angle. Intravenous and retrograde pyelography showed a filling defect in the renal pelvis, and the isotope renogram suggested impaired renal function. A definitive diagnosis was only made after renal angiography.

It is thought in this case that the carcinoma must have caused the haematuria previously investigated and probably at that stage caused radiological changes which were mistaken as being caused by chronic pyelonephritis. It is of interest to note that there has been no evidence of any secondary spread from this lesion.

**Acknowledgments**

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# A death from tetracycline

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**Case report**

A female of 43 years was admitted with a history of vomiting for 5 days and onset of severe abdominal pain 24 hr prior to admission. A duodenal ulcer had been diagnosed 1 year previously, and since then she had suffered from epigastric discomfort which was relieved by alkalis.

*On admission* she was shocked, the blood pressure being unrecordable. A diagnosis was made of gastro-intestinal perforation. Over the next few hours, following intravenous fluid therapy, her blood pressure rose to 110/70 mmHg. Laparotomy was performed 6 hr after admission when her general condition had improved. A large perforation was found in the first part of the duodenum, and 1·5 litres of bile-stained fluid were aspirated from the peritoneal cavity. The perforation was closed. The liver, gallbladder and pancreas appeared normal.

Post-operatively the patient's condition improved, her blood pressure rose to 140/90; she was apyrexial and gastric aspiration over the ensuing 24 hr was only 620 ml.

Tetracycline was commenced at the time of operation at a rate of 500 mg intravenously, 8 hourly; this was changed to 2·0 g orally daily on the 4th and 5th post-operative days (see Fig. 1).

The patient was oliguric over the first 48 hr post-operatively but subsequently the urine output was adequate (see Fig. 1). Five days post-operatively the patient became drowsy and was noted to be slightly jaundiced with a morbilliform irritating rash over the whole of the body. Serum bilirubin at this time was 6·1 mg/100 ml, urinary urobilinogen was increased and bilirubin was also present. The rash subsided on antihistamine therapy over the next few days and the jaundice faded. Six days after the operation she developed severe diarrhoea and, in view of the history of jaundice and skin rash, tetracycline was cancelled.

In spite of a good urine output with no rise

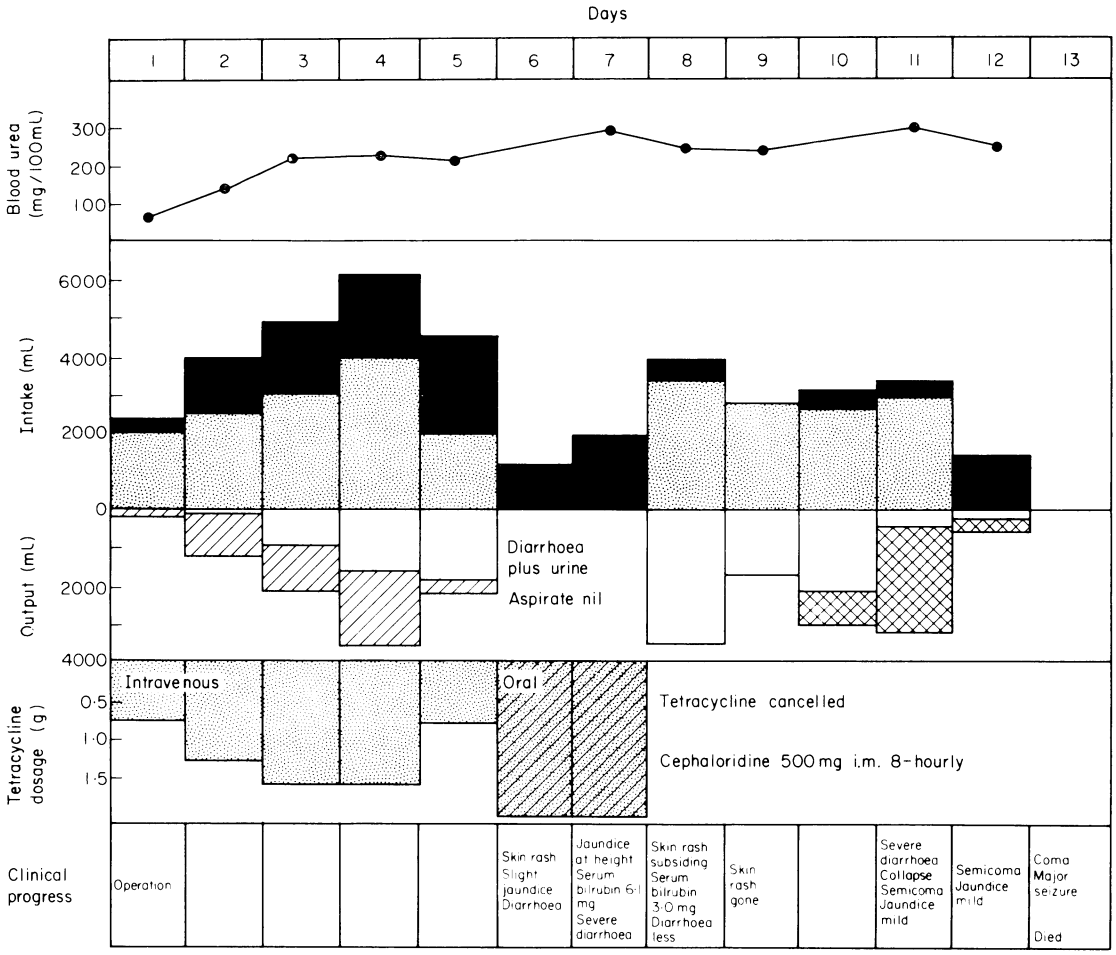


FIG. 1. Clinical progress. Solid columns, Oral; stippled columns, intravenous; open columns, urine; hatched columns, aspirate; cross-hatched columns, stool.

in serum potassium or increasing acidosis, the blood urea remained high (see Fig. 1). A white blood cell count 8 days post-operatively was 32,000 with 83% polymorphonuclear leucocytes, and it was thought that this patient might have septicaemia. She was, therefore, started on intramuscular cephaloridine (500 mg 8 hourly). Nine days post-operatively the patient seemed more alert, but in the evening suddenly collapsed with an unrecordable blood pressure. Her condition temporarily improved after intravenous hydrocortisone and 570 ml of plasma, but she subsequently developed severe diarrhoea and lapsed into coma. That night her temperature rose from an average of 97–99·8°C. The following day she was deeply unconscious; respirations were slow and stertorous; the liver was palpable 2 in. below the right costal margin and was soft in consistency. Her skin was still slightly icteric. In the afternoon she had a major convulsion and died.

## Discussion

This patient was given a total of 5·75 g of tetracycline intravenously over a period of 5 days, followed by a total of 4·0 g orally over the ensuing 2 days.

There was no urine output on the 1st day of parenteral tetracycline and only 150 ml on the 2nd day. This patient presumably had post-operative oliguria superimposed upon preceding normal renal function. Severe pre-operative hypotension, however, may well have produced temporary renal functional impairment.

The danger of giving parenteral tetracycline

in the presence of impaired renal function is well recognized (Shils, 1962; Clendenning, 1965; Wray & Kocen, 1965). In the presence of decreasing renal function, tetracycline given in the usual doses may cause significant effects in proportion to the degree of renal insufficiency and the dosage and duration of treatment. These effects include uraemia, acidosis, loss of weight, anorexia, nausea and vomiting. An unusual type of renal failure arises with progressive azotaemia, acidosis which is often difficult to manage, hypokalaemia and normal or increased volumes of urine (Lew & French, 1966). Electrolyte and acid–base abnormalities have frequently been reported in these patients; Shultz *et al.* (1963) reported hyponatraemia, hypokalaemia and acidosis, and Shils (1962) noted increases in urinary sodium which usually resulted in a diuresis and negative fluid balance. The urine output in our patient was normal, apart from the initial 3 days post-operatively. Metabolic acidosis of moderate degree was present on the 7th and 9th days post-operatively but the acid–base status was normal on the 10th day. The blood urea steadily increased but remained around the same level for 3 days before death. It is of interest that, in spite of the uraemia, the serum potassium remained within normal limits and the serum sodium, which was low immediately post-operatively, was normal at the time of death. It is probable that typical electrolyte abnormalities would have developed had it not been for careful regulation of electrolyte and acid–base status.

The renal failure may be explained on the basis of 'hepatogenic nephrosis', as described by Allen (1962), who stated that the depression of renal function may be caused by glomerular dysfunction without visible lesions rather than by tubular necrosis. On the other hand, liquefactive and congulative necrosis of the renal tubules and cortex have been described (Kunelis, Peters & Edmondson, 1965). Tubular degeneration in several species of animals can be produced by administration of large doses of degraded and non-degraded tetracycline (Lew & French, 1966). The rate of renal functional recovery apparently depends on the level of azotaemia and is slower in cases where the blood urea nitrogen is greater than 50 mg/100 ml (Shils, 1962). The mechanism of tetracycline-induced azotaemia is apparently related to a generalized systemic anti-anabolic effect (Shils, 1963). The treatment should include stopping the drug, a low protein high calorie diet, and regulation of fluid and electrolyte status (Pulliam & O'Leary, 1964); anabolic steroids may help (Shils, 1963).

Our patient, in spite of reasonable control of the acid–base and electrolyte status, died—presumably because of tetracycline-induced hepatocellular damage. The histology of the kidney showed degeneration and albumin exudate in the capsular spaces and tubular lumen. This was considered to be consistent with cholaemic nephrosis (Raeburn, personal communication 1967).

The potential and real hepatotoxic effects of tetracycline have been known for years (Shultz *et al.*, 1963; Kunelis *et al.*, 1965; Schiffer, 1966). Schiff (1953) stated that fatty metamorphosis of liver cells occurred in patients who were receiving intravenous tetracycline over a 3–4-day period. He indicated that the change was reversible with discontinuance. Miller *et al.* (1967) have shown that intravenous tetracycline produces characteristic liver cell changes in normal rat livers. The changes have ranged from an intracytoplasmic globular pattern through a vacuolation effect to a confluent effect in which the liver parenchymal cells have only a peripheral rim of cytoplasm. Fluorescent studies showed tetracycline to be present in the vacuoles and enzyme studies indicated liver cell damage. Lepper (1951) showed that seven patients who had been given chlortetracycline in large doses by mouth and intravenously (a total of 2·0 g by each route) sustained liver damage. All had enlarged livers and jaundice, and five died. It was thought that death was chiefly due to the disease from which they suffered. At necropsy the liver showed vacuolation and fragmentation of the cells. The authors emphasized that it was never seen in a patient given tetracycline by mouth only.

Kunelis *et al.* (1965) reviewed thirty-eight cases of fatty liver of pregnancy and added sixteen of their own. Four patients survived after hepatic decompensation. It was postulated by Meihoff, Pasquale & Jacobs (1967) that these patients may well have survived the syndrome of fatty liver of pregnancy rather than tetracycline-induced hepatic failure.

Whalley, Adams & Combes (1964) described five cases in which liver damage was caused by tetracycline during pregnancy. One patient died. The antibiotic was given intravenously daily in doses of 1–2 g in four cases; the fifth received 1·0 g orally and was the only one in the series not to have been jaundiced. Tetracycline blood levels in these patients were found to be high. It is possible that most of the recently reported cases of fatty liver of pregnancy represent examples of tetracycline intoxication (Kunelis *et al.*, 1965) and are unrelated to the lesion described by Sheehan (1940).

The non-pregnant patients with tetracycline-

induced fatty liver who have been described in five reports appearing in the literature have received much larger doses for a longer period than the pregnant patients in whom fatty liver developed while receiving tetracycline therapy (Schiffer, 1966). It is possible that the liver during pregnancy is more sensitive to agents that depress protein anabolism, such as tetracycline (Kunelis *et al.*, 1965). Impaired renal function resulting in a failure of excretion of the antibiotic is probably also an important factor in producing hepatotoxicity. Many of the pregnant patients with tetracycline-induced fatty livers had tetracycline given for an attack of pyelonephritis (Schiffer, 1966). Rose, Roth & Koch (1965) stated that the persistence of tetracycline in the blood depended primarily on the state of renal function being markedly prolonged in the presence of renal failure. Following a single intravenous injection the mean serum half-life of tetracycline in healthy young males is 8·5 hr (Kunin, Dornbush & Finland, 1959a). In anuric patients the serum half-life may exceed 100 hr (Kunin *et al.*, 1959b). Tetracycline-induced hepatic failure has generally been associated with parenteral dosage of more than 2·0 g day (Meihoff *et al.*, 1967). Our patient received at the maximum 1·5 g intravenously daily, but this was sufficient in the presence of impaired renal excretion of the drug to produce hepatic failure.

The clinical picture of tetracycline hepatotoxicity is characteristic of severe hepatic dysfunction. Its onset may occur at any time during tetracycline therapy and is generally associated with nausea, vomiting, abdominal pain and jaundice. In the pregnant woman the onset of labour may be premature with delivery of a stillborn foetus (Schiffer, 1966). Other manifestations which have been noted in patients with tetracycline toxicity are diarrhoea (Schultz *et al.*, 1963) and gastrointestinal haemorrhage associated with a prolonged prothrombin time (Shultz *et al.*, 1963). Acute pancreatitis (Schultz *et al.*, 1963; Schiffer, 1966; Whalley *et al.*, 1964) is frequently present. The patient finally lapses into coma and shock is generally a terminal event (Shultz *et al.*, 1963; Bateman *et al.*, 1952).

Our patient became jaundiced 5 days after the onset of tetracycline therapy and the jaundice waned over the next 2 days. For this reason it was thought that her clinical symptoms were unlikely to be due to hepatocellular failure. However, she became increasingly comatose, developed severe diarrhoea and collapsed 24 hr before death. Just prior to death she was noted to bruise easily; a major convulsion was the terminal event. In retrospect, the clinical appearance and findings were consistent with progressive hepatocellular failure.

It should be noted that hepatocellular failure progressed in spite of cancellation of the tetracycline 5 days before death. One can only assume that the liver damage had been so great that it had reached an irreversible stage. Kunelis *et al.* (1965) have suggested that cortical damage following multiple fat embolism could produce coma in tetracycline fatalities. Macroscopically, the brain in our patient appeared normal—there was no evidence of cortical atrophy which Kunelis and his associates described (Kunelis *et al.*, 1965). Liver biopsy showed severe fatty degeneration, findings characteristic of tetracycline toxicity (see Fig. 2).

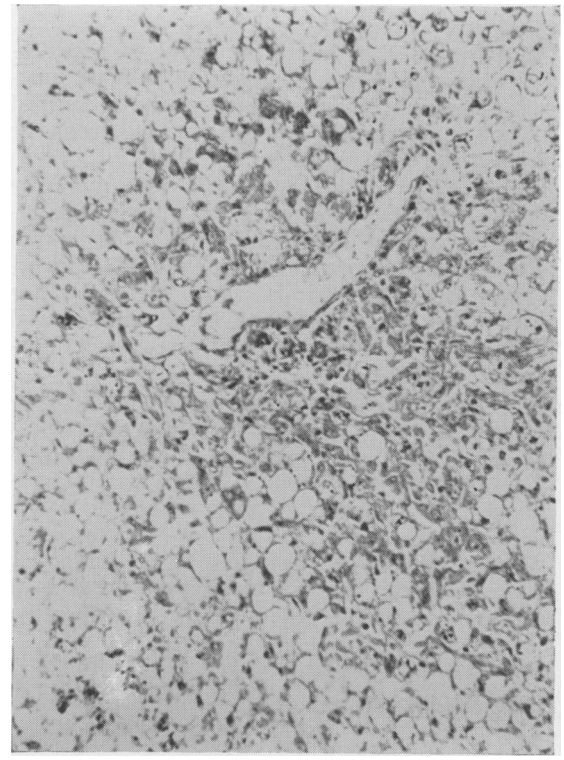

FIG. 2. Section of the liver showing severe fatty degeneration; there are no undamaged cells but those at the periphery are slightly better preserved. × 140.

Liver function tests in previous reports have been normal except for the alkaline phosphatase and serum bilirubin, which were elevated (Schiffer, 1966). Schultz and his colleagues (1963) did more detailed liver function tests on six obstetric patients who died from liver disease following tetracycline therapy. The serum bilirubin and

alkaline phosphatase were elevated in all the patients investigated and the prothrombin time was elevated in four of the five patients examined. Unfortunately, liver function tests were not estimated before death in our patient. Two days following cessation of tetracycline therapy (3 days before death), the thymol turbidity and zinc sulphate turbidity were normal, cephalin cholesterol was increased, the alkaline phosphatase was 14 units and the SGPT was markedly elevated to 238 units. The urine at the time showed increased urobilinogen and the presence of bilirubin.

## Conclusions

(1) Tetracycline should not be given parenterally in a dosage above 1·0 g daily and should never be given by this route when oral therapy is possible. Oral therapy should be substituted as soon as circumstances permit.

(2) Tetracycline should not be given parenterally whenever there is a possibility of renal functional impairment and should not be prescribed by any route in the presence of azotaemia or severely impaired renal function.

(3) The liver during pregnancy seems markedly susceptible to tetracycline and an alternative antibiotic should be prescribed which is known to have no hepatotoxic effects. This applies especially when the drug is being prescribed for pyelonephritis or as a prophylactic against renal infection in the presence of impaired renal function.

(4) The development of renal or hepatic functional impairment during tetracycline therapy is an indication to stop the drug. Since the advent of synthetic penicillins and other potent antibiotics—in particular, cephaloridine—it would seem wise to avoid tetracycline in any acute infection where there is likely to be diminution in renal output. This applies particularly to acute abdominal conditions where post-operative oliguria is likely.

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