continue. A general anaesthetic will therefore be an agent which has a low probability of blocking a synapse, so that when a large number of synapses in series is affected the probability of interruption becomes high.

Many proteins have a structure in which one or more polypeptide chains are curled roughly into a ball having the polar groups pointing outwards and the non-polar groups directed inwards. The chain may enclose a central void which a volatile anaesthetic, being a small non-polar molecule, may enter. If a protein molecule of this nature is subjected to increased pressure one would expect it to become compressed so that the central void is reduced in volume; however, if the central void is already occupied by an anaesthetic, like a toad in the hole, the protein would be more resistant to compression.

When a patient receives a general anaesthetic a large number and variety of protein molecules will have their central voids occupied by the molecules of volatile anaesthetic agents. In the majority of cases their physiological activities are unaffected; however, there are grounds for concluding that the action of the acetylcholine receptor protein molecule is profoundly affected and that this action is responsible for the phenomenon of general anaesthesia. The receptor protein is a tetramer enclosing a central pore which is normally closed but which opens under the influence of acetylcholine or increased pressure to permit a flow of ions which depolarizes the neuronal cell membrane and generates an action potential. It is likely that, when the central pore opens, the central void of the receptor protein molecule is reduced in volume. The characteristics of this reaction, namely the dissociation constant of acetylcholine and its time constant, indicate that the energy required to compress the molecule must be quite small, so that it would be especially susceptible to the "toad in the hole" effect; in addition, at the correct dose a sufficient proportion of synapses would be blocked to cause general anaesthesia.

The central void, being of an irregular shape, can contain non-polar molecules of a large variety of shapes provided they do not exceed a certain size, and this may explain why such a large variety of volatile non-polar molecules can act as general anaesthetics. Most pharmacological actions involve attachment to a surface where the conformational conditions are specific; however, when a molecule is contained within a void, a greater variety of molecules may be admitted and retained.

It is difficult to determine with certainty to what extent the circulation of nerve impulses which may constitute the objective embodiment of consciousness is dependent on transmission across central cholinergic synapses. However, it is likely that the majority are cholinergic, but when they are not cholinergic it is possible that the receptor protein has to undertake an allosteric transformation which is also vulnerable to interference by the presence of an anaesthetic molecule in its central void. Although a great number and variety of proteins will be affected by non-polar molecules in this way, it would seem probable that the synaptic protein molecule is the most vulnerable in this context.

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PANCURONIUM PLASMA CLEARANCE AND AGE

Sir,—It is now widely accepted that age can influence drug disposition, and the report by McLeod, Hull and Watson (1979) of a reduced plasma clearance of pancuronium with increasing age is another example of age-dependent pharmacokinetics. Nevertheless, it seemed appropriate to compare these results with those of Somogyi (1978).

Thirty-eight patients aged 15–77 yr were studied; their weights were in the range 45–88 kg and all received general anaesthesia for elective surgery. They included patients given single (n = 11) and multiple (n = 6) bolus and infusion (n = 21) regimens of pancuronium and were all free from renal, hepatic and neuromuscular disorders. The anaesthetic technique, analysis of pancuronium and pharmacokinetic analysis have been described previously (Somogyi, Shanks and Triggs, 1978). The plasma clearance of pancuronium as a function of age is shown in figure 1.

**Fig. 1.** Pancuronium plasma clearance as a function of age.

There was no statistically significant (P > 0.05) linear relationship between these two variables. The reasons for the differences between these results and those of McLeod and his co-workers are speculative, but it would appear that more detailed studies are required to investigate this and other aspects of the disposition of non-depolarizing muscle relaxants in surgical patients.

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REFERENCES

