uniquely determines olfactory quality is not confirmed, but this conclusion was reached some years ago by Amoore himself, who modified his "site" theory to account for trends rather than for sharp "fit" or "not-fit" categories of molecular shapes.

As regards Wright's spectral theory, this gives a good correlation with the odorants in two broad categories (pleasant and unpleasant), but five pleasant odorants are incorrectly classified as unpleasant on the basis of their Raman spectra.

As regards the "penetration and puncturing" theory of Davies, in which the lipid part of the plasma membrane is held to be responsible for olfactory effects, Schiffman reports that lipid solubility may be necessary for olfactory stimulation to occur (since all the odorants were soluble in ether and there was no trend of odour type as a function of water solubility). There is apparently no evidence against the two-dimensional odour map earlier published by Davies.

So no single physico-chemical variable can account for odour qualities. But how many such variables are required? Schiffman used suitability weighted functions of Raman intensity, molecular weight, number of double bonds, functional group and cyclic structure, these being taken as simultaneous but separate variables which, empirically weighted in combination, are used to correlate molecular properties with the psychological similarity map. Altogether 25 weighting factors are chosen to give the best fit. The final correlation coefficient is 0.76, which in these circumstances is distinctly disappointing: as Wright has pointed out, Amoore's odour similarity values (admittedly over a limited range of odour) have a correlation coefficient of 0.85 with the square root of the molecular weight. Furthermore, as Mazziotti has shown (*Nature*, **250**, 645; 1974), there is even quite a fair correlation between odour type and boiling points, particularly within groups of substances whose molecules have the same functional group. Perhaps Schiffman's most important contribution to the debate is that molecular shape as such is not said to be significant.

Future progress in the field of odour must surely be concerned with mechanism of the initiation of the nervous impulses in the olfactory epithelium. Adrian, many years ago, found that different regions of this epithelium in the rabbit and the hedgehog are relatively selective to stimulation by certain types of odorant molecules. Since the lipids may well be responsible for the initial adsorption of the odorants from the air stream, and since the lipid structure may then be locally disorganised by the odorant molecules, one predicts differing properties of the lipids in the various regions of the olfactory epithelium.

This urgently requires testing experimentally by an analysis of lipids taken from the various regions of the epithelium. Only by experimental tests of such physical theories is there likely to be real progress in the understanding of olfaction.

J. T. DAVIES

Clonal selection hypothesis under fire

BIOLOGICAL research in recent years has acquired various dogmas, the most famous of which is probably the central dogma of the molecular biologists. Immunologists, not to be outdone, have espoused the clonal selection hypothesis as their central concept to provide a framework for the understanding of classical antibody synthesis. A recent statement of this notion says: "Antibody molecules consist of heavy and light polypeptide chains, the variable sequences of the 110 N-Terminal amino acid residues of these chains determine antibody specificities; lymphocytes are cells that express one pair of structural genes for these sequences; *one lymphocyte and all of its descendants make identical antibody molecules* (my italics); these are placed as receptors for antigen on the outer lymphocyte membrane; the attachment of antigen to the combining sites of these receptors is a step in lymphocyte stimulation leading to cell proliferation, antibody secretion, and thus to an amplification of this selected antibody" (second *Annual Report of the Basle Institute for Immunology*, page 1).

Although several of the items of this concept thus stated could be questioned, the present interest is in the italicised phrase which seems to be contradicted in part by a recent communication by Cunningham and Fordham (*Nature*, **250**, 669–671; 1974). These investigators present evidence that sometimes single antigen stimulated cells can engender clones of cells of which not all the members of the clone are producing the same kind of antibody.

Mouse spleen cells were cultured *in vitro* in the presence of bacterial lipopolysaccharide and sheep red blood cells. After 24 h the cells were harvested and dispersed in microdroplets under oil in fresh medium with a mixture of red cells from two standard sheep and complement. In these circumstances the antibody from some of the cells diffuse into the surrounding medium and, in the presence of complement, soon lyses the sheep red cells giving rise to a more or less clear plaque around the antibody-producing cell. The plaque-forming cells were isolated by micromanipulation from the microdroplets and seeded on to a feeder layer of irradiated mouse spleen cells and sheep red cells were again added. After about 2 days some of the isolated plaque-forming cells had divided. Their progeny cells were re-isolated where necessary in the presence of trypsin to disaggregate them and they were added individually to a mixture of fresh medium, complement and red cells from the two standard sheep. These mixtures were pipetted into Cunningham slide chambers (Cunningham and Szenberg, *Immunology*, **14**, 599; 1968), and the resulting (19S) plaques were characterised as either clear, partial or 'sombrero'. Clear plaques are supposed by the authors to arise around cells which have produced an antibody (or antibodies) which recognises antigens common to both the target red cells. Partial plaques have some unlysed red cells and (despite the lack of a morphological criterion of distinction) these are interpreted as arising around cells which produce antibody capable of binding effectively to only one of the kinds of red cell. Sombreros are supposed to arise around cells which are producing antibodies for common specificities but with higher avidity for one of the kinds of red cell than the other. About 10% of all isolated cells formed clones and of these about 10% were found to give rise to heterogeneous plaques. Most of the heterogeneous clones had only two kinds of plaque forming cell. Two had three kinds of cell and one clone (of twelve cells) gave rise to four clear plaques, five sombreros and two partials. One could not be diagnosed.

On the basis of these results the authors postulate that, contrary to the precepts of the clonal selection theory, diversity in relation to antibody-producing capacity can commonly (if not always) arise after contact with antigen rather than be pre-existent. The approach is ingenious and owes much to the use of the polyacrylamide gel microculture plates developed by Marbrook and Haskill (*Cell. Immunol.*, in the press). Whether the evidence presented by Cunningham and Fordham will withstand the barrage of criticism which will be put up by the immunological establishment remains to be seen but it is healthy that after such a long run unopposed, the Clonal Selection Theory is taking a few knocks.

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