of pre-eclampsia. Only prompt and active treatment prevented a higher incidence of eclampsia. The single case of eclampsia occurred in a 16-year-old unbooked patient who presented at term with a blood pressure of 200/150 mm. Hg, no significant increase in weight, and no albumin in the urine. It became apparent in the management of these young patients that proteinuria was not a constant feature and its absence should not lull one into a false sense of complacency.

Increase in Prematurity Rate.—It has been shown in this study that young primigravidae have an increased tendency to begin spontaneous labour before term. These findings are in marked contrast to those of Clough (1958), who reported on 175 young primigravidae and stated that these patients went beyond the expected date of confinement more often than older primigravidae. Both Bochner (1962) and Stearn (1963) found that the birth weights were much the same as in the control groups. Of more significance was the finding of a corrected prematurity rate of 7% in young primigravidae and of 2% in the controls. Of nine studies included in Table II, a prematurity rate of 10% or greater is demonstrated in five (Aznar and Bennett, 1961; Bochner, 1962; Hassan and Falls, 1964; Jarvinen and Katila, 1959; Poliakov, 1958). This prematurity rate is to some extent reflected in a higher perinatal mortality rate in the younger patients.

Increased Frequency of Prolonged Labour.—There is no uniformity of opinion on what constitutes prolonged labour. In the reported studies on young primigravidae the upper limit for labour varies from 24 hours (Poliakov, 1958; Aznar and Bennett, 1961) to 48 hours (Sinclair, 1952). The reported average duration for normal labour varies from 9 hours and 42 minutes to 16 hours and 32 minutes (Clough, 1958; Hassan and Falls, 1954). Further analysis of these studies revealed that the first stage, rather than the second stage, was what determined the duration of labour. Though labour may be prolonged, as shown in this study, there is an increased incidence of spontaneous birth. Fear of labour has been ascribed as a cause of prolonged labour (Aznar and Bennett, 1961). Stearn (1963) found no significant prolongation of labour. He stated that these girls were taken from their families and immediate friends; thus no fear of labour had been instilled into them, and one of the more potent causes of inertia was therefore not experienced. In the present study the definite tendency to conservatism in view of the high illegitimacy rate probably

accounted to a certain extent for the increased incidence of prolonged labour.

Conclusions

Pregnant adolescents demonstrate an increased tendency to at least two major complications in pregnancy—namely, toxæmia of pregnancy and prematurity—which should be avoided by more adequate antenatal care; these patients should therefore be seen at least weekly after the 32nd week.

From the standpoint of pure physical ability the young primigravida does very well—in many respects better than the slightly older patient. A high incidence of spontaneous vaginal delivery can be expected and operative intervention thereby avoided.

Summary

A series of 100 consecutive white primigravid patients aged 13 to 16 years was analysed and compared with a control group of 100 consecutive white 22-year-old primigravid patients.

In the former there was a high incidence of hypertension and toxæmia. The prematurity rate was higher than in the control group, as was the perinatal mortality. There was also a greater incidence of prolonged labour. Though the foetal head was not engaged before labour in half the patients, the instrumental delivery and caesarean section rate was very low. A comparison between this series and other published studies is made.

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Renal Failure after Cholangiography

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Renal failure after the use of intravenous radiological contrast media has often been described, and their nephrotoxic properties have been investigated experimentally (Killen and Lance, 1960). Attention has mostly been directed towards angiographic agents. In this paper we describe two cases of renal failure after the use of iodipamide (Biligradin) in intravenous cholangiography. This agent, which is the methylglucamine of N,N'-adipic-di-(3-amino-2,4,6-tri-iodobenzoic acid), has until recently been regarded as innocent in this respect (Lindgren *et al.*, 1966).

Case 1

A 77-year-old woman was admitted to Westminster Hospital on 18 October 1966 with a history of fluctuating painless jaundice for three weeks, itching of the skin, and dark urine. She noticed pale stools on one occasion. Two years previously she had been an

inpatient at another hospital with abdominal pain and vomiting. At that time a plain film of the abdomen showed a calcified opacity, thought to be a gall stone. An intravenous cholangiogram was performed, 20 ml. of 30% iodipamide being used, but no concentration of dye was seen. Surgery was not undertaken. She had no history of past renal disease.

On her last admission she was a frail, mildly jaundiced woman who weighed 38 kg. Bilateral basal crepitations were heard in the respiratory system, but there was no evidence of congestive cardiac failure. The blood pressure was 160/100. The liver was palpable three fingerbreadths below the costal margin; it was smooth and not tender.

Investigations.—Haemoglobin 76%. Electrolytes normal. Blood urea 41 mg./100 ml. Urine protein-free. Liver-function tests: bilirubin 3.2 mg./100 ml. (conjugated 2.1 mg./100 ml.). Alkaline

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phosphatase 81 K.A. units. S.G.O.T. 20 units. S.G.P.T. 30 units. Flocculation tests normal. X-ray examination of the abdomen showed slight hepatic enlargement, but no opaque calculi were reported.

A diagnosis of obstructive jaundice was made and she was transferred to the surgical unit for operative treatment, but this had to be deferred because of the onset of bronchopneumonia. However, while she was being treated for this her jaundice faded and the liver-function tests improved. During treatment of the bronchopneumonia she became confused and uncooperative. Her fluid intake was poor and consequently she became dehydrated. At no stage, however, was she oliguric. When the serum bilirubin had fallen below 2 mg./100 ml. an intravenous cholangiogram was arranged in case a normal biliary system without gall stones could be demonstrated, when the need for operation would be obviated. Blood urea taken on the morning of the cholangiogram (28 October) was later reported to be 79 mg./100 ml. An intravenous injection of 35 ml. of 50% solution of iopamide (Biligradin forte) was given, but the patient collapsed with diarrhoea and vomiting, later becoming breathless, with cold cyanosed extremities. Her blood pressure was 110/70, and the investigation was abandoned. She recovered spontaneously but anuria developed. For five days after the cholangiogram she passed no urine at all, and at three days her blood urea was 249 mg./100 ml.

Over the course of three weeks she was haemodialysed five times. Her renal function improved, and for a week before her terminal bronchopneumonic illness the blood urea fell spontaneously and the daily urinary output varied between 840 and 1,500 ml. A specimen of urine passed after the period of anuria showed many pus cells, moderate numbers of red cells, and squamous epithelial cells with granular and hyaline casts. There was a mild degree of proteinuria (30–100 mg./100 ml.). She died on 4 December, and at necropsy, besides evidence of bronchopneumonia, there was a dilated, thickened bile duct with heavy bile-staining of the liver. No stones were found in the bile ducts. The kidneys, which were not contracted, showed an irregular cortex with an adherent capsule. Microscopical examination showed the changes of chronic pyelonephritis. Because of post mortem autolysis a histological diagnosis of acute tubular necrosis could not be definitely established, especially as at the time of her death, which occurred five weeks after the cholangiogram, renal function was well on the way to recovery.

Case 2

A 42-year-old man was admitted as an emergency case to the Gordon Hospital on 7 July 1964 with a five-day history of severe epigastric pain and vomiting. He had had four similar but milder attacks in the preceding seven months, one of which was diagnosed elsewhere as acute pancreatitis. He took a moderately high amount of alcohol, and smoked 20–30 cigarettes a day. His previous illnesses included a nephrectomy performed in 1940 for a traumatic injury to his right kidney.

On examination he was afebrile. The only abnormal findings were tenderness and guarding in the epigastrium. A diagnosis of acute pancreatitis was made.

Investigations.—Haemoglobin 99%. White blood count 15,600/cu. mm. (81% polymorphs). Erythrocyte sedimentation rate 34 mm./hour. Electrolytes normal. Blood urea 30 mg./100 ml. Liver-function tests normal. Serum amylase 188 Somogyi units, falling to 85 and rising to 178 after a week. Urine: moderate albuminuria (30–100 mg./100 ml.). X-ray picture of chest and abdomen normal.

His symptoms persisted and he developed an intermittent fever. Three days after his admission a cholecystogram was performed after the administration of two doses of Solu-biloptin (each dose containing 3 g. of the calcium salt of β -3-dimethylamino-methylamino-2,4,6-tri-iodophenyl propionate). The gall-bladder area was obscured by gas shadows and no opacification of the biliary tract was seen. A barium-meal examination four days later showed gross widening of the duodenal loop, and it was thought that a pseudo-pancreatic cyst was present. Because of persistence of his symptoms and the radiological findings, a laparotomy was arranged after an intravenous cholangiogram. This was undertaken on 17 July 1964, and 20 ml. of 50% iopamide was injected; but the films were of poor quality because of residual barium. On his return from the x-ray department the patient collapsed, and remained hypotensive for 10 minutes. Laparotomy was postponed until next day, when he was noticed to be icteric.

Operation.—A very large pancreatic cyst was found, and biopsy of a frozen section showed it to be a benign cystadenoma associated with recent pancreatitis. The cyst was drained with a Portex tube, brought out through the abdominal wall, no attempt being made to drain the cyst into the intestine because of gross inflammatory reaction around the pancreas. An operative cholangiogram was performed by injecting 5 ml. of sodium diatrizoate (45% Hypaque) into the common bile duct. This did not reveal any dilatation of the ducts or obvious stones, and a subsequent film showed dye in the duodenum. No hypotension occurred at any time during the course of the operation.

After the operation the patient became oliguric and passed 300 ml. of urine the next day and 150 ml. the day after. This urine contained a trace of protein and moderate numbers of red and white cells but no casts. An intravenous injection of 20 g. of mannitol failed to produce a diuresis. The oliguria persisted and the blood urea rose to a maximum of 287 mg./100 ml. on the tenth post-operative day. The most likely cause of the renal failure was thought to be acute tubular necrosis secondary to use of the contrast media employed in cholangiography. It was considered to be unlikely that the acute tubular necrosis was a sequel to the operation, because no episode of hypotension occurred during this procedure. Obstruction to the urinary tract was excluded by retrograde catheterization of the left ureter.

Fortunately his renal failure was not severe enough to require dialysis. Diuresis ensued, and six weeks after the operation his blood urea and urine output were normal. His health has since been excellent.

Discussion

Oral cholecystographic media have been described as rare causes of renal failure (Seaman *et al.*, 1963; Harrow and Winslow, 1966). One such agent (Bunamiodyl) was withdrawn from the market after several reports of renal failure following its use (Seaman *et al.*, 1963). The action of these substances appears to be a direct one upon the renal tubules, which exhibit generalized degenerative changes (Fink *et al.*, 1964). Pre-existent renal disease is often found in such cases. Angiographic agents, such as sodium diatrizoate, have also been shown to have a direct nephrotoxic action (Killen and Lance, 1960). No case of renal failure attributable to a nephrotoxic action of iopamide is known to the makers (P. Bye, personal communication, 1966). However, recently a rapid injection of iopamide into the renal artery has been shown to produce swelling of the renal cortex and medulla in cats: likewise, intravenous cholangiography in the human produces an increase in renal size radiologically (Lindgren *et al.*, 1966). This, however, occurs only when the iopamide is injected rapidly.

There can be little doubt that in Case 1 the intravenous cholangiogram precipitated acute renal failure. Two weeks previously the patient was known to have a normal serum urea. At the time that the cholangiogram was performed this had risen to 79 mg./100 ml., but dehydration had presumably produced a reduction in the glomerular filtration rate over the preceding week. There was no evidence of oliguric renal failure until Biligradin was administered, when the patient became anuric. In retrospect, the dose given was excessive in view of the patient's small stature. Post mortem examination revealed chronic pyelonephritis, which had been unsuspected in life. The fact that renal function was recovering during the last few weeks of the patient's life confirms that renal failure in this case was an acute episode, and not the result of chronic renal disease. The kidneys must have been vulnerable, because of chronic damage, though this fact could not have been known at the time the radiological investigation was performed.

In Case 2 oral cholecystography had been performed seven days before renal failure developed: the agent used has been recorded as a rare cause of renal failure (Seaman *et al.*, 1963), but presumably it had been excreted by the time this complication occurred. Iopamide was given the day before operation, and sodium diatrizoate during the operation. Although the

latter has a nephrotoxic action, this is weak (Killen and Lance, 1960), and it is unlikely that such a small dose injected into the biliary tree would cause anuria. Neither did the blood pressure fall during operation to suggest tubular necrosis secondary to renal ischaemia. Renal failure often occurs as a consequence of a summation of insults to the kidney, and it has been suggested that, if possible, surgery should be postponed until several days after such radiological investigations (Milne, 1965). This case supports such a suggestion. The fact that this patient had only one kidney may have rendered him especially vulnerable to nephrotoxic agents.

An alternative possibility to a direct nephrotoxic action of iodipamide is that renal tubular damage occurred as a result of a fall in blood pressure. Iodipamide has a markedly hypotensive action (Saltzman and Sundström, 1960). At no time, however, did either patient's blood pressure fall below 110/70. Tubular necrosis from this cause is therefore unlikely.

It has been shown that the intravenous injection of both urographic and cholegraphic media provokes intravascular aggregation of red blood cells and a sludging effect (Lindgren and Saltzman, 1962). Whether this is responsible for the renal damage is not known.

The two cases quoted here suggest that iodipamide may on rare occasions cause renal failure where there are potentiating circumstances such as impaired hepatic function and pre-

existing renal disease, or where surgical operations have been performed within hours of cholangiography.

Summary

Two cases of renal failure after intravenous cholangiography are described. In each case there was evidence that the patient was predisposed to develop renal failure. The first patient, who had unsuspected chronic pyelonephritis and a mild degree of jaundice, became anuric immediately after cholangiography. The second, who had only one kidney, developed oliguric renal failure after cholangiography, performed within 24 hours of laparotomy.

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Plasma Salicylate Levels in Acute Poisoning in Adults

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Admission of poisoned patients to hospital is steadily increasing (H.M.S.O. Report, 1966; Matthew and Lawson, 1966). Acute salicylate poisoning accounts for about 15% of these admissions in adults, and this particular type of poisoning is likely to present as a medical emergency wherever aspirin is freely available. Infants and toddlers are particularly sensitive to accidental or therapeutic poisoning with the drug, and there may be severe acid-base imbalance with no clear relation between the ensuing symptoms and the level of salicylate circulating in plasma. In adults, however, the situation is somewhat simpler. The normal therapeutic use of aspirin results in plasma salicylate levels of a few milligrams per 100 ml., while the treatment of rheumatic conditions may require the maintenance of levels of 25 or 30 mg./100 ml. Within this range and beyond, one or more of the features of salicylism become evident in those suffering from acute poisoning. In such cases a reliable clinical assessment of the severity of poisoning is often difficult to make (Cumming, Dukes, and Widdowson, 1964; Beveridge, Forshall, Munro, Owen, and Weston, 1964). The patient is almost invariably conscious and will usually admit to taking an overdose, but the quantity consumed will be exaggerated or minimized. In addition, vomiting will frequently have occurred, so that the actual amount of drug absorbed is unknown.

Our experience confirms that in these circumstances a knowledge of the plasma salicylate level, and its rate of change during the period immediately following admission, provides a valuable indication of the severity of poisoning and a very useful guide to the type of treatment required. In view of this, and

of the fact that 60% of admissions to the Poisoning Treatment Centre occur between the hours of 5 p.m. and 8 a.m. the next day, it is clearly desirable to have available a method of estimating plasma salicylate which is simple and reliable enough to be carried out equally well by physicians in the ward side-room as by the staff of the chemical toxicology laboratory. We find that the method devised by Trinder (1954) meets these demands.

Report

During the two years from January 1 1964 to December 31 1966, 1,674 adults were admitted to the Poisoning Treatment Centre, Royal Infirmary, Edinburgh; 214 of them were suspected on clinical grounds, or from the recent history, to be suffering from salicylate poisoning. In most of these cases estimations of plasma salicylate were performed, either in the ward side-room or in the laboratory, on heparinized blood specimens taken before gastric aspiration and lavage (Matthew, Mackintosh, Tompsett, and Cameron, 1966). The assay was that of Trinder (1954), as described in detail by MacDonald (1965). The reaction was most conveniently carried out with 5-ml. portions of reagent and 0.5 ml. of plasma or salicylate solution (40 mg./100 ml.), in disposable tubes (10-ml. plain bottles, Stayne Laboratories Ltd.), the absorbance being measured in standard cuvettes (EEL Spectra); the whole procedure can be completed within 10 to 15 minutes.

The results are shown in the Table. Figures in parentheses represent estimations carried out in the laboratory for patients admitted to other hospitals in the region, although not necessarily for salicylate poisoning. One of this group of cases, however

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