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Membrane Expansion by Vinblastine and Strychnine

HIGH concentrations of vinblastine, strychnine and colchicine were reported to convert normal erythrocytes to cells similar to hereditary spherocytes[1]. The suggestion was made that the drugs specifically altered membrane microfilament proteins. We have found that vinblastine and strychnine expand erythrocyte membranes in the same way as many non-specific lipid-soluble cationic drugs[2–5]. The effects reported by Jacob *et al.*[1] may result from this non-specific membrane-expanding action, and may have little to do with the hypothetical presence of microfilaments.

Fig. 1 shows that strychnine sulphate and vinblastine sulphate protected human erythrocytes from osmotic haemolysis[2–7]. The biphasic pattern with vinblastine is typical of lipid-soluble drugs and anaesthetics[8,9]. Low drug concentrations expand the membrane, increase the surface/volume ratio, protecting the cell from osmotic haemolysis; high drug concentrations, however, over-expand the membrane, increase the cell Na^+ (making the cells more fragile) and haemolyse the cell directly with membrane invagination and budding[10].

Since many lipid-soluble anaesthetics have these properties, actions of these two drugs on membranes do not prove that there are microfilaments in the membrane. Freeze-fracture-etch electron microscopy of erythrocyte ghost membranes incubated with or without 10^{-4} M vinblastine (unpublished work) do not reveal such microfilaments in the fracture- or etch-faces of the membrane[11,12]; there is, however, evidence for actin-like filaments subtending into the cytoplasm[13]. The membrane concentrations for vinblastine and strychnine are calculated at between 20 and 80 mmol/kg of dry membrane. Membrane concentrations of hydrophobic drugs in the range 10–90 mmol/kg membrane result in a wide variety of non-specific perturbations, such as membrane expansion, fluidization and permeability changes[2–10].

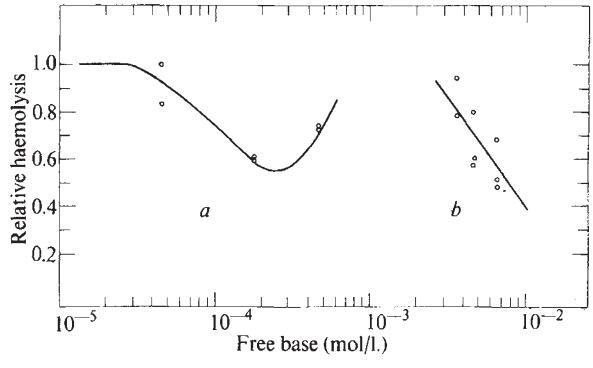

Fig. 1 Protection of human erythrocytes against hypotonic haemolysis by vinblastine sulphate (*a*) and strychnine sulphate (*b*). The relative haemolysis value of 1.0 represents 60% release of haemoglobin in the absence of any drug.

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Rabbit Memory Cells Are Not Restricted to the Affinity of Circulating Antibodies

DURING the primary immune response against certain antigenic determinants there is a progressive increase in the average intrinsic association constant of circulating antibodies[1]. Antibodies synthesized several weeks after antigen injection have higher affinity for the homologous ligand than those synthesized earlier[2]. According to clonal theories of antibody formation, the shift in the population of circulating molecules must reflect a shift in the population of high rate antibody-forming clones[3–6].

Since there is good evidence that the characteristics of the surface receptors of a given immunocyte are similar in affinity to those of the antibodies potentially produced[7] and that the specific binding of antigen to the cell surface is necessary for the initiation of antibody production[8–10], the rationale of a progressive selection of clones by antigen limitation is offered. The decay of antigen in the organism—enhanced by the presence of circulating antibodies—progressively limits antibody secretion to those clones endowed with the highest affinity[5,11,12].

It is not well known whether selection of high rate antibody-forming cells is paralleled by a similar shift in the memory cell population. To answer this question (short of a direct assay of the memory cells), several investigators have resorted to the study of the affinity or avidity of synthesized antibodies by measuring them as soon as possible after challenge, on the assumption that if a selection favouring high affinities has taken place at the level of memory it would be reflected in a similar restriction of the early secondary response. However, these experiments conducted in two different ways gave opposite results. (1) The secondary challenge was performed in the intact animal[13,14], or using high numbers ($\geq 10^6$) of