A physiological role for the prostaglandins in parturition whereby these substances cause the uterus to contract by enhancing the myometrial response to circulating endogenous oxytocin can at present be only an interesting hypothesis, but the recent development of accurate methods of measuring plasma oxytocin and prostaglandin during labour may allow it to be tested soon.

Encouraging results have been obtained with the potentiation of the uterine response exhibited when oxytocin and prostaglandin $F_{2\alpha}$ or prostaglandin E_2 are administered simultaneously. This technique enables the prostaglandin to be infused at one-fifth the usual abortifacient dose and virtually eliminates gastrointestinal side effects. The preliminary work suggests that the abortifacient efficiency of this combination is high, probably because the prostaglandin enables the oxytocin to exert its very specific stimulatory action on the

myometrium in an efficient manner. A more detailed study of the use of the potentiation of oxytocin and prostaglandin effects to produce mid-trimester abortion is underway.

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Nephrotoxic Lesions from 5-Aminosalicylic Acid

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Summary

5-Aminosalicylic acid given to rats as a single intravenous injection led to necrosis of the proximal convoluted tubules and of the renal papilla. These two lesions developed at the same time and the cortical lesions did not appear to be a consequence of the renal papillary necrosis. Since the compound possesses the molecular structure both of a phenacetin derivative and of a salicylate these observations may be relevant to the problem of renal damage incident to abuse of analgesic compounds and suggest the possibility that in this syndrome cortical lesions may develop independently of renal papillary necrosis.

Introduction

5-Aminosalicylic acid has structural similarities to both the *p*-aminophenol-derived phenacetin analgesics and the salicylates (see Formula). In a study of the comparative nephrotoxicity of aspirin and phenacetin derivatives (Calder, Funder, Green, Ham, and Tange, 1971) 5-aminosalicylic acid was found to have the unique property of inducing both necrosis of proximal convoluted tubules and renal papillary necrosis. In this paper

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we are concerned with the evolution of the renal lesion produced by 5-aminosalicylic acid and its possible relation to renal damage associated with prolonged and excessive intake of compound analgesic preparations.

Methods

Sixty female hooded rats weighing about 200 g were given water to drink and a pellet diet. Animals were individually marked, anaesthetized with ether, and given a single intravenous injection of the sodium salt of 5-aminosalicylic acid in a dose of 1.4, 2.8, or 5.7 mM/kg. Animals were killed in pairs by bleeding under ether anaesthesia 24, 48, and 96 hours and one and two weeks after injection. Ten animals were used as controls and given a single intravenous injection of 1 ml of normal saline. Twenty animals were killed six hours after a single intravenous injection of 5-aminosalicylic acid 5.7 mM/kg. Tissues were fixed in 10% formalin and processed for paraffin embedding or in glutaraldehyde and osmium tetroxide for embedding in Araldite for thin sections and examined by light microscopy.

Kidney and muscle K^+ was measured by flame photometry in 10 control animals and in 20 experimental animals killed 24 hours after intravenous injections of 5-aminosalicylic acid (5.7 mM/kg).

Results

The animals became cyanosed after the injection of 5-aminosalicylic acid; this effect was transient. All the animals recovered from the effects of injection and anaesthesia and remained apparently well until killed. Lesions were found only in the kidneys, both the cortex and the medulla being affected. No histological changes were found in the heart, lungs, liver, pancreas, or intestine.

By 24 hours after injection the cortical lesion consisted of necrosis of proximal convoluted tubular epithelium, usually of the distal third but sometimes in more proximal segments. The lesions were focal, involving individual cells or all cells in isolated segments or groups of tubules, with intervening tubules being spared (Fig. 1). At 48 hours frequent mitoses were seen in neighbouring tubule cells. At 96 hours in some animals there were persistent signs of cortical damage; dilated tubules were lined by flattened epithelium and interstitial round-cell infiltrates were present. No abnormalities were found in the cortex at one or two weeks.

A variety of lesions were found in the medulla. These comprised necrosis of the tip of the papilla (Fig. 2) or of a portion of the tip or sometimes partial necrosis affecting Henle's loops, vessels, and interstitial cells but sparing the collecting

FIG. 1—Rat kidney. Necrosis of adjoining segments of proximal convoluted tubules. (H. & E. $\times 127$.)

FIG. 2—Rat Kidney. Necrosis of renal papilla. (H. & E. $\times 37$.)

ducts (Fig. 3). The epithelium of collecting ducts near the tip of the papilla was filled with eosinophilic droplets that stained with periodic-acid Schiff. In plastic-embedded materials these were found to be accompanied by numerous clear vacuoles (Fig. 4). Only rarely were mitoses observed in these cells. Droplets were found in all animals given the highest dose of 5-aminosalicylic acid and killed six hours after injection and were the only lesions found in these animals. Droplets were still present in animals killed at 48 hours but at 96 hours they had disappeared, leaving apparently normal collecting duct epithelium. Mitotic figures and irregularities in cell size

were frequently seen at 48 hours in the more proximal cells of the collecting duct. Frank papillary necrosis was present at one and two weeks in a few animals. In others damage to the renal papilla was indicated by an infiltrate of mononuclear and polymorphonuclear cells among eosinophilic remnants of basement membranes of capillaries and Henle's loops.

Necrosis of the renal papilla was seen in 23 of the 60 animals and necrosis of proximal convoluted tubules in 13 animals. Lesions in both regions were most commonly seen at 48 hours, and cortical damage was observed only in animals with renal papillary necrosis. At one and two weeks lesions were found only in the renal papilla; some of the cortical lesions found at 96 hours were severe enough to suggest that they would not have completely resolved, and this absence of cortical lesions at one and two weeks reflects only the inconstant occurrence of renal damage. Higher doses of 5-aminosalicylic acid tended to produce more severe renal lesions both in the cortex and in the medulla, but there were exceptions to this and the severity of the renal damage could not be consistently related to dose. The proportion of animals without renal lesions was similar at all dose levels.

FIG. 3—Rat kidney. Necrosis of interstitial tissue, Henle's loops, and capillaries at the tip of the renal papilla. Collecting duct epithelium is intact. (H. & E. $\times 206$.)

FIG. 4—Rat kidney. Droplets and vacuoles in collecting duct epithelium at the tip of the renal papilla. (Plastic embedding. Alkaline toluidine blue. $\times 206$.)

Estimations of renal and muscle K^+ 24 hours after injection of 5-aminosalicylic acid were not significantly different from those in control animals. The incidence of renal damage in these animals was similar to that recorded in the first experiment.

Discussion

These findings show that a single compound with a structural resemblance to both salicylic acid and phenacetin can produce damage to segments of the nephron in both the cortex and the medulla and seem to be relevant to the problem of renal damage associated with analgesic abuse (Spühler and Zollinger, 1953; Kincaid-Smith, 1967).

The sporadic and incomplete incidence of renal lesions in this series of experimental animals, evident at all dose levels, recalls the sporadic incidence of renal damage in patients taking analgesics over long periods. The factors responsible for this variable experimental effect may be of importance in indicating the nature of the processes responsible for the variable incidence of the clinical syndrome. It has been shown that aspirin and phenacetin derivatives, if acutely nephrotoxic to rats, produce necrosis of proximal convoluted tubules rather than renal papillary necrosis (Calder *et al.*, 1971). It is therefore of interest that 5-aminosalicylic acid, which has the structural characteristics of both analgesic groups, should produce a combined lesion of the renal cortex and medulla. Such a pattern suggests that synergism between components or metabolites of combined analgesic preparations may be responsible for the cortical and medullary components of the renal damage associated with analgesic abuse and reinforces previous suggestions (Green, Ham, and Tange, 1969; Calder *et al.*, 1971) that analgesic compounds may have a toxic effect on the renal cortex rather than on the medulla alone.

Droplet formation in the collecting duct epithelium of the tip of the papilla is the only lesion found six hours after injection of 5-aminosalicylic acid. Similar droplets have been found after temporary renal ischaemia (Sheehan and Davis, 1960)

and in papillary necrosis produced by ethyleneimine (Oka, 1913), especially when necrosis is confined to a small portion of the papilla (Funder, Ham, and Tange, unpublished). The combination of droplets in collecting duct epithelium, mitoses in collecting duct epithelium in adjacent regions of the medulla, and damage to epithelium in proximal convoluted tubules resembles the lesion produced in rats by experimental K^+ deficiency (Milne, Muehrcke, and Heard, 1957). No evidence for K^+ deficiency was obtained in these animals and it is improbable that such deficiency could have developed so quickly. Thus it is apparent that the experimental renal lesions produced by 5-aminosalicylic acid are not mediated by K^+ deficiency, but it is conceivable that similar disorders of intracellular structure and function may be involved, and this may also prove to be an indication of the processes preceding renal papillary necrosis however produced.

It should not be inferred that 5-aminosalicylic acid is directly concerned in the genesis of renal damage incident to analgesic abuse or that it is necessarily nephrotoxic in man. 5-Aminosalicylic acid is known to be a metabolite of salicyl-azosulphapyridine (Hanngren, Hansson, Svartz, and Ullberg, 1963), and renal lesions have not been noted in a series of patients treated intermittently with this drug (Cuthbertson, 1971) over a 10-year period.

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MEDICAL MEMORANDA

Spontaneous Rupture of Testicular Teratoma

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A case of teratoma of a testis presenting as sudden spontaneous rupture of the testis without previous injury is described.

Case Report

An 18-year-old youth was out walking when he experienced a sudden severe, sickening pain in the right scrotum, which started to swell up rapidly. He was taken to hospital and admitted to the general surgical ward by the casualty officer with a diagnosis of ? strangulated right inguinal hernia.

When seen in the ward the patient was obviously in pain. He was emphatic about the sudden onset of his symptoms and was not aware of any recent injury to the scrotum, though during the previous month he had noticed that his right testicle was larger than the left. The only relevant point in the past history was the information subsequently offered by his parents—namely, that his left testicle was undescended at birth. As they were not concerned about this they had never again checked the position of the testicle.

On examination the left testicle was in the scrotum but was about half the normal size. The right scrotum was swollen, tense, bluish, and very tender but did not look inflamed. The swelling extended to the groin, with pronounced thickening of the cord. The right testicle could not be felt as the patient resented any handling of the scrotum. The most likely diagnosis was thought to be acute torsion of the testicle, and preparations were made to explore the scrotum.

With the patient under general anaesthesia an incision was made in the oedematous right scrotum. A bulging, bluish swelling was exposed. A nick was made with care in the sac and a gush of fresh blood was obtained. It soon became obvious that this was a haematocoele. After the blood was evacuated by suction the contents of the scrotum were inspected. There was no evidence of torsion of the testicle, which was of normal colour and seen though it was enlarged to twice the normal size. The cord was oedematous, but not twisted, with good pulsation throughout. There was a stellate tear in the lower pole of the testis through which fresh, bright red blood was spurting. The testicular core was digitally explored through the rent in the tunica vaginalis and was felt to be cystic and necrotic. In view of the possibility of malignancy it was