inhibition of adenylate cyclase by opiate drugs, with or without prostaglandin stimulation, correlated well with the potencies of the same drugs in displacing labelled naloxone from receptor binding sites in these cells.

The results obtained in the hybrid cell line, however, cast some doubt on the view that an interaction of opiates with a prostaglandin-stimulated mechanism is a crucial component in their actions. Sharma *et al.*, for example, found several cultured cell lines that showed increased formation of cyclic AMP in response to PGE_1, but only in those cells that possessed specific binding sites for opiates was this response blocked by morphine. Even in those cells that did respond to morphine the drug also depressed basal adenylate cyclase activity in the absence of added PGE_1, an effect not seen in brain homogenates. Traber *et al.* (1974), furthermore, showed that the interaction between morphine and PGE_1 was non-competitive. All these results suggest that morphine may not act at the same site as PGE_1.

In their most recent paper (this issue of *Nature*, page 57), Gullis, Traber and Hamprecht describe a novel action of opiate drugs in the hybrid glioma–neuroblastoma cells. They found that low concentrations of morphine and levorphanol (but not dextrorphan) stimulated the formation of cyclic GMP, while depressing the concentration of cyclic AMP. These effects were blocked by naloxone, which by itself at low concentrations had no effect on cyclic nucleotide levels. At higher drug concentrations a somewhat complicated picture emerged, since morphine, levorphanol, dextrorphan and naloxone all caused increases in cyclic AMP levels. The latter effects seem unlikely to be associated with the specific pharmacological actions of these drugs. The stimulation of cyclic GMP formation by low concentrations of opiates, however, represents a novel mechanism that could possibly explain the actions of these drugs in reducing cyclic AMP levels and antagonising prostaglandin effects on cyclic AMP, since reciprocal interactions between the two cyclic nucleotides have been found in a variety of other biological situations.

Recent findings by Klee, Sharma and Nirenberg (*Life Sciences*, 1975, in the press) also provide new insight into the processes of tolerance and dependence at a cellular level. They found that on continued exposure of the cultured hybrid cells to morphine the cells adapted by an increased adenylate cyclase activity. The cells thus show 'tolerance' in the sense that their cyclic AMP contents are similar to those found in normal cells, in spite of the continued presence of morphine, and they show 'dependence' in the sense that when the opiate is withdrawn from the cultures cyclic AMP levels rise to abnormally high values. Recovery from the 'addicted' state is slow, as it requires the return of adenylate cyclase activity to normal values. These results support the suggestions made several years ago that opiates may act as enzyme inducers in the process of

Crossed lines

from Pamela Hamlyn

SINCE human beings are inclined to choose their own mates and to produce a mere handful of offspring, it is hardly surprising that mapping of their genes by classical methods has not been as successful as that of the much more accommodating fruit fly. The mapping of human genes, that is, locating them on the twenty-four chromosomes, is of particular interest as an approach to the understanding of human diseases which arise from the inheritance of faulty genes. It is therefore very fortunate that other methods exist for gene mapping. Of these, the formation of a hybrid cell between two different cell types is probably the most important.

Recently a group of scientists working at the National Institutes of Health (Bethesda) have described two different hybrid cell lines which they suggest might be useful for the location of globin genes, and in addition possibly provide information on genetic factors involved in the regulation of their transcription (Deisseroth *et al.*, *Proc. natn. Acad. Sci. U.S.A.*, **72**, 1102; 1975).

One of the hybrid cell lines was formed by fusing Friend mouse erythroleukaemia cells with human fibroblasts. The Friend cells grow in culture and synthesise very low levels of haemoglobin but can be stimulated by the addition of dimethylsulphoxide (Me_2SO) so that 20–50% of the cells give a positive reaction for haemoglobin as detected by benzidine staining. The hybrid cells retain most of the chromosomes of both parents but do not synthesise haemoglobin even when Me_2SO is added to the culture medium, although it can be inferred that at least the β-globin gene is retained. This behaviour—the 'extinction' of the characteristic protein of a specialised cell, when that cell is fused with a relatively undifferentiated cell—is a well documented characteristic of this type of cross. In general it is not clear at what site extinction takes place although conjecture favours transcription of the gene. In these experiments a 'probe' of complementary (c) DNA, made by transcribing purified globin mRNA with reverse transcriptase, has shown that globin mRNA is not present in these hybrids, suggesting that extinction takes place at the level of transcription or mRNA processing.

The other hybrid cell line described was formed by fusing the same line of mouse erythroleukaemia cells with erythroblasts from human bone marrow. Erythroblasts are red blood cell precursors. They contain globin mRNA as detected by a cDNA probe and haemoglobin as detected by benzidine staining. These Friend cell–erythroblast hybrids behave quite differently from the Friend cell–fibroblast cross. They retain only four human chromosomes but continue to synthesise haemoglobin provided Me_2SO is added to the culture medium. However, although both parent cells are haemoglobin producers, only mouse globin mRNA is detected in the hybrid cells, suggesting that only mouse haemoglobin is being made.

The authors have explained how they think these hybrid cell lines might be used for gene mapping. They propose that in the Friend cell–fibroblast cross the extinction of the mouse globin genes is controlled by a regulatory locus on the human chromosomes. If further chromosome losses were to occur then this locus might be lost, the globin genes re-expressed, and the chromosome(s) involved in controlling globin gene expression defined. Re-expression of originally suppressed genes has been observed in other cell hybrids so that their scheme might be feasible.

The human globin structural genes are probably located on the chromosome normally lost when a Friend cell–erythroblast hybrid is formed since they are not expressed in these hybrids. To assign the genes to chromosomes more accurately, hybrids will have to be isolated which contain only a few more chromosomes than normal Friend cell–erythroblast hybrids but which do synthesise human haemoglobin. If this is accomplished it will be interesting to compare the gene locations with those obtained by hybridising labelled globin mRNA to chromosomes *in situ*, a method already used to obtain tentative assignments of globin structural genes (Price, Conover, and Hirschhorn, *Nature*, **237**, 340; 1972).