Major groove or minor groove?

SIR—A recent correspondent[1] re-emphasized that the major grooves of nucleic acid double helices provide more discriminating binding sites than do the minor grooves for proteins that recognize specific nucleotide sequences. Because of his mistaken impression that the major groove is accessible only in B-type double helices he went on to argue that proteins which have A-type DNA-RNA hybrids as binding partners would interact only with the less discriminating minor grooves.

It is true that A-DNA, the longest known[2] A-type structure, has a major groove that is clenched shut. This most compact A form also has the smallest axial component of nucleotide length (h = 0.26 nm). But the A family of double helices is quite polymorphic[3] and less condensed allomorphs are observed usually under more hydrated conditions. They have nucleotide lengths nearly as large as in B-DNA (h = 0.34 nm) and major grooves that are wide — big enough to accommodate a third polynucleotide chain in some cases[4].

Despite their substantial morphological differences, all the A allomorphs have the same types of rotations at each nucleotide bond. Little energy therefore can be needed to widen the major groove of any A-type helix to B-like dimensions. In these circumstances it is wrong to presume that the proteins involved in transcription, reverse transcription or priming of DNA synthesis cannot be involved with recognition sites in the major grooves of their substrates because of a structural constraint inherent in A-type double helices.

STRUTHER ARNOTT
Department of Biological Sciences,
Purdue University,
West Lafayette,
Indiana 47907, USA

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X chromosomes and dosage compensation

SIR—The suggestion that the primary function of X-chromosome inactivation in mammals might be one of sex-determination rather than dosage compensation made by Chandra[1] is a challenging one. Chandra questions whether dosage compensation is necessary, in view of Kacser and Burns' demonstration[2] that metabolic fluxes are insensitive to changes in enzyme activity of a factor of two. However, notwithstanding Kacser and Burns' work, the fact remains that all autosomal monosomies in the mouse (and also in humans) are lethal at an early embryonic stage[3,4], and autosomal trisomies too are either prenatal lethals or result in malformation or retardation of young born alive[3]. Thus, it appears that for the X chromosome, with females having two copies and males only one, dosage compensation is indeed vital.

The original suggestion that X-chromosome inactivation is a form of dosage compensation therefore remains entirely reasonable. This seems particularly so in view of recent discoveries concerning the X–Y pairing segment. It was predicted long ago that the human X might have a pairing segment which was non-inactivated[5]. The grounds for such a prediction were obviously that if the function of X-inactivation was dosage compensation then a pairing segment carrying homologous genes would not require such a function. It is now known that the genes *Xg*, *Sts* and *M1C 2X* on the human X which lie in (*M1C 2X*)[6] or near (*Sts*) the pairing segment do escape inactivation[7,8]. Similarly, in the mouse, according to Keitges *et al.*[9] the *Sts* locus is present on both X and Y, and is not inactivated.

However, although the evidence that the function of X-inactivation is dosage compensation seems compelling, Chandra's suggestion that it originally arose as a means of sex determination may still be valid, and provide a stimulating new view of the possible evolution of X inactivation. In lower vertebrates, as pointed out by Ohno[10], the sex chromosomes are not heteromorphic. It is possible that in an ancestor of the mammals with homomorphic sex chromosomes, sex determination was achieved by inactivation of relevant genes in one sex. This inactivation might then have provided a basis from which dosage compensation might evolve, as the chromosomes became heteromorphic in the course of evolution of the mammals. The mechanism of X-chromosome inactivation in its present form appears to involve travel of some signal along the chromosome from an inactivation centre[11,12]. If a mechanism of this type were present from an early evolutionary stage then the means would be available for inactivation to increase in extent so as to involve not only sex determining genes but also all loci in respect of which the X and Y had become heteromorphic.

In this connection the *Sts* locus is interesting. In the mouse, the locus is said to be present on both X and Y, and not inactivated[9]. In man, it is present on the X only, and although it is not inactivated the ratio of activities in XX and XY is not 2:1 but 1.6:1[7], as a result of reduced activity of the allele on the inactive X. Could this be a transitional state? If so, there may be a third type of species with respect to *Sts* still to be discovered, so that there are, (1) mouse, X and Y homologous, no inactivation, (2) man, X and Y non-homologous, partial inactivation, (3) unknown species, X and Y non-homologous, total inactivation. Another point to be expected from such a system of evolution of X-inactivation would be that originally the sex determining loci on the X would lie near the inactivation centre. Whether they would still do so today, in view of the rearrangements of the X that have occurred during evolution[13] is uncertain, but this point may be worth bearing in mnd when considering candidate loci.

MARY F. LYON
MRC Radiobiology Unit,
Chilton, Didcot,
Oxon OX11 0RD, UK

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Scotophobin resurrected as a neuropeptide

SIR—With the important role of neuropeptides in brain function and behaviour now established[1-3], it is interesting to review a piece of earlier work that never gained full credibility. Ungar and co-workers[4,5] claimed to have isolated, sequenced, and synthesized a specific polypeptide, scotophobin. They further claimed scotophobin to be a memory molecule. Scotophobin was obtained from the brains of animals trained to avoid the dark (passive avoidance training) and was injected into untrained animals[5]. The naive recipients were reported to have changed their behaviour so as to avoid the dark. Ungar *et al.*[5] concluded that acquired information at a molecular level had been transferred.

From the outset, the accuracy of Ungar and co-workers'[5] structure for scotophobin was questioned[6], and more recent views include the idea that the artificial peptide might influence behaviour, but that no scotophobin may actually be synthesized in rat brain[7]. A review of the memory-transfer experiments more generally was made by Irwin[8], who wrote that "From the beginning, the transfer paradigm became mired in an endless debate over the specificity of the behaviour allegedly transferred"[8]. Irwin went on to observe that "In the long run it was not