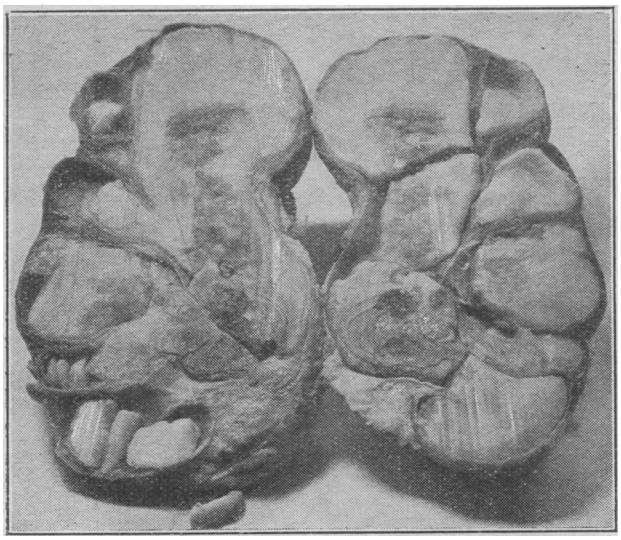

FIG. 2.—The calculus of the right kidney.

The left kidney weighed 720 g. and contained one main calculus measuring approximately 18.5 by 8 cm., together with several smaller calculi. The lower end of the main calculus extended down into an elongated portion of the renal pelvis and contained a laminated brown oval stone appearing older than the rest. The remainder of the main calculus extended in a coralliform fashion into dilated calices, leaving a narrow rim of renal tissue. The main portion of the stone was composed of a hard white laminated material possessing radial markings. A natural joint was present between the main calculus and another at the upper pole of the kidney. The surfaces of the joint were convex and concave, and were covered by a smooth thin layer which was denser and whiter than the subjacent stone. Several other smaller calculi were present in some calices. The rim of renal tissue varied in thickness from 2 to 10 mm. At the upper pole and on the lateral border were moderately sized areas of renal tissue 10 mm. in thickness. The ureter was only slightly thickened.

The calculi of both kidneys were composed of carbonates and phosphates. No trace of urates or oxalates was found even in the denser pelvic stones.

Microscopical sections from the recognizable areas of kidney substance in each kidney showed a flattened single layer of pelvic epithelium, separated by a layer of fibrous granulation tissue from functioning renal tissue. Most of the glomeruli showed thickening of the capillary basement membrane; a few were shrunken, but none were obliterated. In some areas the tubules were dilated. There was moderate interstitial fibrosis. The arteries were narrowed by thickening of the intimal connective tissue and by medial hypertrophy.

Summary

A case of bilateral renal calculi of exceptional size is recorded. Despite the distortion of the kidneys into mere rims of renal tissue thinly covering the calculi (a state which was shown by *x*-ray examination to have been present for at least three years), renal function had been adequate until the subject contracted a terminal acute respiratory infection.

Reference is made to other giant renal calculi recorded in the literature.

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PETHIDINE AND LIVER DAMAGE

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Detoxication of pethidine by the liver has been proved by the animal experiments of Bernheim and Bernheim (1945). This has been verified by Way, Swanson, and Gimble (1947), who suggested that in patients with severe hepatic impairment the desired therapeutic effect of pethidine might be obtained with smaller dosage. A review of the literature has failed to reveal any case report to substantiate this view, and it is therefore felt that the following cases will prove of interest in support of the hypothesis.

Case Reports

Case 1.—The patient, a man aged 40, had a history of repeated haematemesis. Laparotomy in November, 1950, revealed a cirrhotic liver and splenomegaly. Liver biopsy showed early multilobular cirrhosis. Liver-function tests on April 19, 1951, gave the following results: van den Bergh, direct reaction, very feeble, delayed; serum bilirubin, 1.6 mg. per 100 ml.; serum alkaline phosphatase, 8.3 units per 100 ml.; serum colloidal gold, 5; zinc turbidity, 10 units; thymol turbidity, 5 units; thymol flocculation, ++++; cephalin cholesterol, ++++. Hippuric acid excretion was impaired. Urinary urobilinogen was present in dilution 1:40.

On May 1 splenectomy was performed under D-tubocurarine chloride, thiopentone, nitrous oxide, oxygen, and pethidine anaesthesia. The patient's condition was satisfactory at the end of operation, and morphine, 10 mg., was given on three occasions for post-operative sedation. Pethidine was administered in divided doses as follows: during operation, 100 mg.; first post-operative day, 100 mg.; second day, 200 mg.; third day, 400 mg.; fourth day, 200 mg. Up to the third post-operative day the patient's progress was satisfactory. That evening he became delirious and disorientated, a condition which was attributed to uraemia. The blood urea, however, was 39 mg. per 100 ml. His condition remained unchanged during the fourth day, when, on bearing in mind the possibility of drug intoxication, the pethidine was discontinued. The following morning he was much improved and was quite lucid. He had complete amnesia for the second to fourth post-operative days. His subsequent progress was uneventful.

Case 2.—A woman aged 25 had a history of subacute hepatic necrosis in 1943, and haematemeses on two subsequent occasions. Clinical examination revealed marked ascites, enlarged spleen, but unpalpable liver. On May 16, 1951, liver-function tests showed: van den Bergh, direct reaction, feeble, prompt; serum bilirubin, 1.6 mg. per 100 ml.; serum alkaline phosphatase, 15 units per 100 ml.; serum colloidal gold, 5; zinc turbidity, 9 units; thymol turbidity, 7 units; thymol flocculation, ++++; cephalin cholesterol, ++. Urinary urobilinogen was present in dilution 1:40. The A/G ratio (Howe's technique) was 1.05:1. On May 25 splenectomy and spleno-renal anastomosis were performed under D-tubocurarine chloride, thiopentone, nitrous oxide, oxygen, and pethidine anaesthesia. The operation lasted four hours, during which time 0.45 g. of thiopentone, 50 mg. of D-tubocurarine chloride, and 50 mg. of pethidine were administered. A frozen section of the liver showed a nodule of excellently regenerated liver tissue

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 extravenous 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-oxide–oxygen anaesthesia. During the subsequent 24 hours 500 mg. of pethidine was administered and the patient became very delirious. Pentabarbitone, 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 ½ 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 thiopentone 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.

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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