lying in an area of old cirrhosis. For post-operative sedation the patient was given 100 mg. of pethidine at minimal intervals of six hours, 600 mg. being given in the first 48 hours. On the second post-operative day she became progressively more drowsy, there was marked nystagmus, and the pupils were widely dilated and just reacting to light. Pethidine administration was discontinued that evening, and the following morning she was fully conscious, although nystagmus persisted for a further 24 hours. There was complete amnesia for the first two post-operative days.

Case 3.—This patient, a man aged 32, was under treatment for primary syphilis. He had had 6.45 g. of neoarsphenamine and 15 g. of bismuth oxychloride during the previous nine weeks and was admitted to hospital with cellulitis, possibly due to an extraveneous injection of arsenical. His liver was slightly enlarged and tender, and urinary urobilinogen was present in a dilution of 1:50, although he was not jaundiced. Because of generalized pruritus and pain he was given 400 mg. of pethidine in 24 hours, after which a collection of pus was drained under nitrous-oxygen-anaesthesia. During the subsequent 24 hours 500 mg. of pethidine was administered and the patient became very delirious. Pentobarbitone, 300 mg., was given, but it only made the delirium worse, necessitating the administration of 7.2 ml. of bromethol, following which he slept for 12 hours. Slight delirium returned after this interval, but was again controlled by "mist, three-fifteens," composed of potassium bromide, 15 gr. (1 g.); chloral hydrate, 15 gr. (1 g.); tinct. opii, 15 min. (0.9 ml.); aqua chlor. to $\frac{1}{2}$ oz. (15 g.). The following day he was quite lucid, with amnesia since before operation.

Case 4.—A man aged 30 had Banti's syndrome. Liver-function tests showed van den Bergh, direct reaction negative; serum bilirubin, 0.8 mg. per 100 ml.; serum alkaline phosphatase, 17 units %; serum colloidal gold, negative; zinc turbidity, 3 units; thymol turbidity, 6 units; thymol flocculation, negative; cephalin cholesterol, ++++. Splenectomy and spleno-renal anastomosis were performed under D-tubocurarine chloride, thiopentone, nitrous oxide, oxygen, and pethidine anaesthesia. The patient was induced with 20 mg. of D-tubocurarine chloride and 0.35 g. of thiopentone. During the remainder of the operation, which lasted 3 hours 15 minutes, a further 0.1 g. of thiopentone and 40 mg. of D-tubocurarine chloride, together with 50 mg. of pethidine, were administered.

Commentary

Cases 1 and 2 had a significant degree of liver-function impairment as demonstrated by recognized laboratory investigations. It was reasonable to suppose on clinical grounds that Case 3 had some degree of hepatic dysfunction (McLachlan, 1945).

In spite of the administration of pethidine in dosage not considered to be in excess of normal, the first three cases all showed signs of pethidine overdosage—namely, delirium and amnesia. A normal adult subject should tolerate 100 mg. of pethidine parenterally or orally every four hours (Batterman and Himmelsbach, 1943). Excessive dosage results in cerebral irritation, and widely dilated pupils and nystagmus have been reported as toxic reactions following overdosage (von Brücke, 1940). Cessation of toxic signs on withdrawal of the drug in these cases supports the assumption that they were due to the pethidine. These cases serve as an illustration of the fact that in the presence of liver damage toxic signs occur with therapeutic overdosage of pethidine.

Pethidine now holds a recognized place in anaesthesia. From the above one would not be surprised to find that patients with liver damage require much less pethidine than normal subjects to maintain satisfactory anaesthesia. This is illustrated by Cases 2 and 4. The average dose of pethidine during anaesthesia appears to be in the region of 25 mg. per half-hour (Mushin and Rendell-Baker, 1950; Johnson, 1951). The larger the dose of thiopentone used for induction of anaesthesia the smaller are the increments of pethidine required for its maintenance. With dosage of thio-

pentone of the order of that given in Cases 2 and 4 one would have expected to require a greater amount of pethidine than was actually administered.

Summary

Four cases of pethidine administration in the presence of liver damage are described.

Toxic reactions followed administration of normal therapeutic dosage in three of them.

Requirements of pethidine to maintain anaesthesia were less than normally anticipated in two of the cases.

These four cases support the hypothesis of Way *et al.* that in patients with severe hepatic dysfunction the desired therapeutic effect of pethidine can be obtained with smaller dosage.

We are indebted to Professor C. A. Wells for his helpful criticism and permission to publish these cases.

REFERENCES

- Batterman, R. C., and Himmelsbach, C. K. (1943). *J. Amer. med. Ass.*, 122, 222.
Bernheim, F., and Bernheim, M. L. C. (1945). *J. Pharmacol.*, 85, 74.
von Brücke, S. (1940). *Wien. klin. Wschr.*, 53, 854.
Johnson, P. Dunbar (1951). *British Medical Journal*, 2, 705.
McLachlan, A. E. W. (1945). *Diagnosis and Treatment of Venereal Diseases*. Livingstone, Edinburgh.
Mushin, W. W., and Rendell-Baker, L. (1950). *Brit. J. Anaesth.*, 22, 235.
Way, E. L., Swanson, R., and Gimble, A. I. (1947). *J. Pharmacol.*, 91, 178.

Medical Memoranda

Extensive Intraperitoneal Haemorrhage of Unknown Origin

The cause of extensive intraperitoneal haemorrhage is usually obvious—such as ectopic pregnancy, spontaneous rupture of the spleen and liver, and ruptures of aneurysms and blood vessels. Excluding the obvious pathological and traumatic conditions, Brewer and Marcus (1948) report nine cases from the literature and add one of their own of intra-abdominal apoplexy in which no definite bleeding-point was found. A further case of interest is reported.

CASE REPORT

A married woman aged 44 had had one normal pregnancy 16 years ago. Her menstrual periods were normal, lasting three to four days, with a 25-day cycle. Her last period had occurred 18 days previously. Sharp spasmodic lower abdominal pain began on the day before admission and was increasing in severity. On the day of admission an apparently normal period started, although it was a week early. She had not had any morning sickness or noticed any breast changes. Her only past illness had been rheumatoid arthritis during the past ten years.

On examination she was seen to be very pale, wasted, and collapsed. Her temperature was 96° F. (35.6° C.), pulse 88, and respiratory rate 20. No abnormality was found in her respiratory and cardiovascular systems. Her abdominal movements were restricted and there was tenderness and guarding over the lower abdomen.

On vaginal examination the uterus was anteverted and normal in size. Pressure in the fornices caused extreme pain. An indefinite boggy mass was felt in the pouch of Douglas which suggested blood clot. On speculum examination blood was seen to be issuing from the external os. A diagnosis of intraperitoneal haemorrhage was made, and this was thought to be due to a ruptured ectopic pregnancy.

At laparotomy under general anaesthesia the abdomen was opened by a subumbilical midline incision and found to contain between 2 and 3 pints (1.1 and 1.7 litres) of blood and blood clot. The Fallopian tubes and ovaries were first palpated and then inspected, but no cause for the bleeding was found. The liver and spleen were next palpated, but no abnormality was observed in the upper abdomen except for a few filmy adhesions. Loops of intestine were drawn out and inspected. The abdomen was

mopped dry, but no indication of the cause of the bleeding was found. The left ovary and tube were adherent to the side wall of the pelvis, and their appearance suggested the development of an early endometriosis, so they were removed.

Meanwhile the patient was receiving a blood transfusion, as her condition was deteriorating. It was thought that she would not stand having the incision extended upwards for inspection of the upper abdomen, and as there was no further bleeding the abdominal wall was closed in layers. A large-bore rubber drainage-tube was left draining the abdomen, so that any further bleeding might be detected quickly. No further bleeding took place. The patient's condition improved after 2 pints (1.1 litres) of blood had been given, and her blood pressure rose from 60/40 to 100/75. The improvement continued.

The following are the results from blood investigations taken four days later: bleeding-time, $3\frac{1}{2}$ minutes; clotting-time, $4\frac{1}{2}$ minutes; haemoglobin, 85%; rhesus factor, "D" positive; white cells, 3,000 per c.mm.; Wassermann reaction, negative; Kahn test, negative.

The pathological report states that an early acute salpingitis and an acute peri-oophoritis were present. The lumen of the tube contained pus; the mucosal rugae, muscular coat, and serosa were infiltrated by polymorphs. The ovary contained a follicular cyst and a corpus luteum as well as a number of small cysts lined by columnar epithelium just beneath the surface. These cysts had resulted from peritoneal metaplasia due to peri-oophoritis.

The patient made an uneventful recovery, and was well when seen two months later.

I am indebted to Mr. Vivian H. Barnett for permission to publish this case.

H. G. WOLSKEL, M.R.C.S., L.R.C.P., M.R.C.O.G.,
Senior Registrar, Royal Salop Infirmary.

REFERENCE

Brewer, A. C., and Marcus, R. (1948). *Brit. J. Surg.*, 36, 198.

Obstruction of the Urethra by Sulphamerazine Crystals

Numerous cases of sulphonamide anuria have been recorded since the first report by Smith *et al.* (1940). Southworth and Cooke (1939) and Tsao *et al.* (1939) had previously reported marked oliguria, but had not appreciated the significance of it. This form of anuria is due to obstruction of the lower end of the ureter by a sludge composed of epithelial debris and possibly some crystals of the drug. In the male infant a similar obstruction can occur in the urethra, and, although it is apparently not a rare occurrence, it has as yet received little attention.

Rice-Edwards (1950) reported a case of retention of urine due to a collection of crystals in the urethra following the administration of "cremomerazine." Ellison Nash (1951) mentions this complication of sulphamerazine therapy in children and states that it may occur after four-hourly administration of the drug. The following case is reported in detail to draw attention to this complication and to emphasize the simple precautions necessary when administering sulphamerazine to children.

CASE REPORT

A boy aged 3 years and 10 months and weighing 2 st. 13 lb. (18.6 kg.) was admitted to Southmead Hospital under the care of Dr. Beryl Corner and referred to the genito-urinary department. He had developed pneumonia three days before admission, and this had been treated by sulphamerazine in the form of cremomerazine. Forty-eight hours after starting the course of treatment the child developed acute retention of urine, and had passed no urine for 24 hours before admission.

His mother stated that she had been instructed to give the child two teaspoonfuls of cremomerazine four-hourly, and had been supplied with enough for three days—that is, a 4-oz. (114-ml.) bottle, which contained 12 g. of sulphamera-

zine in suspension. She admitted that rather more than two teaspoonfuls had been given at each dose and that the bottle was emptied in less than 36 hours. The child had therefore received 12 g. of sulphamerazine in that time. His past medical history revealed nothing abnormal other than slight chronic bronchitis following whooping-cough 18 months previously.

On admission he was in great distress, with a tense distended bladder. The whole penis was swollen, and by separating the oedematous lips of the external urinary meatus a whitish paste could be seen in the urethra. A probe was inserted just inside the meatus and a small amount of the paste was dislodged. The child immediately passed about 50 ml. of urine, but the flow was then cut off with intense strangury, leaving the bladder still distended.

He was taken to the theatre and a general anaesthetic administered. The paste was removed by passing a fine rubber catheter through which the urethra was continuously irrigated with sterile water. It took three to four minutes to clear the penile urethra; then the catheter passed easily into the bladder and 150 ml. of opalescent fluid was withdrawn.

The oedema of the penis was less next morning, but did not disappear for two days.

The urine from the bladder was examined and found to contain sulphonamide crystals and large quantities of amorphous debris. Specimens of urine were collected at six-hourly intervals, and it is of interest to note that crystals were still present in the specimens taken six and twelve hours after operation in spite of a copious fluid intake and administration of alkalis.

COMMENT

The cause of this obstruction appears to be similar to that of obstruction of the ureter in adults, except that in the child there are more crystals and less epithelial debris in the sludge. The urethra in the male infant is so small that it can be blocked by sludge more readily than the ureter. It will be noticed that the point at which the sludge impacts is in the distal part of the penile urethra just before it opens out to form the navicular fossa.

Cremomerazine is a palatable suspension of sulphamerazine and is particularly suitable for children. It is easily administered and is a great asset to the doctor in general practice. However, like all other suspensions of sulphonamide drugs, it is not perfect and if allowed to stand even for a few hours a sediment will appear in the bottle. Unless the bottle is thoroughly shaken before each dose is given, the quantity of sulphamerazine received by the patient is apt to be increased as the bottle is emptied.

The dosage recommended for children of from 3 to 10 years of age is two teaspoonfuls—that is, 1 g. of sulphamerazine—every 12 hours. The interval of 12 hours is emphasized on all bottles supplied. It will be noticed that in our case the child was given two teaspoonfuls every four hours, making three times the recommended dose. Owing to the relatively slow excretion of sulphamerazine, an adequate blood level can be maintained with 12-hourly doses. If, however, it is given four- or eight-hourly, like most other sulphonamides, the dose must be reduced accordingly.

The further precautions necessary when administering this drug are those common to all the sulphonamide group. An output of at least 1,500 ml. of alkaline urine a day in an adult (less according to age) should be aimed at.

Usually a probe inserted in the external urinary meatus is enough to dislodge the sludge and promote a free flow of urine, but urethral irrigation may be necessary.

ASHTON MILLER, M.D., F.R.C.S.,
Consultant Urologist, United Bristol Hospitals.

J. P. MITCHELL, F.R.C.S.,
Urological Senior Registrar, United Bristol Hospitals.

REFERENCES

- Nash, D. F. Ellison (1951). *Ann. roy. Coll. Surg. Engl.*, 8, 193.
Rice-Edwards, J. T. (1950). *British Medical Journal*, 2, 1445.
Smith, E., Evelyn, K. A., and Nolan, J. F. (1940). *Canad. med. Ass. J.*, 42, 27.
Southworth, H., and Cooke, C. (1939). *J. Amer. med. Ass.*, 112, 1820.
Tsao, Y. F., McCracken, M. E., Chen, J., Kuo, P. T., and Dale, C. L. (1939). *Ibid.*, 113, 1316.