and Alkjaersig, N. (1959). *J. clin. Invest.*, **38**, 810.
Steinmann, B. (1963). *Schweiz. med. Wschr.*, **93**, 172.
Steichle, D. F., and Herschlein, H. J. (1962). *Med. Welt*, **3**, 141.
von Kaulla, K. N. (1963). *Chemistry of Thrombolysis : Human Fibrinolytic Enzymes*, p. 79. Springfield, Illinois.

Medical Memoranda

Paracetamol and the Kidney

Brit. med. J., 1967, 2, 615–616

Phenacetin had been used for many decades before its nephrotoxic properties were recognized (Spühler and Zollinger, 1953). Because of the general belief that paracetamol is safe, it has become a popular substitute, but hepatic damage with disturbance of glucose metabolism has now been reported (Davidson and Eastham, 1966 ; Thomson and Prescott, 1966). The following case suggests that it can also cause renal lesions. It was taken in the form of a proprietary preparation (Beserol, Lobak), which contains paracetamol 450 mg. and chlormezanone 100 mg. in each tablet.

CASE HISTORY

A 45-year-old European man underwent partial gastrectomy for duodenal ulcer in 1962, and was given Beserol for wound pain ; he took two to four tablets a day for two months. Ten months later he again started Beserol, now because of " sinus headaches " and nervous tension, but in vast quantities—12 tablets a day for four months, followed by 25 to 40 (average 30) daily for another six months. When this was realized Beserol was stopped and the tension treated with chlordiazepoxide 15 mg. daily. Seven months later he developed right loin pain and passed blood and fragments of tissue in the urine. An intravenous pyelogram showed no excretion of contrast medium, and he was admitted to the Salisbury Central Hospital on 2 September 1965.

He denied having taken other analgesics, apart from an occasional aspirin or proprietary compound tablet for headache.

Examination revealed a thin sallow man with no loin tenderness or other physical abnormality ; the blood pressure was 135/85 mm. Hg. The urine was acid and contained neither protein nor glucose ; microscopy disclosed numerous red and white blood cells but no casts, ova, or crystals ; three specimens were sterile, and there were no acid-fast bacilli. The haemoglobin was 11.4 g./100 ml., white cells 7,500/cu. mm., and differential count and film normal. The postprandial blood glucose was 110 mg./100 ml. on two separate occasions, and the blood urea was 130 mg./100 ml. ; serum electrolytes and proteins were normal. There was no methaemoglobinaemia or sulphaemoglobinaemia.

Cystoscopy (Mr. R. M. Honey) was normal apart from haemorrhages surrounding the right ureteric orifice. Retrograde pyelograms: both kidneys were unduly small (10 cm. long), with signs of papillary necrosis on the right (Fig. 1) but not on the left (Fig. 2).

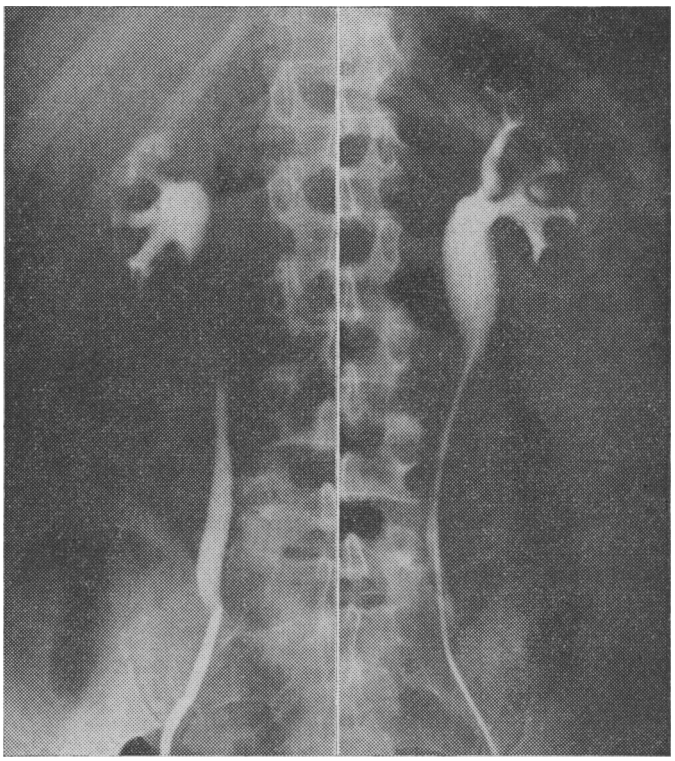

FIG. 1 FIG. 2

FIG. 1.—Retrograde pyelogram showing small right kidney ; upper and middle calices are clubbed, with some leakage of contrast medium into renal substance. FIG. 2.—Retrograde pyelogram showing small left kidney, but apparently normal caliceal system.

On a low-protein diet the blood urea fell to 54 mg./100 ml. during the next three weeks ; serum creatinine 3.5 mg./100 ml., creatinine clearance 25 ml./minute. He was discharged from hospital but did not return for follow-up, though six months later he was back at work and apparently well.

Discussion

The history of renal colic and the passage of fragments of tissue in the urine suggested the diagnosis of renal papillary necrosis, which was confirmed radiologically. In the absence of diabetes or urinary infection or obstruction, a history of analgesic abuse was sought and he was found to have taken large quantities of a preparation containing paracetamol. Renal disease did not become apparent until seven months after he discontinued the Beserol; similar behaviour is recognized with phenacetin (Case Records, 1966), though other cases improve when the drug is stopped (Jacobs and Morris, 1962). There was radiological evidence of papillary necrosis only on the right, but bilateral damage was indicated by the smallness of both kidneys, as well as by azotaemia. This is difficult to reconcile with the claim that papillary necrosis precedes, and indeed causes, renal shrinkage (Dawborn *et al.*, 1966), unless one accepts the presence of necrosis in the face of an apparently normal left caliceal system (Fig. 2); antecedent parenchymal damage seems more likely. In this case there was nothing to incriminate phenacetin. The patient's frankness about Beserol suggested that he did not conceal the consumption of other freely-available medications. Chlormezanone and chlordiazepoxide do not appear to damage the kidneys.

The patient had ingested 3.7 kg. of paracetamol during the previous six months at the rate of 11–18 g. a day: these amounts are comparable with the quantity of phenacetin known to have been nephrotoxic (Levin *et al.*, 1962). He closely resembles the group of patients with chronic renal disease and unstable personality reported by Dawborn *et al.* (1966). His reason for liking Beserol—apparent improvement in power of concentration—was that given by workers in the Swiss watch industry who took phenacetin and often suffered toxic effects (Moeschlin, 1957).

The occurrence of renal damage, of the type caused by phenacetin, in one who had taken very large quantities of paracetamol demands reappraisal of the latter substance. Paracetamol is the major metabolite of phenacetin in the body and is responsible for most, if not all, its therapeutic activity (Brodie and Axelrod, 1949). If paracetamol were also responsible for the toxic effects attributed to phenacetin, several alternative explanations for the latter could be discarded. Contamination of phenacetin with 4-chloroacetanilide has been blamed (Harvald *et al.*, 1960 Schnitzer *et al.*, 1965), but does not occur when phenacetin and paracetamol are made according to the *British Pharmacopoeia*. Methaemoglobin formation by phenacetin has been incriminated (Moolten and Smith, 1960), but such activity is due to its other metabolite, *p*-phenetidin; this is not formed by paracetamol, which is excreted in the urine, mostly as the glucuronide (Schnitzer and Smith, 1966).

In healthy human volunteers phenacetin causes a greater renal-tubular-cell excretion than paracetamol (Prescott, 1965), but Clausen (1964) has questioned the relevance of this observation to the pathogenesis of analgesic nephrotoxicity. Though Schnitzer and Smith (1966) found that phenacetin, paracetamol, 4-chloroacetanilide, and *p*-phenetidin did not produce renal lesions in rats similar to those ascribed to phenacetin in man, paracetamol and phenacetin have similar acute toxic effects on rats, with congestive and degenerative changes in the renal tubules (Boyd and Bereczky, 1966). Preparations containing phenacetin had been taken by all 36 patients with renal lesions and a history of analgesic abuse, except one who had taken only aspirin and paracetamol (Prescott, 1966). Irrespective of the actual mechanism of kidney damage, the effect may actually be due to the paracetamol to which phenacetin has been converted.

With more prolonged and intensive use—and abuse—paracetamol, alone or in combination with other substances, may prove to be as nephrotoxic as phenacetin. It is not intended to denigrate paracetamol on the basis of a single case, but some caution in its use is warranted until the situation is clarified.

Addendum.—Since this paper was accepted evidence has been cited that paracetamol may induce methaemoglobinaemia when given in abnormally high doses, but not in normal therapeutic amounts (Thomas *et al.*, 1966). This may, of course, be relevant to the mechanism of renal damage.

Dennis M. Krikler, M.B., M.R.C.P., M.R.C.P.Ed.,

Formerly Physician, Salisbury Central Hospital, Salisbury, Southern Rhodesia. Now Honorary Clinical Assistant to Outpatients, Medical Professorial Unit, Westminster Hospital, London S.W.1, and Honorary Clinical Assistant, Department of Gastroenterology, Central Middlesex Hospital, London N.W.10.

References

Boyd, E. M., and Bereczky, G. M. (1966). *Brit. J. Pharmacol.*, **26**, 606.
Brodie, B. B., and Axelrod, J. (1949). *J. Pharmacol. exp. Ther.*, **97**, 58.
Case Records of the Massachusetts General Hospital (1966). *New Engl. J. Med.*, **275**, 159.
Clausen, E. (1964). *Lancet*, **2**, 123.
Davidson, D. G. D., and Eastham, W. N. (1966). *Brit. med. J.*, **2**, 497.
Dawborn, J. K., Fairley, K. F., Kincaid-Smith, P., and King, W. E. (1966). *Quart. J. Med.*, **35**, 69.
Harvald, B., Valdorf-Hansen, F., and Nielsen, A. (1960). *Lancet*, **1**, 303.
Jacobs, L. A., and Morris, J. G. (1962). *Med. J. Aust.*, **2**, 531.
Levin, N. W., Rubenstein, A. H., Abrahams, C., Jordaan, J. C., and Posel, M. M. (1962). *S. Afr. med. J.*, **36**, 555.
Moeschlin, S. (1957). *Schweiz. med. Wschr.*, **87**, 123.
Moolten, S. E., and Smith, I. B. (1960). *Amer. J. Med.*, **28**, 127.
Prescott, L. F. (1965). *Lancet*, **2**, 91.
—— (1966). Ibid., **2**, 1143.
Schnitzer, B., and Smith, E. B. (1966). *Arch. Path.*, **81**, 264.
—— —— and Golden, A. (1965). *Amer. J. Path.*, **46**, 917.
Spühler, O., and Zollinger, H. U. (1953). *Z. klin. Med.*, **151**, 1.
Thomas, J., McLean, S., Starmen, G. A., and Carroll, P. R. (1966). *Lancet*, **2**, 1360.
Thomson, J. S., and Prescott, L. F. (1966). *Brit. med. J.*, **2**, 506.