octapeptide hormones—arginine vasotocin and ichthyotocin—have been identified in the neurohypophysis of fish[3], and Lederis[4] has shown that at least the former resides in elementary granules, one of the neurone types may be vasotocinergic and the other ichthyotocinergic. Such a possibility can be tested only by isolation of the two types of neurones and identification of the hormones they produce.

We thank Dr Gunther Sterba for allowing us to report that in recent work on the pre-optic nucleus of the carp, *Cyprinus carpio*, he has identified dark and light cells very similar to those described above.

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Enzyme Induction in Man caused by Smoking

Higher animals may change in their response to drugs because of a decrease in the sensitivity of drug receptor sites in the organism, or because of accelerated drug metabolism. The latter has been explained[1] on the basis of drug induced stimulation of liver microsomal enzymes, for example, many compounds have been listed which induce microsomal oxidizing enzymes in rats, and phenobarbital has been shown to stimulate the metabolism of the anti-coagulant coumarin in man[2]. We now report the induced enzyme metabolism of nicotine in man by tobacco smoking.

The recovery of nicotine from urine after administration by (*a*) intravenous injection; (*b*) inhalation of nicotine vapour; and (*c*) smoking to male subjects (age 21–40 yr, not taking other drugs) whose urine was maintained acidic was determined by gas–liquid chromatography[3]. Maintenance of an acid urine minimizes intra- and inter-subject variations in excretion of bases[4–6], and in these conditions the excretion of unchanged nicotine is virtually complete in 8 h. (Smoking (*c*) was measured from the amount of nicotine in the main stream smoke[7].)

The results of the nicotine experiments are shown in Fig. 1; variation between subjects was small. Whatever the route of administration, the percentage recovery of nicotine in the urine remained constant within ±8 per cent for each subject, and was greater for non-smokers (55–70 per cent) than for smokers (25–50 per cent) (Fig. 1). Non-smokers were not given nicotine more than once every 3 weeks during the trials; nicotine recoveries were the same throughout the trial period.

The increased metabolism of nicotine by smokers cannot be attributed to the increase in the nicotine dose resulting from inhalation, because the recovery of nicotine excreted unchanged in the urine was the same for subjects after intravenous injection and smoking, and was also the same when subjects inhaled or deliberately non-inhaled while smoking, that is, recoveries of nicotine in the ranges of doses used were not affected by the dose of nicotine absorbed.

Subjects were classified as non-smokers if they did not smoke more than thirty cigarettes or three cigars a year. One current non-smoker (G. O. J., Fig. 1) had been a heavy smoker some years before the trials; a lower recovery of nicotine was observed in this subject than in other non-smokers. It is possible that the tolerance to nicotine lasts for at least 2 months, for one smoker (J. F. T., Fig. 1) abstained from normal cigarette smoking during a 2 month period of the trial; the nicotine recovery remained as expected for a smoker.

Thus the clear difference in nicotine recovery in smokers and non-smokers indicates that habitual smoking induces enzyme metabolism of nicotine. Preliminary results indicate that it is not by an increased metabolism to cotinine because recoveries of cotinine from the urine of smokers and non-smokers were comparable.

Others have demonstrated for the dog and rabbit[8], and for the rat[9], that chronic exposure to nicotine leads to a decreased percentage excreted unchanged in the urine. Werle and Uschold[9] injected rats with nicotine daily for 10 days and from their results concluded that progressively less was excreted in the urine.

Indirect evidence of an acquired metabolic tolerance to nicotine in man by tobacco smoking has been presented by Rottenstein and co-workers[10]; intravenous injection to smokers did not cause nausea but in non-smokers the same dose produced nausea and vomiting.

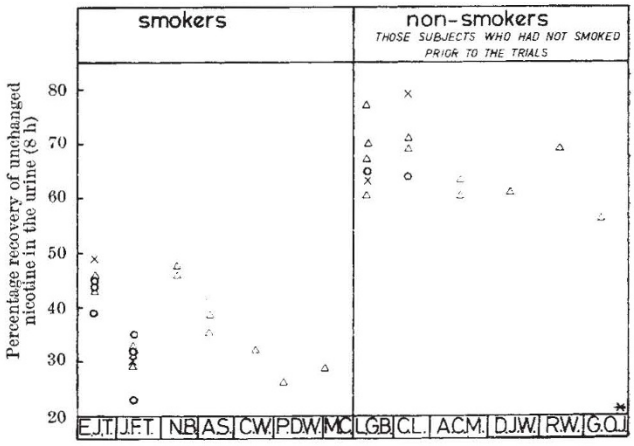

Fig. 1. The percentage recovery of unchanged nicotine in the urine (8 h) of human subjects with various routes of drug administration; urine maintained acidic. ⊙, Intravenous administration (1·0–2·0 mg); ×, inhalation of nicotine (0·1–0·5 mg); △, smoking (0·05–2·3 mg). * This subject had been a heavy smoker, but had stopped smoking some years before the trials.

The rate of development of the acquired tolerance to nicotine and the possibility that nicotine or other constituents of tobacco smoke stimulate the metabolism of other compounds is being investigated.

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