of declared AIDS cases. Only limited information is available and the rapid diffusion of HIV infection among drug addicts in large Italian cities (such as Milan, Florence and Rome)[2], although showing an increasing prevalence (1981–1985), does not illustrate national differences, in particular for southern Italy.

An epidemiological study involving 160 centres in large and small cities from all over Italy and including more than 18,000 drug addicts has recently been carried out. Seropositivity was only scored when two enzyme-linked immunosorbent assay (ELISA) tests were positive. Seropositivity among drug addicts was 54% in the north of Italy, 39% in the centre and 26% in the south. Preliminary data suggest that seropositivity in drug addicts varies not only from big to small cities, but also that an unexplained geographical distribution exists[3].

In order to update information on the rise of seropositivity, we evaluated 451 sera collected in Rome between 1979 and 1986, selecting people giving up drug abuse at different times (see figure). In addition, a study of 513 sera of addicts who started abusing drugs from 1981 onwards, shows that from 1983 to 1984 no evidence of behaviour modification can be observed. Data on antibodies to HIV in sera of drug addicts in Rome stored in different years before 1983 show that the evolution of seropositivity is not homogeneous in different areas of the same city. All these data demonstrate that, despite a prevention campaign, no decrease of seropositivity in new drug addicts has been observed. In addition, our data show that 15% of 460 partners of seropositive persons are also seropositive by both two ELISA tests and a Western blot test. This category represents a very high risk group for the possible extension of the infection in Italy among the general population.

Steps to prevent HIV infection in drug addicts should include recommendations not only for avoiding the sharing of syringes but also for avoiding at-risk sexual intercourse. In our opinion care and prudence are needed when partial data are used for general comparison although a common trend shared in Western countries is now evident.

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Elemental metallic irrelevance

SIR—Regardless of the eventual outcome of the polemic concerning the role of aluminium in the aetiology of Alzheimer's disease, evidence gleaned from elemental metallic contamination of brain tissue[1] is likely to be as irrelevant as would be searching for improvements in rheumatoid arthritis in patients with gold threads sewn into their bodies. There are other similar examples: the infrequency of poisoning from years-long exposure to embedded ballistic lead[2]; and the lack of toxicity from accidentally-ingested elemental mercury[3].

The chemistry of ionized metals is as diferent from that of their zero-valence states as should be economic considerations from the legitimate rationale for publication of scientific findings. Regardless of the market value of the stocks of manufacturers of various metal wares, the search for the culprit in Alzheimer's disease will go on.

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Inositol phosphates and calcium entry

SIR—Neher's summary[1] of current thinking on "receptor-operated Ca^{2+} channels" which was inspired by Kuno and Gardner's[2] experiments, nicely encapsulates the apparent contradictions in the three presently proposed mechanisms as to how these channels operate. It may be, however, that the experimental results are not as contradictory as they seem.

Ca^{2+}-mediated Ca^{2+} entry as shown by Von Tscharner *et al.*[3] is, at least in some tissues, demonstrably not the principal mechanism of receptor-mediated Ca^{2+} entry. In these tissues a complete temporal dissociation can be shown between the Ca^{2+} pulse caused by intracellular mobilization, and the sustained Ca^{2+} rise caused by Ca^{2+} entry (for example, refs 4–6). Perhaps, therefore, Ca^{2+}-stimulated Ca^{2+} entry is a supplementary mechanism, or a further modulation of inositol phosphate-mediated mechanisms. Evidence that a diffusible second messenger is controlling Ca^{2+} entry (but that the messenger is not Ca^{2+}) is found also in the experiments of Susuki *et al.*[7].

Kuno and Gardner's results[2], showing an effect of Ins(1,4,5)P_3 on inside-out membrane patches, are easily reconciled with our proposal[8] that Ins(1,3,4,5)P_4 plays a key role in Ca^{2+} entry. The union of the two hypothesis lies in our experimental observations[8] that there is an absolute requirement for a Ca^{2+}-mobilizing InsP_3 to be present in order that InsP_4 can exert its biological effect. Further experiments[9] have shown us that we cannot substitute for InsP_3 with Ca^{2+} (taking eggs of *Lytechinus variegatus* to the brink of activation with the Ca^{2+} ionophore ionomycin, does not sensitize them to InsP_4). We interpret these data as InsP_4 needing the obligatory help of an InsP_3 molecule to control Ca^{2+} entry[9]. This strengthens our suggestion[8] that the two molecules are acting together, most likely by a mechanism related to that proposed by Putney[10] in which InsP_3 indirectly controls Ca^{2+} entry because there is rapid re-filling of the InsP_3-sensitive Ca^{2+} pool from outside the cell. But this refilling requires a Ca^{2+} pump in the endoplasmic reticulum, and such an indirect mechanism is not consistent with Kuno and Gardner's[2] data.

If, however, InsP_4's role is to 'short-circuit' Ca^{2+} transport between the endoplasmic reticulum and plasma membrane[9] (perhaps by forming a link analogous to a gap junction), then Ca^{2+} passage through the InsP_3-controlled pore in the endoplasmic reticulum would be the rate-limiting step for Ca^{2+} entry. Such a mechanism could unite Kuno and Gardner's data with ours, assuming that some aspect of the preparation of their inside-out patches had constitutively activated the InsP_4-mediated process (for example, washing the cells, exposure to high KCl medium, or in Fig. 3 of Kuno and Gardner[2], pretreatment of the cells with PHA). This latter suggestion does not necessarily require any particular mechanism; it simply accommodates our experimental observation[8,9] that both InsP_3, and InsP_4 are required to see a biological effect.

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Scientific Correspondence

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