9. May, G. *Br. J. ind. Med.* **39**, 128 (1973).
10. Kimbrough, R.D. (ed.) *Halogenated Biphenyls Terphenyls, Napthalenes Dibenzodioxins and Related Products* (Elsevier, Amsterdam, 1980).
11. Hay, A. *The Chemical Scythe; Lessons of 2,4,5-T and Dioxin* (Plenum, New York, 1982).
12. Hardell, L. & Sandstorm, A. *Br. J. Cancer* **39**, 711 (1979).
13. Hardell, L. *Scand. J. Work envir. Hlth* **7**, 119 (1981).
14. Moses, M., R. Wilis, K.D. Crow, J. Thornton, A. Fischban, H. Anderson & Selikoff, I.J. *Am. J. Ind. Med.* **5**, 161 (1984).
15. Moody, L. W.E. Halperin, M.A. Fingerhut & Landrigan, P.J. *Am. J. ind. Med.* **5**, 157, (1984).

Dosage compensation and X-chromosome inactivation

SIR — It is now common practice to use the terms dosage compensation and X-chromosome inactivation interchangeably. It is argued here that this equation is technically incorrect and, more importantly, that it obscures a nontrivial facet of mammalian physiology. The proposition is that in flies and mammals, dosage compensation allows males to survive their monosomy for the X chromosome. In mammals, X inactivation is then a device that prevents females from expressing a tetrasomic level of X-chromosome gene product. That is, X inactivation allows females to survive dosage compensation. If we call X inactivation dosage compensation, we are overlooking something in males. That something is dosage compensation.

The idea of dosage compensation and its definition originated with H.J. Muller in his studies of *Drosophila*[1]. In the context of the issues of his day, Muller saw dosage compensation from a selectionist perspective concerned with optimal phenotypes. In this view, dosage compensation was the mechanism by which selection has achieved equality of expression of sex-linked genes in single-X males and two-X females. In the modern context, however, we are forced to add an element to the Mullerian view: dosage compensation not only equilibrates male to female phenotypes but also — and perhaps primarily — equilibrates a male's single X to his two sets of autosomes. The point we seem to overlook is that a *Drosophila* male (or the heterogametic sex in any organism with a chromosomal sex determination system) is aneuploid and aneuploidy is deleterious.

We know from an extensive study of aneuploidy in *Drosophila*[2] that any heterozygous autosomal deficiency greater than about 3% of the haploid genome is a lethal condition. On the other hand, a *Drosophila* male is deficient for a whole X chromosome (about 20% of the genome). The issue, then, transcends his similarity to his sister. He requires dosage compensation for his survival. In *Drosophila melanogaster*, dosage compensation is effected by the elevation of the rate of transcription of the lone X in males relative to either of the X chromosomes in females[3-5]. More to the point, mutations in *Drosophila* which fail to hypertranscribe the X chromosome in males are male-specific lethals[6].

Aneuploidy in mammals, as in *Drosophila*, is deleterious. Mammalian males, like *Drosophila* males, have a congenital aneuploid condition for a considerable fraction of their genomes. We infer that dosage compensation in mammals, as in *Drosophila*, balances the expression of the single X chromosome in males to the autosomal complement; that is a male's single X is hypertranscribed relative to his autosomes. Hypertranscription in *Drosophila* males presents no problem for *Drosophila* females, as they transcribe their two X chromosomes at a basal rate balanced to the autosomes. However, in a species in which X hypertranscription is a property of all X chromosomes in either sex, the female has become, in a formal sense, a hyperploid. Since hyperploidy is also a deleterious condition, she would require a second system to achieve X to autosome balance. One option is to inactivate one of the two X chromosomes.

If mammalian X chromosomes are hypertranscribed in the interest of male survival, X-chromosome inactivation must be dosage-compensation compensation in the interest of female survival. This inference may be of some heuristic value in that it implies the existence in mammals of a class of genetic elements which function to modify X-chromosome expression and to which we might want to give some thought.

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1. Muller, H.J. *Proc. 6th Int. Congr. Genet.* (Ithaca) **1**, 213-255 (1983); *Harvey Lec. Ser.* **43**, 165-229 (1950).
2. Lindsley, D.L. *et al. Genetics* **71**, 57-184 (1972).
3. Ananiev, E.V., Faizullin, L.Z. & Gvozdev, V.A. *Chromosoma* **45**, 193-201 (1974).
4. Lucchesi, J.C. *Am. Zool.* **17**, 685-693 (1977).
5. Lucchesi, J.C., Rawls J.M. & Maroni, G. *Nature* **248**, 564-567 (1974).
6. Belote, J.M. & Lucchesi, J.C. *Nature* **285**, 573-575 (1980).

High time for psychoimmunology

SIR — The term "psychoimmunology" was coined by Solomon[1] to describe his early studies of the effects of behaviour on immune function and on susceptibility to certain experimentally-induced disease processes. More recently, "psychoneuroimmunology"[2] has been used to refer to studies of the neuroendocrine mechanisms mediating the effects of behaviour on immune function — and vice versa. But in a News and Views article, "Psychoimmunology before its time", John Maddox questions the explanatory potential and, by implication, the heuristic value and practicality of pursuing such research[3].

Despite an erroneous characterization of what is "psychosomatic", the article correctly implies that much of the impetus for studying interactions between the central nervous system (CNS) and the immune system derives from observations that psychosocial factors influence the development and progression of disease. To phrase this as a "familiar theme in literature", however, is to impart a scientific triviality to such phenomena. In fact, there is a voluminous scientific literature that documents the integration of mind and body. To justify this scepticism, Maddox points out that the mechanism for such phenomena is unknown, but this does not mean it is unknowable — or that the phenomena are less real. In an attempt to account for such phenomena, then, it is quite reasonable to hypothesize that changes in immune function may mediate the effects of psychosocial factors on the development and/or progression of some pathophysiological states. Such a hypothesis is tenable, however, only if it can be shown that the CNS plays some role in the modulation of immunity.

In referring to a *kind* of connection that is made *plausible* by several unconnected observations, the article begrudgingly acknowledges a functional relationship between the CNS and the immune system. This is not the common knowledge that it is implied to be. That it is accepted at all is, in large part, a result of psychoneuroimmunological research conducted over the past 10 years. The scepticism expressed in the article, however, is not directed at the experimental findings of psychoneuroimmunology. It is fabricated, instead, out of unreferenced claims attributed to "psychoimmunologists": we know of no serious investigators who "talk as if there is no state of mind which is not faithfully reflected by a state of the immune system". The hypothesis that a behavioural state may have immunological consequences, however, cannot be dismissed as easily. After all, there are neurophysiological and neuroendocrine consequences to behaviour and accepting a link between the CNS and the immune system, it would be reasonable to expect that influences are exerted in the opposite direction. Analyses of the interactions between behaviour and the immune system are not a traditional part of either immunology or the behavioural or neurosciences, but perhaps they should be.

Space does not permit us to do more than point to the article's superficial analysis of the studies by Laudenslager *et al.*[4] and Schleifer *et al.*[5], the evaluations of research based on the time consumed and its cost, the false analogy between the (unreferenced) claims of psychoimmunologists and attempts to link states of mind with the development of cancer, or the difficulty of conducting psychoneuroimmunological research and the implication that the results obtained are neither reproducible nor significant. The basic flaw in the argument is revealed by what is claimed to be a crucial unanswered question: if a person's affective response to some event is capable of influencing immune function, why, the article asks, would such a person be more likely to die of a heart attack or even an automobile accident?

This question is not crucial; it is not even relevant. The relationship between an affective state and immune function may be