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Introductory Remarks to the Second Session

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Introductory remarks to the second session

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It is challenging indeed to be invited to introduce this broad-ranging session, for it encompasses virtually all levels of the effects of pressure and its antagonism by narcotics from the molecule to man. The papers will take us from the talk of Dr A. MacDonald on the reversible effects of pressure on molecules, and thereby cell structure and function, (MacDonald 1982) to Dr K. Miller and his co-workers, who will discuss the action of pressure on membranes and mammals such as mice to produce the high pressure nervous syndrome. Dr Miller will also discuss the protective action against these effects of pressure afforded by five anaesthetic gases, which led to his introduction of the controversial 'Critical volume hypothesis' for the mechanism of general anaesthesia (Miller *et al.* 1973).

Dr M. Halsey, like Dr Miller, an ex-student from the Oxford group, will show us that the effects of pressure and anaesthetics are not as simple as we would wish. Disagreeing with his Oxford colleagues in regard to the critical volume concept, he has generated his 'multisite expansion hypothesis' (Halsey *et al.* 1978). He will lead us also into measurements of the electrical activity of the brain in conjunction with research on synaptic transmitters in rodents and baboons; an area of increasing focus for many of us.

In the final paper of this session, my French colleague, Dr Naquet, whose study of the effects of pressure in man has closely paralleled my own research in England and the U.S.A., will discuss his French colleagues' difficult and stressful human research on the clinical, psychometric and electrophysiological aspects of the effects of pressure to depth equivalents of 300–610 m (Naquet & Rostain 1980; Rostain *et al.* 1982; Bennett 1982). This will bring into focus in man the molecular, cellular and membrane effects of pressure and identify how these come together in the total man to produce h.p.n.s and how anaesthetics are antagonistic.

At the end of this session we should have a broad overview of some of the more important aspects of how man's neurological system reacts to exposure to high pressures. We should also quickly be aware that the problems are far from simple and that pressure *per se* is both a formidable limitation to the ability of man to function effectively deep in the ocean, but also a golden key to assist our understanding of the mechanism of general anaesthesia.

Unfortunately, pressure remains largely unrecognized except perhaps by a few zealots, such as our speakers today, as a unique physiological research tool equally as important as the common fundamental parameters, temperature and volume; this is rather surprising. Indeed, if we look at the fundamental basis for the reactions of any physico-chemical system, including living cells, the simplest equation applicable at ordinary pressures, and known surely to all scientists, is

$$PV = nRT$$

i.e. at constant volume the higher the temperature the higher the pressure. Thus pressure and temperature are antagonistic in their effects, pressure causing a decrease in volume and

temperature an increase. Too often in our studies at pressure we have ignored this fundamental interaction of pressure and temperature.

We need to remember also that the laws of evolution and natural selection have developed life in several pressure planes. Man indeed is restricted to very narrow pressure limits near the 1 atm to which he has been exposed for generations. Similarly there are animals deep in the ocean who cannot survive at 1 atm, but who have developed at hundreds of atmospheres pressure. So pressure in a physiological sense is very relative and we should not be surprised that pressure changes in man do produce most fundamental effects in probably nearly all tissues.

Dr MacDonald will show us that even the simple amoeba 'rounds up', that high pressure and low temperature weakens the cohesiveness of cytoplasm subunits and cell cleavage is inhibited. Even the ultrastructural components of cells, such as the microtubules in mammalian brain neurons, are susceptible.

Pressure too is often biphasic. Thus pressure may stimulate motor activity through its excitatory effect on the central nervous system but at higher pressures motor activity is often reduced. Even more complex is the fact that mammalian hearts show a pressure bradycardia whereas the hearts of cold-blooded vertebrates indicate a pressure tachycardia.

At the membrane level we need to remind ourselves of the structure of a lipid bilayer with its lipid–protein structure. The challenge here is where is the site of action by the pressure or anaesthetic? Is it in the lipid by changing the fluidity and molecular order or membrane expansion, or is it by conformational changes in the protein? Do these changes affect ion transport through the protein pores? At the synapse, what happens to transmitter release?

The critical volume theory to be described by Dr Miller is indeed attractive and like all the many historic mechanisms of anaesthesia proposed in the past may have some relevance. However, it is already evident that this theory, which relies on expansion of neuronal membranes by about 0.5% as the prime mechanism of general anaesthesia, and constriction of the membranes by 1% as the cause of pressure effects or h.p.n.s., is too simple. Indeed Franks & Lieb (1982) of Imperial and King's College have recently confirmed that small increases in area and volume have been detected at clinical concentrations of anaesthetics, but dispute whether changes in thickness occur. So for red cell membranes in the presence of halothane, the observed volume expansion of 0.1% and area expansion of 0.4% implies a thickness decrease of only 0.3%.

These workers similarly threw considerable suspicion on the possible role of lipid bilayer fluidity, which may perturb some crucial membrane poteins. One of the more important criticisms is that increased fluidity predicts an increase in anaesthetic potency with rising temperature, whereas in fact the opposite is true.

Nevertheless, Franks & Lieb infer that the most promising line of argument for lipid involvement rests on bilayer permeability. A Fellow of the Royal Society, Dr A. Bangham, and his co-workers showed that leakage of cations from lipid vesicles is markedly enhanced by general anaesthetics and that this is reversed by high pressure (Bangham *et al.* 1965). Indeed, on the basis of surface tension changes in monolayers at raised pressures of gases, which I made at Dr Bangham's laboratory in the 1960s (Bennett *et al.* 1967), I also noted increased ion permeability in cat brain during exposure to raised pressures of nitrogen but not helium (Bennett & Hayward 1967).

But then again if we consider the range of pressure reversal effects for difference anaesthetics, as reported by Dr Halsey, there is a nonlinearity. Some anaesthetics exhibit a plateau greater

than 50 atm, some are almost linear, and some continue to increase. This led Dr Halsey to suggest that general anaesthesia may be produced by expansion of more than one site and that pressure does not necessarily act directly on the same molecular site as the anaesthetic.

Franks & Lieb's (1982) analysis of the data is much more plausible in support of protein rather than lipid as the primary site of action and indicates that general anaesthetics act by binding directly to a protein and inhibiting its normal function – perhaps by competing for the binding of some endogenous ligand such as a neurotransmitter.

Then pressure reversal could be due to pressure 'squeezing' the anaesthetic molecules out of target sites, while the decrease in gas-phase potency with increasing temperatures may simply be due to heat driving the anaesthetic off these sites.

The final question I will leave you with is the relevance of this wealth of molecular, membrane and cellular work to what we call the high pressure nervous syndrome in man. We will learn from Dr Naquet of the tremors, myoclonic jerking, vomiting, fatigue and somnolence seen in deep human diving with oxygen–helium. These are the effects of the pressure, not the helium, and there is a wide individual susceptibility.

In fact, h.p.n.s. comprises two effects, one due to the rate of compression (the faster the compression the worse the h.p.n.s) and the other due to the increased hydrostatic pressure (the higher the pressure the worse the symptoms). To reach pressures of 60 atm (absolute) some seven or more days of compression are required to prevent incapacitating h.p.n.s.

Yet most of the isolated tissue or small mammal laboratory work uses rapid compression in less than one day, often with large adiabatic thermal increases. Is the same effect being measured?

At any even this brief introduction should serve to identify that we have come a long way from the tadpole study of Johnson & Flagler (1950), which so clearly and simply identified pressure reversal of anaesthesia. Although the secret of the mechanism of general anaesthesia remains as elusive as our knowledge of the aetiology of consciousness itself, there can be no doubt that pressure has been a fascinating research key to helping increase our knowledge in this area and still, much remains to be done if funding can be obtained.

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