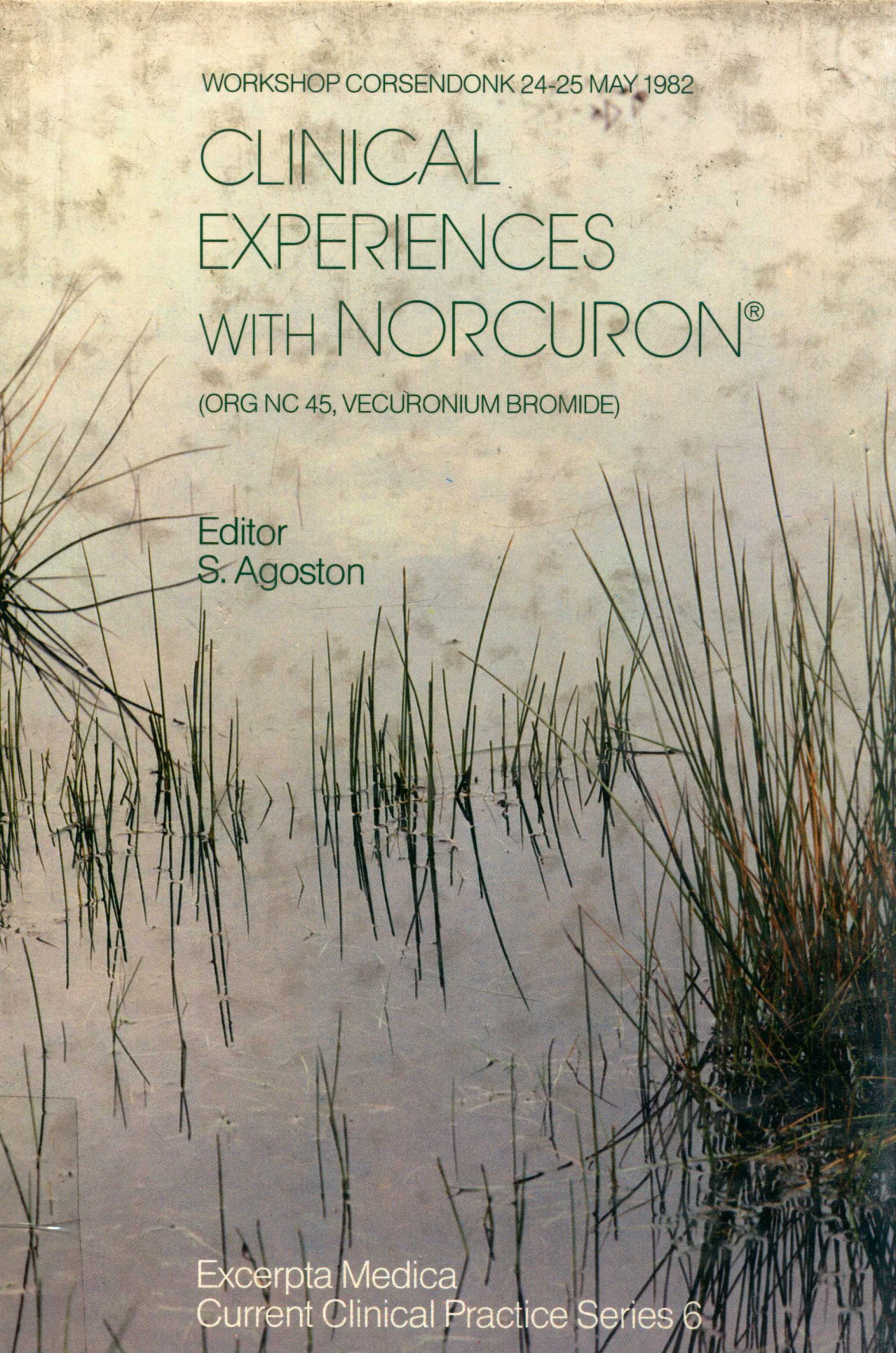
WORKSHOP CORSENDONK 24-25 MAY 1982

CLINICAL EXPERIENCES WITH NORCURON®

(ORG NC 45, VECURONIUM BROMIDE)

Editor
S. Agoston



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CLINICAL EXPERIENCES WITH NORCURON®

Preface

This book contains lectures given during a symposium, held on 24-25 May 1982, in Corsendonk, Belgium, devoted entirely to the recently developed nondepolarising neuromuscular blocking drug Norcuron® (vecuronium bromide), hitherto popularly known as Org NC 45.

The timing of the meeting coincided with the end of the 'Research and Development' phase for this new compound. This meant that all the basic knowledge necessary for the full-scale use of vecuronium bromide in everyday anaesthetic practice had been gathered. The goal of the organisers of the symposium was to review the extensive pharmacological and clinical data accumulated during the previous two years, and to provide potential users of the new drug with an interpretation of the pertinent facts directly from the scientists who had largely been responsible for generating them.

In editing the papers, no attempt was made to change any of the statements made by the various authors so that their individual views are presented and not those of the editors.

Thanks are due not only to all participants who were kind enough to submit their manuscripts in time for publication, but also to all other research workers and clinicians who conducted individual studies and contributed to the multicentre trials on vecuronium bromide. Last, but not least, I would like to express my gratitude to Dr F.J. Richardson (Institute for Anaesthesiology and Intensive Care, University Hospital, Groningen) and Dr P. Denissen for editing the various manuscripts, as well as Ms K. Tkach of Excerpta Medica for her dedicated co-operation.

S. Agoston

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Contents

The discovery of vecuronium bromide

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It is both relevant and fascinating to trace the evolution which led to the discovery [1] of vecuronium bromide (Org NC 45) (Fig. 1) which promises to be of significant clinical utility and which is a scientific phenomenon in the sense that it has such a high selectivity of action. This review may also indicate the way to future developments in the form of even quicker- and shorter-acting nondepolarising neuromuscular blocking drugs.

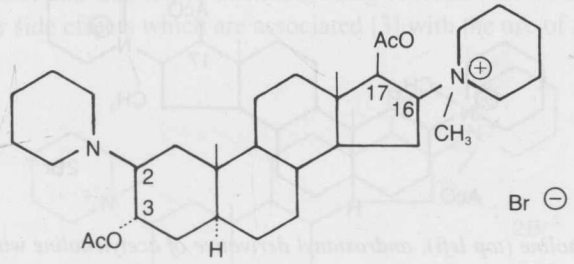

Fig. 1: Vecuronium bromide.

My initial brief on entering industry in 1959 was to confer nonhormonal properties on a steroid molecule. An obvious approach to solving this was to confer significantly more hydrophilic properties on androstanes and pregnanes to the extent that they would become readily water soluble so that the steroid nucleus would be transportable to unusual target sites in man. In order that the molecules would potentially be capable of selective drug action at some of these sites it was rational to introduce 1,2-amino alcohol functions stereoselectively to the steroidal nuclei since such molecular fragments occur in endogenous neurotransmitters such as noradrenaline and acetylcholine (Fig. 2) [2].

This led, inter alia, to the nondepolarising neuromuscular blocking drug shown in Figure 3, which is an androstanyl derivative of acetylcholine. This drug has one-sixteenth the potency [2] of d-tubocurarine chloride (d-TC) as a neuromuscular blocker. A short survey of existing drugs in this area suggested that a bis-quaternary

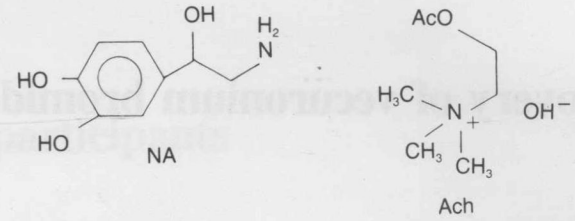

Fig. 2: Examples of endogenous 1,2-amino alcohol derivatives. Noradrenaline (left) and acetylcholine (right).

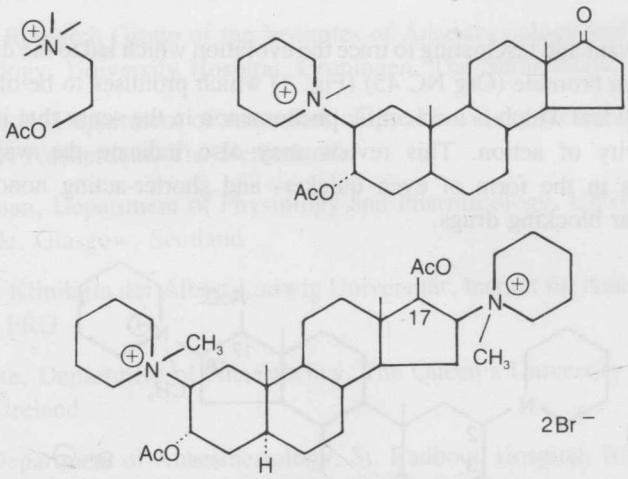

Fig. 3: Acetylcholine (top left), androstanyl derivative of acetylcholine with potency one-sixteenth that of d-TC (top right) and pancuronium bromide (below).

analogue would be of significantly greater potency.

From 1959 to 1964 our team gained extensive experience in the stereoselective introduction of 1,2-amino alcohol functions into steroid skeletons and this facilitated the synthesis of the bis-quaternary pancuronium bromide (Org NA 97) (Fig. 3) within a few weeks. d-TC was reported in the 1960s as bis-quaternary and it was not until over a decade later that the correct mono-quaternary structure was decribed (Fig. 4). It is ironic that pancuronium bromide is analogous to the erroneously reported bis-quaternary d-TC and that vecuronium bromide is, like the 'true' d-TC, mono-quaternary.

From 1968 onwards pancuronium bromide was established as an agent of distinct clinical utility, and pharmacologists and anaesthetists alike encouraged our industrial group to develop new nondepolarising relaxants related to pancuronium bromide but with a quicker onset and a shorter time-course of action.

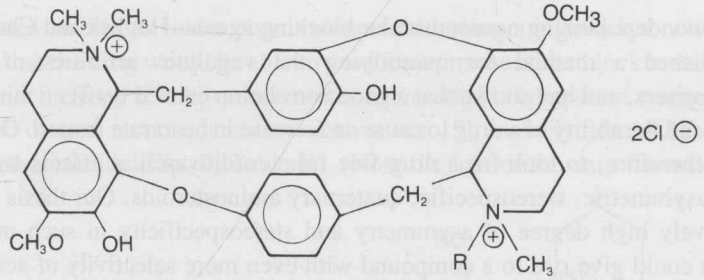

Fig. 4: Revised structure of d-TC (1964: R = CH_3, 1970: R = H).

The existing animal model showed a good correlation in terms of potency between animal and man (Fig. 5, Table I). Table I also serves to show that high potency is associated with the presence of a 17-acetoxy group in the molecule, since changing to a 17-OH or 17-H substituent lowers the potency by factors of 40 and 5 respectively. Note that the same does not hold for the 3-acetoxy group and its 3-OH analogues.

However, there was no animal model predictive of onset and duration of action in man at this time, and this led to attention being focused instead on removing the cardiovascular side effects which are associated [3] with the use of all the clinically

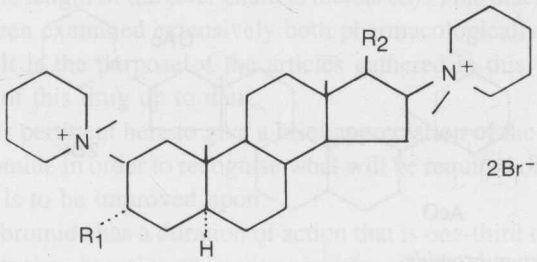

Fig. 5: Basic structure of pancuronium bromide and its analogues (see also Table I).

Table I: Relative potency of pancuronium bromide and analogues (see also Fig. 5) in cats and in man.

Compound	Substituent		Potency	
	R_1	R_2	Cat	Man
Org 6338	OAc	H	10	10
Org 6502	OH	H	8	
Pancuronium bromide	OAc	OAc	50	50
Dacuronium bromide	OAc	OH	< 2	1
Org NE 35	OH	OAc	33	25
Org NA 96	OH	OH	1	1

available nondepolarising neuromuscular blocking agents. Hughes and Chapple [4] had published a method for quantifying the vagolytic activities of several nondepolarisers, and had shown that a good correlation existed between this activity in the cat and the ability of a drug to cause an increase in heart rate in man. Our group decided, therefore, to look for a drug free from cardiovascular effects amongst a range of asymmetric, stereospecific, quaternary aminosteroids. Our thesis was that the relatively high degree of asymmetry and stereospecificity in such molecular structures could give rise to a compound with even more selectivity of action than pancuronium bromide.

In addition to making a potent blocker with high selectivity it was planned to design, synthesise and test a range of compounds having sufficiently different physical properties so that the time course of action of some of the compounds would be quicker and shorter than pancuronium bromide in both cat and man.

The standard compound, pancuronium bromide (Fig. 6), was tested in cats and its activities to affect neuromuscular blockade and to reverse bradycardia induced by vagal stimulation were compared [5]. A comparison of ED_{50} values, as shown in Table II, gave an index of 3.4 for the standard. Using this crude index as a guideline

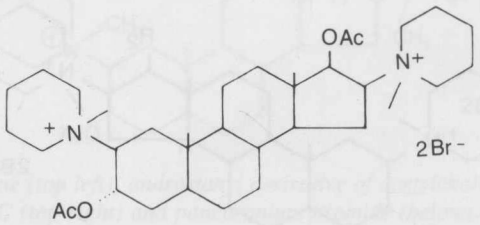

Fig. 6: Pancuronium bromide.

Table II: Relationship between the vagolytic effect and the neuromuscular blockade produced in cats by vecuronium bromide and various analogues (see also Fig. 7) and by pancuronium bromide. V = vagolytic ED_{50}; N = ED_{50} neuromuscular blockade.

Substituent (17β)	V:N
CH_3CO*	63
CH_3CH_2CO	0.4
$CH_3(CH_2)_2CO$	0.7
$(CH_3)_2CH_2CO$	0.2
Pancuronium bromide	3.4

* Vecuronium bromide.

we initiated studies to find a potent compound having a high index, which would indicate that the drug would be able to produce neuromuscular block in man without having much effect, if any, on heart rate. A remarkable compound emerged from a series of diester mono-quaternary derivatives [5], namely, the 3,17-diacetoxy monomethobromide (Fig. 7, Table II). (Note the loss of the very favourable index

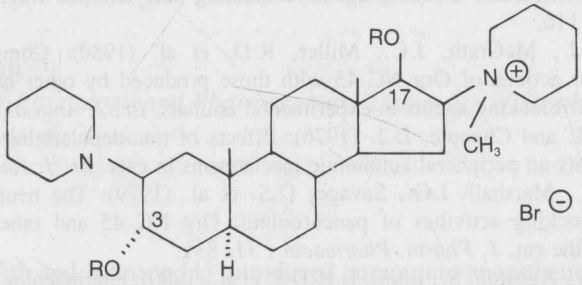

Fig. 7: Basic structure of vecuronium bromide and other diester mono-quaternary derivatives (see also Table II).

value of 63 as the length of the ester chain is increased). This diacetate, vecuronium bromide, has been examined extensively both pharmacologically in animals [3, 6] and clinically. It is the purpose of the articles gathered in this book to bring the clinical profile of this drug up to date.

However, it is pertinent here to give a brief appreciation of the clinical profile of vecuronium bromide in order to recognise what will be required of future research if this compound is to be improved upon.

Vecuronium bromide has a duration of action that is one-third to one-half as long as that of pancuronium bromide when given in a dose that produces the same depth of block. It has a very similar speed of onset of action. However, due to its relative freedom from side effects and shorter duration of action it can be given in higher doses to gain a faster onset of action without side effects and without producing a prolonged block difficult to reverse – unlike most other nondepolarisers. Further, it appears to lack any significant cumulative effect and therefore offers particular advantages for use in renal failure patients. The full scope of the clinical versatility which vecuronium bromide offers remains to be determined.

With all its advantages vecuronium bromide is, however, still not a nondepolarising equivalent of the depolariser, suxamethonium chloride, in terms of onset and duration of action. It remains to be determined whether such a compound is still required and, indeed, if it is feasible to invent or discover such a drug. It may well be that a new drug having only one single advantage over vecuronium bromide, namely, a significantly faster onset of action, will be the ideal relaxant.

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Preclinical pharmacology of vecuronium bromide

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Introduction

In 1942, Griffith and Johnson [1] introduced curare into anaesthetic practice, and, ever since, the safety of surgical operations has been greatly increased by the concurrent use of neuromuscular blocking drugs and anaesthetic agents. As surgical techniques advance, remedial surgery comes to be carried out on patients who would formerly have been regarded as too ill for it to be attempted. Consequently, it has become increasingly important that anaesthetists be armed with neuromuscular blocking drugs free from the kinds of unwanted effects, especially cardiovascular side effects, characteristic of the older drugs of this class. Vecuronium bromide (Org NC 45) is just such a selective neuromuscular blocking drug free from unwanted side effects.

Neuromuscular transmission

Skeletal muscles are innervated by myelinated motor nerve fibres, the cell bodies of which lie in the anterior horns of the spinal cord or in the brain stem. Near its end, each nerve fibre branches, and, in most mammalian muscles, each branch innervates a single muscle fibre at a focal point on its surface (Fig. 1). A single nerve fibre together with the muscle fibres which it innervates is called a motor unit, and a muscle as a whole is composed of thousands of such units.

The inset to Figure 1 is a diagram of the neuromuscular junction, showing how nerve terminals are inserted into indentations in the muscle fibre membrane. Figure 2 is a diagram of the neuromuscular junction enlarged still further to show the acetylcholine-containing vesicles congregated in the terminal and the locations of the acetylcholinesterase enzyme and the postjunctional acetylcholine receptors.

When an impulse reaches the nerve terminal, calcium ions enter it and, by a process not yet fully understood, cause the vesicles to discharge their content of acetylcholine into the junctional cleft, where it interacts briefly with the

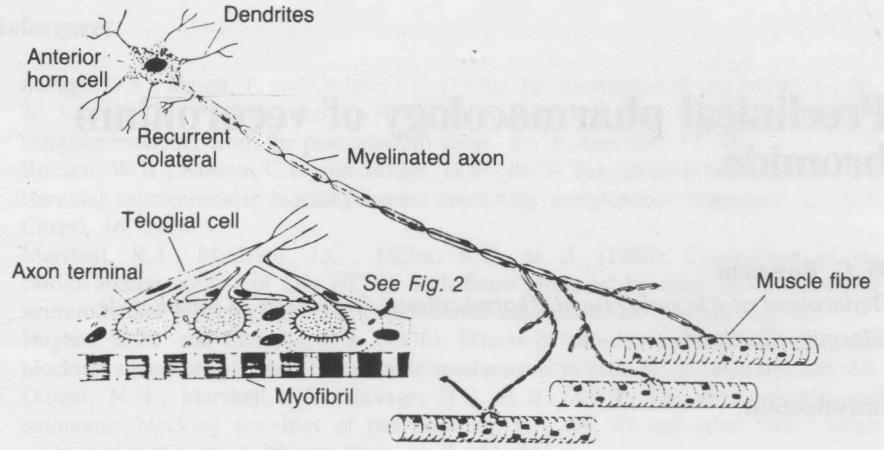

Fig. 1: Diagrammatic representation of a motor unit containing focally innervated muscle fibres. A motor endplate is enlarged as the inset on the left, and a unit of this is further enlarged in Figure 2. Reprinted with permission from [2].

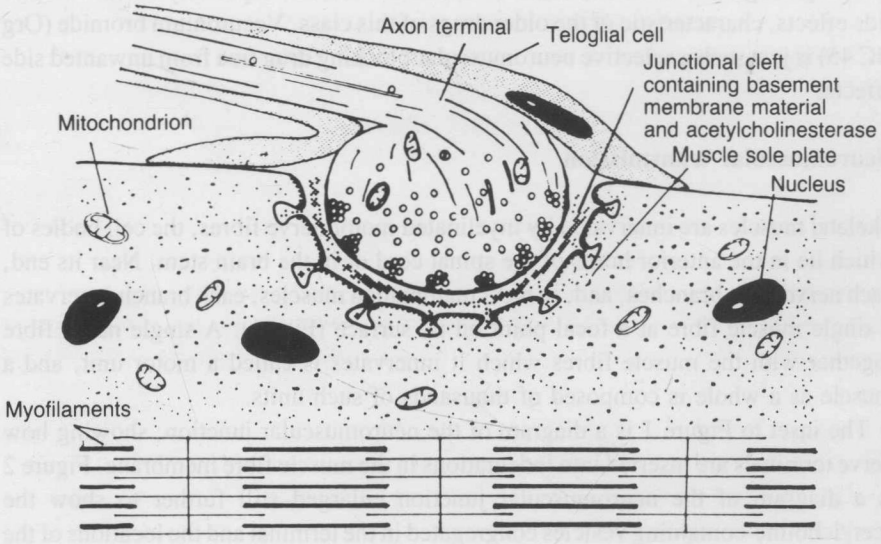

Fig. 2: Diagrammatic representation of a neuromuscular junction enlarged from the motor endplate of Figure 1. The axon terminal contains mitochondria, microtubules, microfilaments and synaptic vesicles. The dots on the crests of the junctional folds indicate the positions of acetylcholine receptors. Reprinted with permission from [2], slightly modified.

acetylcholine receptors (cholinoceptors). Figure 3a diagrammatically represents the interaction between acetylcholine and its receptors. Receptors are protein-based structures, and are embedded in the bimolecular lipid membrane of the motor endplate. When acetylcholine interacts with the receptors, a conformational change is induced in the receptor protein in such a way that an ion channel opens, allowing sodium and potassium ions to flow along their concentration gradients. The main movement consists of sodium ions travelling inwards. As a result, the membrane of the endplate is locally depolarised, giving rise to the endplate potential which initiates the excitation-contraction coupling sequence. If the receptors are blocked by an antagonist (e.g. tubocurarine chloride), as depicted in Figure 3b, then acetylcholine can no longer interact with them to cause the opening of ion channels, transmission is blocked, and the muscles remain in flaccid paralysis.

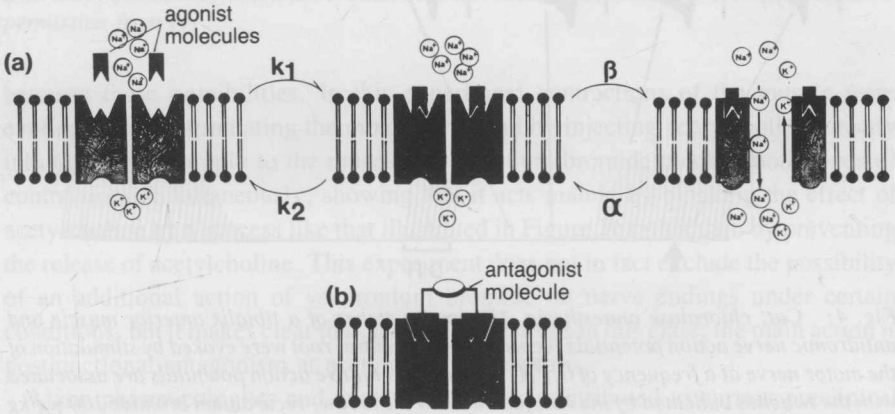

Fig. 3: a: Diagrammatic representation (probably oversimplified) of the interaction between agonist molecules (e.g. acetylcholine) and cholinoceptors at the motor endplate. The diagram implies that two agonist-receptor combinations are needed to cause the conformational change in the receptor protein that opens the ion channel, but this is not known. It also implies that Na^+ and K^+ ions move through the same channel, but this might not be so. The two-tailed black circles represent membrane lipids. For further explanation see text. b: A hypothetical interaction of an antagonist molecule (two-point attachment) with cholinoceptors. No conformational change can occur so that ion channel opening is prevented.

Vecuronium bromide (Org NC 45)

Vecuronium bromide is one of a series of pancuronium bromide analogues designed and synthesised by Savage and his colleagues at the Organon Laboratories in Newhouse, Scotland [3]. It differs from pancuronium bromide only by the absence of