SCIENTIFIC CORRESPONDENCE

Major groove or minor groove?

SIR-A recent correspondent1 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 known² 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 polymorphic3 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 cases4.

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

- Wang, J.-H. Nature 319, 183–184 (1986).
 Franklin, R.E. & Gosling, R.G. Acta crystallogr. 6, 673–677
- Arnott, S. et al. Cold Spring Harb. Symp. quant. Biol. 57,
- 4. Arnott, S. & Bond, P.J. Nature new Biol. 244, 99-101 (1973).

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 Chandra¹ is a challenging one. Chandra questions whether dosage compensation is necessary, in view of Kacser and Burns' demonstration2 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 alive3. 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 Xchromosome 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-inactivated⁵. The grounds for such a prediction were obviously that if the function of Xinactivation 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 MIC 2X on the human X which lie in (MIC $2X)^6$ 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 Ohno¹⁰, 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 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 inactivated9. 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 1.6:17, 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 Xinactivation 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 evolution¹³ 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

- Chandra, H.S. Nature 319, 18 (1986); Proc. natn. Acad. Sci. U.S.A. 82, 6947-6949 (1985).
- Kacser, H. & Burns, J.A. Genetics 97, 639-666 (1981).
- Epstein, C.J. Trends Genet.1, 129-134 (1985)
- Magnuson, T. et al. J. exp. Zool. 236, 353-360 (1985). Lyon, M.F. Am. J. hum. Genet. 14, 135-148 (1962)
- Buckle, V., Mondello, C., Darling, S., Craig, I.W. & Goodfellow, P.N. Nature 317, 739–741 (1985).
 Shapiro, L.J. & Mohandas, T. in Cytogenetics of the Mammalian X chromosome Part A (ed. Sandberg, A.A.) 299–314 (Liss, New York, 1983).
- Goodfellow, P. N., Pym, B., Mohandas, T. & Shapiro, L.J. Am. J. hum. Genet. 36, 777-782 (1984).
 Keitges, E., Rivest, M., Siniscalco, M. & Gartler, S.M.
- Nature 315, 226-227 (1985).
- 10. Ohno. S. Sex Chromosomes and Sex-linked Genes (Spring-
- er, Berlin, 1967) 11. Lyon, M.F. in Congenital Malformations 67-68 (Interna-
- tional Medical Congress, New York, 1963). 12. Rastan, S. J. Embryol, exp. Morph. 78, 1–22 (1983)
- 13. Buckle, V.J. et al. Cytogenet. Cell Genet. 40, 594-595

Scotophobin resurrected as a neuropeptide

SIR-With the important role of neuropeptides in brain function and behaviour now established1-3, it is interesting to review a piece of earlier work that never gained full credibility. Ungar and coworkers4.5 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 animals⁵. 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's structure for scotophobin was questioned6, and more recent views include the idea that the artificial peptide might influence behaviour, but that no scotophobin may actually be synthesized in rat brain7. A review of the memory-transfer experiments more generally was made by Irwin8, 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