MATTERS ARISING

Monkeys are insensitive to pyrogenic effects of human α-interferons

SCHELLEKENS *et al.*[1] injected rhesus monkeys intramuscularly with preparations of human α-interferon (HuIFN-α) of two types. One came from human blood leukocytes and had a specific activity of $10^{6.2}$ U per mg protein; the other species (IFN-α_2) was derived from *Escherichia coli* by recombinant DNA techniques and had a specific activity of $10^{7.6}$ U per mg protein. Equivalent numbers of antiviral units of the two preparations gave equal protection to the monkeys against infection of the skin with vaccinia virus. Three hours after the first injection, the monkeys given leukocyte interferon (500,000 U per kg body weight) had significantly more fever and lower white blood cell counts than those dosed with the same amount of the bacterial product. It was suggested that the leukocyte interferon preparation (presumably a mixture of different α-interferon species[2,3]) might be more toxic because it contained one or more interferon species other than IFN-α_2. If, then, the α_2 species also produces significantly fewer side effects in man at the same antiviral dose, substantially larger amounts might be used clinically: the authors suggested the possibility of a 10 times larger dose.

Schellekens *et al.* put forward a second explanation for their results—that the toxic effects reflected impurities present in their leukocyte preparation (which was ~1% pure). Results with more highly purified HuIFN-α preparations derived in our laboratory from lymphoblastoid cells (Namalwa line) support this view. In a toxicological study, patas monkeys (4–7 kg body weight) were dosed daily for 15 days with 2×10^6 IU per kg body weight (four times more than was used by Schellekens *et al.*). The batch used had a specific activity (before addition of human serum albumin, 1.5 mg per ml, as a stabilizer) of $10^{7.2}$ IU per mg protein. There were no consistent changes in either rectal temperature at 2, 4 or 6 h after the first dose or peripheral white blood cell counts at 3, 7, 10 and 15 days. In another study (H. Nakatani, personal communication), rhesus monkeys (1.2–2.1 kg body weight) were dosed each day for 3 months with 1×10^6 IU per kg body weight of another batch with a specific activity of $10^{7.9}$ IU per mg protein. There was no significant change in rectal temperature 2 or 6 h after the first dose, or in white cell counts at any time during the study. (No major pathological or other changes were observed in the monkeys in either study.) Both Namalwa interferon preparations, as well as other routine preparations issued for clinical use with a specific activity of $\geq10^{8.0}$ IU per mg protein, have nevertheless produced fever and leukopenia in patients (ref. 4 and T. J. Priestman, personal communication). These were not caused by contamination with bacterial endotoxin.

It is clear that tests in monkeys cannot yet be used to predict whether a particular human IFN-α preparation will be pyrogenic in man, and phase I (dose-tolerance) studies such as those already carried out with our Namalwa interferon[4] will be needed for each type of preparation.

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WEISSMANN AND SCHELLEKENS REPLY—Finter and his colleagues conclude from their experiments that the pyrexia arising in rhesus monkeys following injection of <1% pure, blood leukocyte interferon is due to impurities in the preparation (our second explanation[1]), rather than to a particular species of interferon other than IFN-α_2 which might be present in such leukocyte interferon preparations. This conclusion is not warranted, however, because it is based on their finding that highly purified lymphoblastoid (Namalwa) interferon does not cause fever in patas and rhesus monkeys and there is no evidence that lymphoblastoid interferon contains the same spectrum of interferon species as leukocyte interferon. Thus, the formal possibility of a peculiar interferon species in blood leukocyte interferon preparations still remains.

Nevertheless, we also believe it more likely that the presence of impurities in the leukocyte interferon preparation was responsible for pyrexia in rhesus monkeys, and we agree that in regard to monitoring side effects such as pyrexia, rhesus monkeys may not be a reliable model system.

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Do antidepressants induce dopamine autoreceptor subsensitivity?

ACCORDING to Chiodo and Antelman[1], repeated daily treatment of rats with tricyclic antidepressants results in a 'subsensitivity' of dopamine autoreceptors. Using extracellular single unit recording methods, they measured the responsiveness of neurones located within the substantia nigra zona compacta, to a low (4 μg per kg, intravenously) dose of apomorphine. In these experiments, the effects of apomorphine were dramatically attenuated in rats that had been treated for 10 days with amitriptyline, imipramine or iprindole as compared with saline-treated rats.

We have attempted to reproduce these results by examining the effects of cumulative intravenous doses of apomorphine, using very similar electrophysiological methods. Male Wistar rats were treated twice daily for 10 days with imipramine (10 mg per kg, $n=20$), amitriptyline (10 mg per kg, $n=11$), or saline ($n=35$) intraperitoneally. At 48 (±4) h after the last treatment, rats were anaesthetized with chloral hydrate and firing rate was recorded in zona compacta neurones that had been identified according to the criteria of Bunney *et al.*[2]. Apomorphine was administered sequentially at 90-s intervals at doses from 4 to 128 μg per kg. As compared with saline, neither amitriptyline nor imipramine appreciably altered the inhibitory effects of any dose of apomorphine on firing rate.

Several considerations may account for our failure to duplicate the results of Chiodo and Antelman: for example, we used Wistar rats, whereas Chiodo and Antelman used Sprague–Dawley rats. This explanation seems unlikely because a second laboratory (MacNeil and Gower, see below), using Sprague–Dawley rats,

0028-0836/82/280301—03$01.00