and salivary (Bonner, T. I. *et al.*, submitted) glands, and as the muscarinic PI effect is characteristic of these glands (see ref. 11), M4 again is thought likely to be M₂ glandular. Identification of M3 and M5 is required, however. The five muscarinic subtypes so far found by DNA cloning fall into two clear functional groups (see table). More subtle functional or regulatory differences should now be sought, to account for the individuality of the isoforms (which are highly conserved — there is 89–96 per cent amino-acid identity between rat, pig and man^{7,10} — as are the GABA_A receptor isoforms).

In their paper this issue³, Caron, Lefkowitz and colleagues report an interesting case of the cloning of a DNA for a G-protein-linked receptor by cross-receptor-hybridization. The authors used transfection in COS cells to identify a human genomic clone which they had obtained by hybridization at reduced stringency with a gene probe for the β_2 -adrenergic receptor. They obtain a ligand-binding profile clearly characteristic of a serotonin receptor (5-HT_{1A} type) in the transfected cells, and confirm this result immunochemically. The amino-acid identity between this receptor and any adrenergic receptor in the seven presumed transmembrane domains found in all of them is about 45 per cent. The level of nucleotide homology in very restricted regions is obviously sufficient to allow the low-stringency hybridization of the β_2 and the 5-HT_{1A} DNAs, providing hope that genes encoding other subtypes in this series may be cloned using this technique.

This report of Fargin *et al.*³ provides a subtype sequence which can be compared with another revealed in a notable recent achievement by Julius *et al.*¹². These authors, again, used the oocyte receptor-expression system, in this case cloning in an RNA expression vector and screening the RNAs for induction of a 5-HT response in oocytes, thus selecting pools sequentially until a single positive clone was isolated. The exceptional sensitivity of the 5-HT_{1C} response in the oocyte (down to 5 fg receptor mRNA) and a rich source of receptor mRNA (choroid plexus) make this an especially favourable case for this strategy, previously initiated for the same receptor by Lubbert *et al.*¹³. Both the 5HT_{1C} and the 5HT_{1A} receptors^{3,12} have the seven membrane-crossing predicted structure now familiar for G-protein-linked receptors. If the two are aligned on this basis, their similarity (20 per cent overall) is low (suggesting different functions), indeed less than that of either with the human β -adrenergic receptor. Of those sites where identical residues do occur, 70 per cent are in the seven membrane domains but even when only those segments are considered, identity is only 35 per cent. Hence, these two 5-HT₁ receptor subtypes differ even more

than any of the pairs of muscarinic subtypes⁷. The 5-HT_{1C} receptor has been linked to PI turnover, although the transduction system of the 5-HT_{1A} receptor is still uncertain.

These and other recent examples of receptor functional subtypes based upon different DNA sequences establish this situation as a general phenomenon. Why are the subtypes maintained with great evolutionary stability? One reason must be for tissue and regional specialization. Sometimes this is obvious, as in the case of cardiac muscle versus brain muscarinic subtypes. But all the M1–M4 genes are expressed to a similar extent in the brain¹¹. The subtypes of a receptor can confer different sensitivities to the transmitter and to possible modulators, as well as alternative transduction pathways for different effector systems^{12,8}. Pre- versus postsynaptic locations of a given receptor often require a different behaviour and hence different subtypes. Finally, some of the isoforms, especially those seen by genomic cloning, are likely to be developmental specializations. How receptor subtypes may operate here is beautifully illustrated by the recent report¹⁴ of the late Stephen Schuetz and colleagues. The nicotinic receptor in mammalian skeletal muscle has embryonic (γ) and adult (ϵ) subtypes with a clear functional difference¹⁵, ϵ producing a channel of fourfold shorter lifetime and twice the conductance of the γ -channel. Jaramillo *et al.*¹⁴ deduce that it is the properties of the γ -channel which permit the current flow needed for early spontaneous contractions. These contractions will lead to the darwinian selection¹⁶ of the final innervation and initiate neuromuscular differentiation, which then will require the adult receptor subtype. Presumably, equivalent mechanisms occur in other receptors in the developing brain.

As these and other clues to the meaning of receptor subtype diversity are uncovered, we can recall what St Thomas Aquinas said about types: "Types and shadows have their ending, for the newer rite is here". To distinguish the receptor types from the shadows, the newer rite is molecular biology. □

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Daedalus

Cleaning up the papers

THE computer revolution once promised to give us the "paperless office". Instead, it has created even more paper: print-outs, document drafts, reports and memos, all in embarrassing profusion, all losing importance rapidly as they are replaced by updated versions, but gaining nuisance value from the proliferation of their numberless photocopies. Daedalus is resigned to the bureaucracy; but he is distressed at the great waste of resources. So he is inventing an erasable and re-usable paper.

His pilot scheme borrows from the chemistry of picture restoration. The white lead-carbonate pigment in an old oil painting is slowly attacked by atmospheric hydrogen sulphide, and darkens over the years into black lead sulphide. The picture restorer applies hydrogen peroxide to bleach this back to white lead sulphate, restoring the original brightness and sparkle of the painting. Many types of paper carry a loading of white mineral material, so DREADCO's chemists are devising a paper loaded with lead sulphate. A special dot-matrix printer, its ribbon impregnated with sodium sulphide, locally reacts the sulphate to black lead-sulphide characters. A complementary erase head, generating ozone from an electric discharge, can oxidize unwanted characters back to lead sulphate again. Thus the draft can be edited *in situ*, or even erased completely back to pristine white paper. The whole system is rather poisonous and smelly, but Daedalus hopes to invent a less noxious chemistry and a suitably durable base material when he has proved the basic concept.

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David Jones