One can now imagine that either arsenite or the insoluble compound(s) derived therefrom are responsible for the fact that the yeast cell is much sooner "saturated" with arsenate than with phosphate as is shown by Table I. Following ROTHSTEIN, we suppose that an irreversible block of the transport system is developed during As absorption, which causes the observed differences in P uptake and As uptake. It seems to us, however, that the observed inhibition is not characteristic for As accumulation: HOLZER[3] has shown that P uptake proceeds only when the level of orthophosphate in the cell is decreased below a certain value by incorporation of the phosphate into other compounds. Apparently the orthophosphate concentration in the cell regulates the rate of P absorption. When As is taken up by the cell it is, however, not incorporated into stable arsenate esters analogous to the phosphate esters and it is transformed into other compounds as arsenite and arsenite products to a relatively small extent (10 %–50 % of total As uptake) (*cf.* Table III). Therefore the internal orthoarsenate concentration rises continuously until, finally, it causes a complete block of As uptake.

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Penetration of lipid monolayers by psychoactive drugs

It has been reported that psychotropic drugs, *e.g.*, orphenadrine[1–4] may affect the permeability of biological membranes. SEEMAN AND BIALY[5] studied the surface activity of a great number of tranquilizers and related this characteristic to the clinical potency of neuroleptics. The blocking potency of several local anaesthetics was found by SKOU[6] to correspond with the ability of these compounds to penetrate monomolecular films of lipids extracted from peripheral nerves. The use of monomolecular films consisting of well-defined lipids may give information about the selective action of drugs as was demonstrated for polyene antibiotics, compounds of which were found to interact specifically with sterols[7]. It was hoped that a determination of the penetration of films of different lipid classes by psychoactive agents might provide some clue to the understanding of the site of action of these compounds.

For this purpose monomolecular films were prepared at the air–water interface in a conventional Langmuir trough[7], using cholesterol (Fluka, AG., Switzerland), synthetic phosphoglycerides[8], natural sphingomyelin[9], as well as preparations of cerebrosides and (α and β) gangliosides[10] isolated from beef brain and kindly provided by Dr. R. M. BURTON (Department of Pharmacology, Washington University School of Medecine, St. Louis, Mo., U.S.A.). The area was compressed so as to give initial surface pressures between 6 and 30 dynes/cm. The psychoactive drugs dissolved in dimethylformamide were carefully injected beneath the lipid monolayer and changes in pressure were measured at constant area.

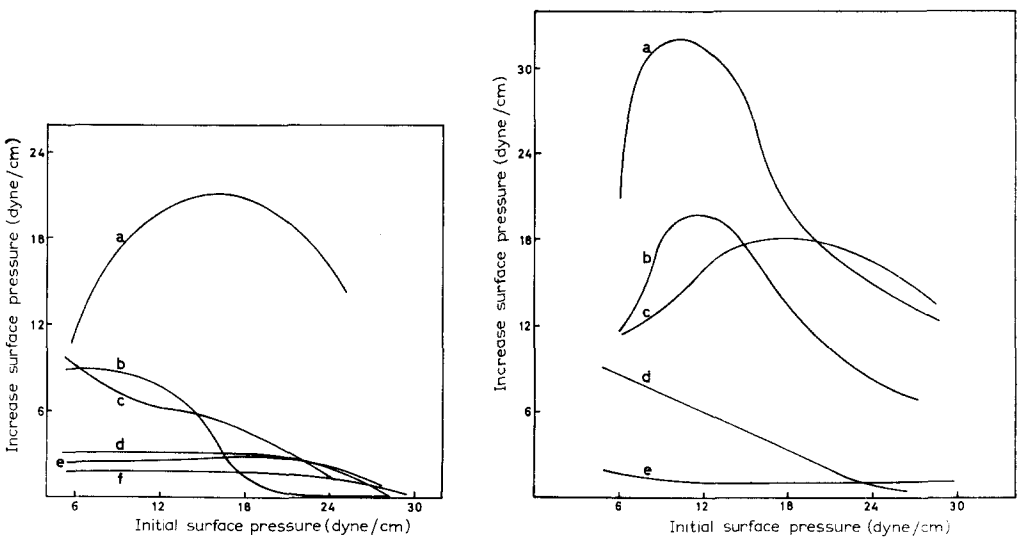

Fig. 1. Penetration of lipid monolayers by orphenadrine; monomolecular films of (a) gangliosides, (b) cholesterol, (c) cerebrosides, (d) phosphatidylethanolamine, (e) sphingomyelin, (f) lecithin were compressed to give the initial pressure indicated on the abscissa and orphenadrine HCl (5.3 μmoles) was injected underneath.

Fig. 2. Penetration of monomolecular films of gangliosides by (a) reserpine (1.2 μmoles), (b) chlorpromazine HCl (5.8 μmoles), (c) meclizine diHCl (4.2 μmoles), (d) meprobamate (6.9 μmoles), (e) pentobarbital sodium (4.3 μmoles).

The action of orphenadrine HCl on various lipid layers is illustrated by Fig. 1. This compound was found to give hardly any interaction with lecithin, phosphatidylethanolamine and sphingomyelin, but at initial film pressures below 18 dynes/cm there was some penetration of cholesterol films while also cerebrosides exhibited some interaction. However, an extremely strong interaction was observed between orphenadrine and gangliosides. Also at high initial pressures of the ganglioside film the pressure increase due to this drug was most significant. Chlorpromazine revealed a similar specificity-pattern. Reserpine was found to give a notable affect on monolayers of cholesterol and cerebrosides at initial film pressures below 24 dynes, but the affect on gangliosides again was most conspicuous. A comparison of the magnitude of interaction of various psychoactive drugs with monomolecular films of gangliosides showed that the activity of reserpine greatly exceeded that of all drugs tested so far (Fig. 2). The results were confirmed by measuring the increase of surface-area of the

monolayers held at constant pressure. Interaction with gangliosides was evoked by psychoactive drugs of various structural types: (a) phenothiazines (chlorpromazine HCl, ethopropazine HCl), (b) Rauwolfia alkaloids (reserpine), (c) diphenylmethanes (meclizine diHCl, orphenadrine HCl), (d) benzodiazepines (imipramine HCl). On the other hand meprobamate exhibited only a limited affect on the ganglioside film, while there was essentially no interaction of pentobarbital sodium with the lipid monolayer (Fig. 2).

The ability of various psychoactive compounds to penetrate the ganglioside films may be relevant to the psychotropic action of the drugs concerned. Recent studies on the subcellular distribution of gangliosides in the central nervous system indicate that these glycolipids are abundant in the synaptic vesicle fractions rich in acetylcholine and acetylcholine esterase[11–13]. BURTON *et al.*[13] suggested a functional role for gangliosides in the transport of acetylcholine from synaptic vesicles through the presynaptic membrane. Thus it can be speculated that those psychoactive drugs which interact with gangliosides may affect the transfer or release of this neurohormone. In this context it is interesting to note that WOOLLEY AND GOMMI[14] observed that the receptor for serotonin in animal tissue is a neuraminidase susceptible lipid. Further studies on the competition between neurohormones and psychoactive drugs in binding to gangliosides may be rewarding.

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