Methyl xanthine diuretics

Caffeine, theobromine, and theophylline were first studied in 1886 and although they are now obsolete they were important before the discovery of the synthetic diuretics in 1951 and especially before organic mercurials were introduced in 1920. They act by depression of renal tubular reabsorption. Caffeine is only a weak diuretic. Theophylline was shown to be better than theobromine by H M Marvin in an excellent early clinical trial (Journal of the American Medical Association 1926;87:2043–6). It was effective in two thirds of patients who were still oedematous after treatment with digitalis. Theophylline also has a direct stimulant effect on the myocardium which was demonstrated at cardiac catheterisation by McMichael and colleagues at Hammersmith Hospital (Clinical Science 1946–48;6:125–35) and shown by them to be greater than that of digoxin in hypertensive right heart failure.

Theophylline is found in the tea plant *Camellia sinensis* (*Theaceae*) a native of China and India but the amount, 0-1%, is small for clinical use so it has to be synthesized. Theobromine is present in the cocoa tree *Theobroma cacao* (*Sterculiaceae*) which comes from the tropical forests of South America. Caffeine is present in both tea and cocoa and in other traditional beverages. In Africa these are coffee *Coffea arabica* (*Rubiaceae*) and the cola nut *Sterculia acuminata* (*Sterculiaceae*). In South America the ancient drink mate is made from a species of holly *Ilex paraguariensis* (*Aquifoliaceae*) while yoco comes from a species of *Paulinia* (*Sapindaceae*). Thus the methyl xanthenes come from six plant families in the Old and New World that have no obvious botanical similarities. As has so often happened with medicinal plants, their therapeutic value was discovered by chance.

Purgatives were often used to treat heart failure before the xanthine diuretics were introduced and several of them were plants—elaterium, senna, aloes, cascara, croton, rhubarb, and podophyllum. Presumably they produced their effect because of the coincidental sodium loss that accompanied diarrhoea.

Theophylline seems to be making an exciting therapeutic comeback. It is now used to control erythrocytosis in patients with renal transplants. It reduces erythropoietin production by adenine antagonism (New England Journal of Medicine 1990;323:86–90).