CHROMOSOMES

Model of *X* Inactivation

from a Correspondent

THE most interesting explanation yet proposed for the mechanism of *X* chromosome inactivation in mammals has been put forward by Brown and Chandra (*Proc. US Nat. Acad. Sci.*, **70**, 195 ; 1973). The chief problem in considering *X* chromosome inactivation is to envisage a mechanism which will lead one whole chromosome of an apparently similar pair to become inactive in somatic cells, while the other retains its normal genetic responsiveness. A step forward came with the discovery that in certain marsupials the inactive *X* is always of paternal origin (Sharman, *Nature*, **230**, 231 ; 1971 ; Cooper *et al.*, *Nature New Biology*, **230**, 154 ; 1971). This led Cooper (*Nature*, **230**, 292 ; 1971) to postulate that the random inactivation of maternal or paternal *X* chromosomes in eutherian mammals has evolved from an earlier simpler system of paternal *X* inactivation.

Although it is still far from clear whether inactivation of paternal *X* is in fact the general rule in marsupials, Cooper's idea is attractive because the sex chromosomes, and indeed the chromatin generally, do seem to become inactive during spermatogenesis ; thus, if the paternal *X* remains inactive in the new zygote, this would seem a simpler system than if it were reactivated, and this followed by a random inactivation. In detail, however, Cooper's model contained difficulties and grounds for criticism (Lyon, *Biol. Rev.*, **47**, 1 ; 1971).

Brown and Chandra's model incorporates the idea of evolution from an ancestral inactivation of paternal *X*, but eliminates many of the difficulties. Basically, they propose a system of two genes controlling the activity of the *X* chromosome ; one, sensitive to parental origin, acts on the second, the receptor, which determines the activity of the *X* chromosome. In marsupials, they suggest, both these genes are located on the *X*, so that if an *X* passes through a male gamete its sensitive gene is inactive, and its receptor gene is never activated. During evolution, they next suggest, the transfer of the sensitive gene to an autosome led to *X* inactivation at random in eutherians. Eutherians thus have an autosomal pair of sensitive genes, of which only the one of maternal origin is active. This gene produces "a single informational entity that attaches to a receptor site on one of the *X* chromosomes encountered at random". In other words, the number of active *X* chromosomes in a eutherian is equal to the number of maternally-derived autosomal sensitive genes.

Such a model fits well with many known facts concerning *X* inactivation. In individuals with chromosome anomalies, if the number of autosomes remains normal, then no more than one *X* chromosome should remain active no matter how many are present and what their parental origin. This is indeed what is observed, even in 2*A* : *XXXXY* or 2*A* : *XXXXX* individuals. Conversely, if the number of autosomes is disturbed, as in triploids or tetraploids, then the number of active *X* chromosomes should depend on the number of maternal sets of autosomes. In particular triploids could have either two maternal and one paternal set, or one maternal and two paternal, and so should be of two types, with two or one active *X* chromosome(s). This again is observed. Tetraploids, if formed by doubling of chromosomes of an originally diploid zygote, should have two active *X* chromosomes, as indeed they do. The piece of evidence which is least well explained by the model is the preferential non-random inactivities of human *X* chromosomes with deletions. But because the non-randomness in this case could be the result of cell selection rather than disturbance of the inactivation mechanisms, this point is not important.

Thus Brown and Chandra's hypothesis has elegance, simplicity and is in principle eminently testable. Individuals with anomalies of the relevant autosome should have alterations of *X* chromosome activity and the type of alteration will depend on the parental origin of the anomalous chromosomes.

If the model proves to be correct, it will be the first clear instance in mammals of the activity of single alleles in autosomes, except for the immunoglobulins which could be a special case. Nucleolar-organizing regions are sometimes found on only one of an autosomal pair. This might fit with Comings's suggestion (*Amer. J. Hum. Genet.*, **20**, 440 ; 1968) that active and inactive *X* chromosomes are distinguished by their site of attachment in the nucleus, if a nucleolus rather than the nuclear membrane is the critical site of attachment (Lyon, *Nature New Biology*, **232**, 229 ; 1971). The active *X* chromosome would be attached to the same nucleolus as the maternal autosome.

One virtue of Comings's model is that it eliminates the need for the unidentified "information entity" which Brown and Chandra postulate, and which does pose something of a difficulty because it must be some unit substance, which can activate only one receptor site. Another general difficulty, met by all models of *X* inactivation proposed so far, is that of explaining how one complete chromosome is activated or inactivated, rather than just a short region. Brown and Chandra's model offers nothing new on this point, hence it has the further endearing quality that, if it should be proved right, there will still be intriguing problems left to tackle.

MYOSIN

Amputating Heads

from our Molecular Biology Correspondent

THE myosin molecule gives the impression of a protein designed by an international committee of protein chemists. It is a chimaera of globular and fibrous parts, contains chains of very high and of low molecular weight, and has complex enzymatic and ligand-binding properties. The long two-stranded α-helical shaft forms part of the lattice of the thick filaments of the myofibril, and the globular heads project out of the filament axis. During the contractile process, when these heads interact with the actin of the thin filaments, their angular orientation changes, but it is by no means clear how this very sizable change in geometry is accomplished. The vague notion of a hinge at some point in the shaft has often enough been invoked, but the evidence in favour of such a region in a superwound double α-helix, behaving hydrodynamically as a rigid rod, has been at best exiguous. There remains, however, the high specificity of tryptic cleavage of the shaft, which occurs about one-third of the way from the end that bears the two globular heads. This has always suggested to the more febrile minds in the field a rather loosely organized segment, or dislocation, in this region. Burke, Himmelfarb and Harrington (*Biochemistry*, **12**, 701 ; 1973) have now given more tangible expression to such a view.

They have examined the properties of the entire myosin shaft, which can be prepared by shearing off the heads with papain. The time course of hydrolysis of these rods with trypsin can be fitted by three rate processes differing over nearly two orders of magnitude in their apparent velocity constants. The fastest process is presumed to be associated with hydrolysis in a uniquely labile region. Next, thermal melting profiles, in which the diminution of α-helical structure with increasing temperature is followed by means of optical rotation, show clear evidence of biphasicity, with one transition below and another above about 50° C. After digestion through the rapid hydrolysis phase and part of the slower phase, the resulting light meromyosin, comprising the terminal two-thirds or so of the shaft, shows only a single co-operative melting transition. Moreover, below this sharp transition the viscosity of the light meromyosin is invariant with temperature, whereas that of the intact rod falls markedly with increasing temperature even before the first optical transition.

The authors infer from all this that there is in the myosin rod a sizable region of α-helix, which melts more readily than the rest, is relatively flexible and in consequence readily attacked by