Draw and explain the characteristics of a log dose response curve that describe the major clinical effect of rocuronium.
Describe the factors encountered in clinical practice that may alter this curve.

THIS IS NOT A MODEL ANSWER BUT HELP TO GET THERE:

First point to the candidate – *be cautious of the iterations of this question*. The token NMBD dose response curve has been asked recurrently over the years – started with **vecuronium** in 1998. Then ?nothing until 2013 reinvented with rocuronium asked again the following year → hiatus then re-invented as the QUANTAL dose response curve 2017.

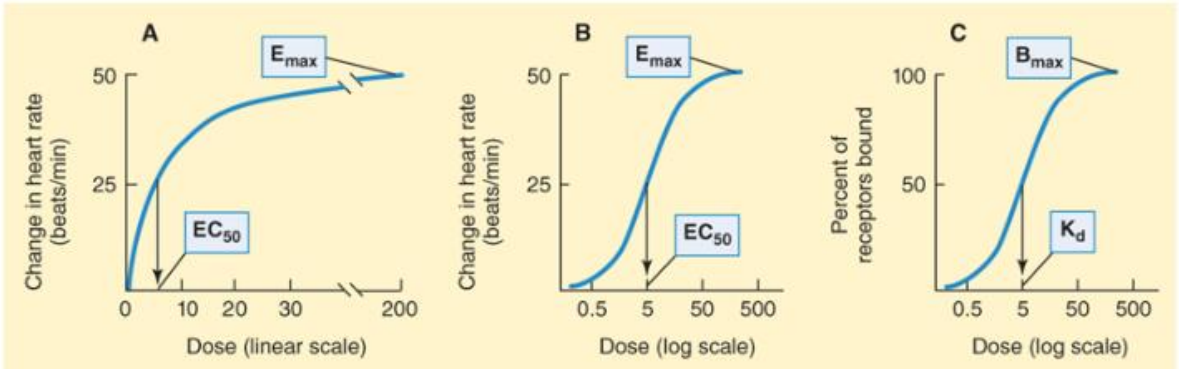
Examiners:
In 2013 they were asking for just the ED95 and how there is 3 phases: first horizontal, then steep, and final horizontal.
2014
Upped the ante a bit:
Most candidates were able to draw a sigmoidal 'graded dose-response curve'
It is important to note that the percentage of nicotinic receptors that are blocked by rocuronium cannot be measured by current clinical methods.
Important features:

1. Neuromuscular block does not occur until a significant amount of rocuronium is given because of the presence of spare receptors
2. The points indicating ED50 and ED95.
3. The middle portion is straight
4. There is a plateau at maximum effect.

Attacking first part:
Goodman and Gillmans:
Dose response curves can be understood to be either graded or quantal

- Graded: as the dose increases the magnitude of the effect/response increases
- Quantal: this is a binary all or none response.
- The graded dose response curves occur within an individual
- The Quantal dose response curves occur in the population – i.e. increasing dose – number of responders increases in discrete all-or-none steps.

Graded dose response curves - Log-dose response curves:
Katzung:
The Graded dose response is noted classically to be a hyperbola.



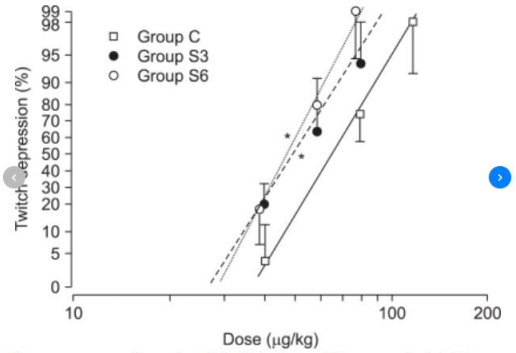
This is traditionally converted to a semi-logarithmic plot because:

- The doses from smallest measureable response to maximum response usually spans several orders of magnitude (Evers and Maze)

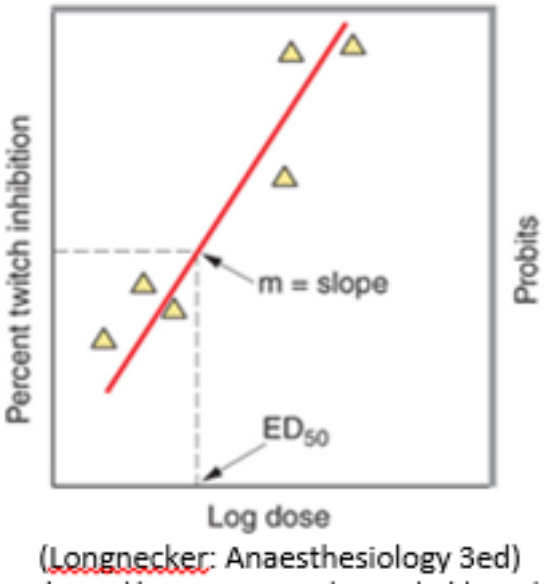
- The hyperbola can be transformed into a sigmoid which:
  - Expands the scale at the low concentrations where effect is rapidly changing and compresses it at high concentrations where the effect is changing slowly
  - usually linearizes the the dose-response range of interest → 20% - 80%.

  BUT OTHERWISE HAS NO BIOLOGIC OR PHARMACOLOGIC SIGNIFICANCE.

What does a log dose-response curve for neuromuscular blocking agents look like in general and for rocuronium more specifically.
Like this:



Dose-response curves of rocuronium obtained by log dose-probit linear regression for twitch depression after chronic pretreatment with clonidine in rabbits. Individual points represent mean (95% confidence intervals) twitch depression (% control) with each dose. *P < 0.001 compared with control values.



(Longnecker: Anaesthesiology 3ed)

Of the recommended texts Longnecker is the only one who has one.
These are called **log-dose probit linear regressions for twitch depression**.
These are victims of tradition because when they were doing the original dose studies they did not have desk-top computers – they had to plot it manually on graph paper and there is special graph paper called log-probit paper.
Here's the originals: Galamine, tubocurarine and pancuronium

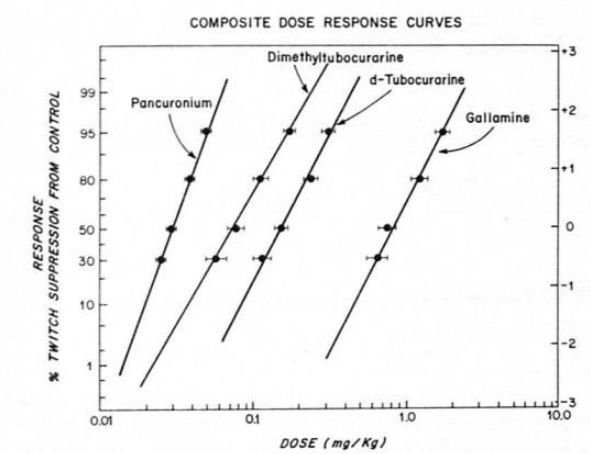


FIG. 2. Each of these dose-response curves, plotted on log-probit paper, represents the average of the individual dose-response curves determined for each of the 9 patients in each agent group. Thus each point is a mean ± S.E.

The probit stuff is quite involved and (for myself) a little hard to understand.
From Millers:
The dose-response relationship for nondepolarizing NMBDs is sigmoidal and has been derived in various ways.

- The simplest method is to perform linear regression over the approximately linear portion of a semilogarithmic plot between 25% and 75% neuromuscular blockade.

Alternatively,

- **the curve can be subjected to probit or logit transformation to linearize it over its whole length**,
- or the data can be subjected to nonlinear regression using the sigmoid E max model of this form:

$$\text{Effect (e)} =_{.} \text{F}\left(\text{dose}_{e}{}^{\gamma}, \text{dose}_{e}{}^{\gamma} + \text{dose}_{e50}{}^{\gamma}\right)$$

BUT from this work sprang forth the 2 x ED95 for intubation:
The MED95 – the mean ED95 (what we now acknowledge that the quoted ED95 for the drug is actually an ED50 for the population) → the MED95 + 3SE would give at least 95% twictch suppression in 99% of the population.

What people probably conceive they should draw:

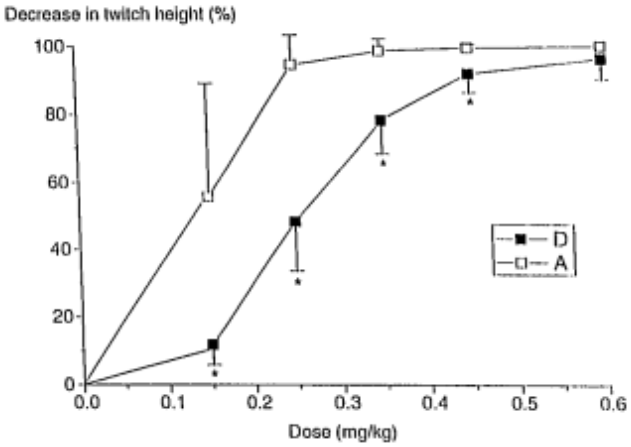


Fig. 1. Cumulative dose–response curves for rocuronium showing percent depression of twitch height (mean ± SD) *versus* dose for the diaphragm (filled symbols) and for the adductor pollicis (open symbols) in six anesthetized patients. *$P < 0.05$ *versus* diaphragm.

Anesthesiology
81:585–590, 1994

Neuromuscular Effects of Rocuronium on the Diaphragm and Adductor Pollicis Muscles in Anesthetized Patients

Jean Paul Cantineau, M.D., Frederic Porte, M.D.,* Gilles d'Honneur, M.D.,* Philippe Duvaldestin, M.D.†*

From Barash:

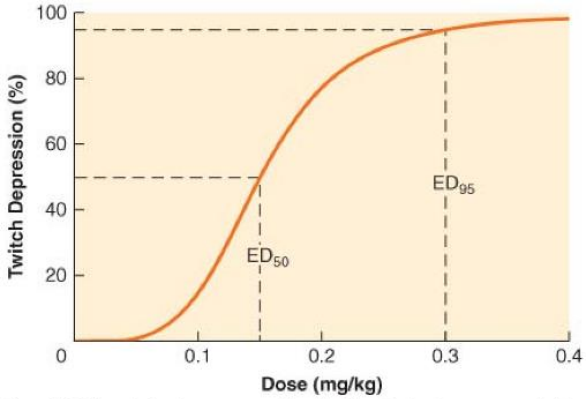


Figure 20.9. Example of a dose-response relationship. The actual numbers are approximately those for rocuronium. The ED_{50} is the dose corresponding to 50% blockade and ED_{95} is the dose corresponding to 95% blockade.

But note THIS IS NOT A LOG DOSE RESPONSE curve.
And unfortunately (or perhaps fortunately) it doesn't need to be log dose response – according to the data the ED50 is fairly well close to half of the ED95.
From the original papers:
When one of the original pioneers - Savarese was doing his original single twitch suppression approach in earlier pre-clinical studies of ester neuromuscular blockers on rats and cats. He had noted in these studies that **the data produced a sigmoid curve if plotted arithmetically**. So the dose axis does not need to be log.

Perhaps what the examiners were thinking was this:
Some sort of construction of our own conception given their comment:

It is important to note that the percentage of nicotinic receptors that are blocked by rocuronium cannot be measured by current clinical methods.

My effort:
According to Barash: a ***speculative*** correlation between %receptor blockade: %twitch height suppression
Accepting according to Stoelting
Rocuronium dose for twitch suppression at adductor pollicis
ED50: 1.47mg/kg → 1.5
ED95: 3mg/kg

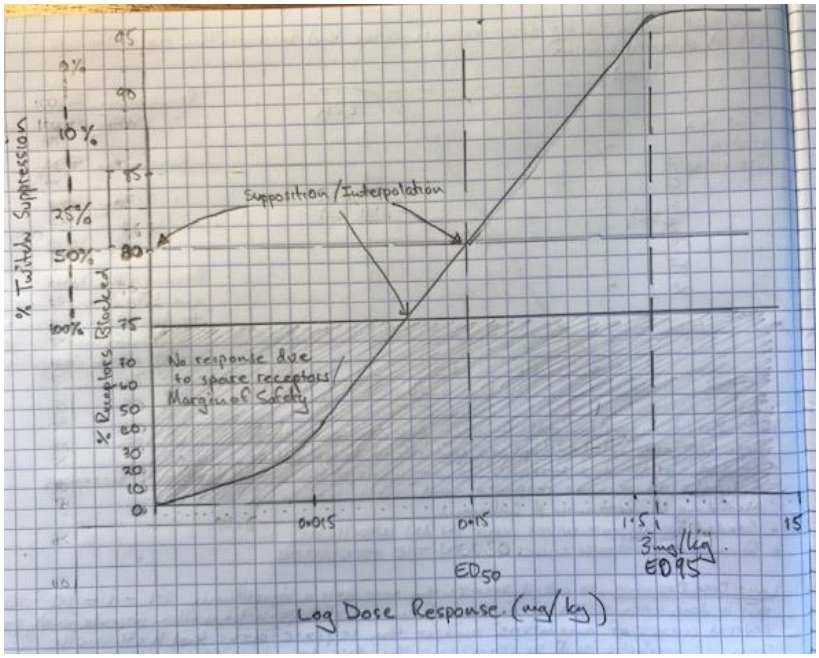


TABLE 21-6

Relationship between % Receptor Occupancy and Train-of-Four Ratio during Nondepolarizing Block

Percent Receptor Occupancy (%)	First TOF Twitch (T_1) (% Baseline)	Fourth Twitch (T_4) (% Baseline)	TOF Ratio (T1–T4 Responses)	TOF COUNT (TOFC)
100	0%	0%	0	TOFC = 0
90–95	0%	0%	0 (T_1 = 0)	TOFC = 0
85–90	10%	0%	0 (T_2 = 0)	TOFC = 1
	20%	0%	0 (T_3 = 0)	TOFC = 2
80–85	25%	0%	0 (T_4 = 0)	TOFC = 3
	80%–90%	48%–58%	0.60–0.70	TOFC = 4
	95%	69%–79%	0.70–0.75	TOFC = 4
70–75	100%	75%–100%	0.75–1.00	TOFC = 4
	100%	100%	0.9–1.0	TOFC = 4
50	100%	100%	1.0	TOFC = 4
25	100%	100%	1.0	TOFC = 4

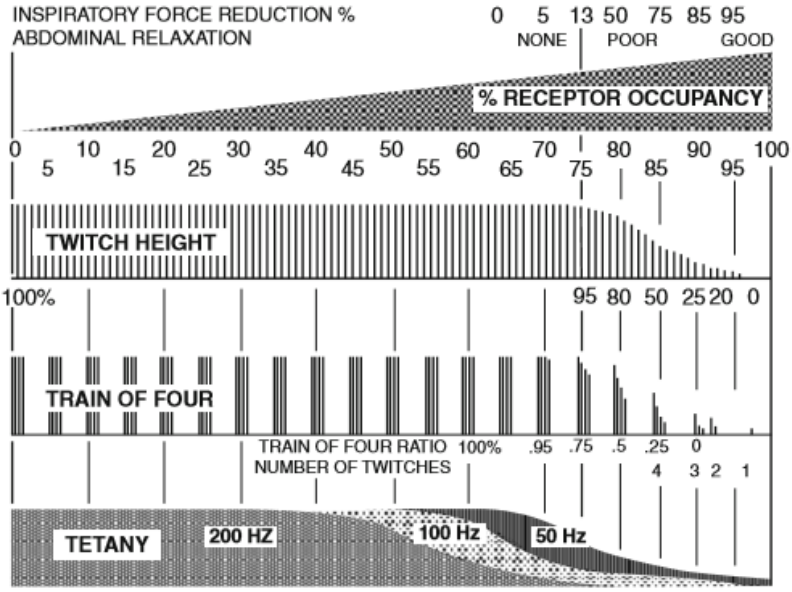


Fig. 50.6 The three most common stimulation modalities in neuromuscular monitoring are single twitch height, train-of-four and tetanus at 50 Hz. They have a fairly reproducible relationship to one another and to the fraction of acetylcholine receptors that need to be blocked (occupied) by the muscle relaxant for a given effect. (From an online lecture Thompson C: Monitoring the Neuromuscular Junction, University of Sydney, 2010, with permission.)

Source: Chris Thompson
http://www.anaesthesia.med.usyd.edu.au/resources/lectures/nmj_monitoring_clt/nmjonitoring.html

This Dr Chris Thompson is in Sydney – Eger and crew liked his picture so much its in their anthology The Wondrous Story of Anesthesia.
I asked him once what the basis was for this inclusive conceptualization and he said he couldn't quite remember and probably conceived and composed it from a number of resources (personal correspondence).
Note the difference in his graph and the table from Barash**. Barash suggests a very steep increase in the number of receptors occupied to twitch height depression**. Barash suggests that from no twitch depression at 75% receptor occupancy to 80 – 85% receptor occupancy the twitch height will have decreased 75%. In Thompsons graph he suggests that the reduction in twitch height is only 50% in progressing from 75 – 85% receptor occupancy. I stuck my receptor occupancy / twitch suppression at 80%: 50% based on best guess based on Barash.

Looking at the original studies the relationship is very steep once you hit 75%:

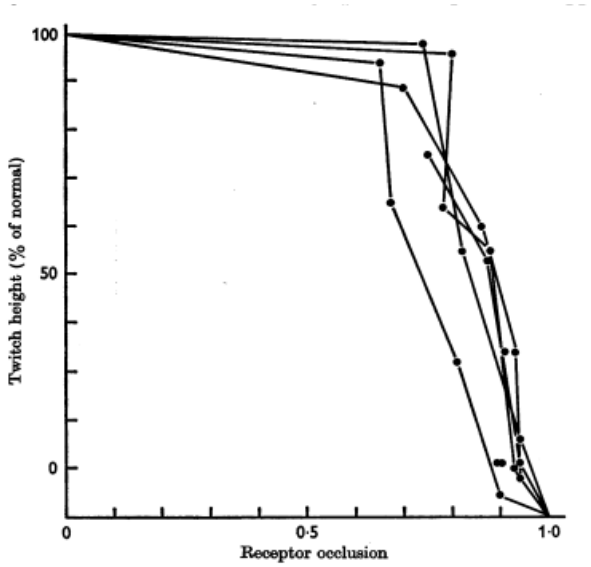
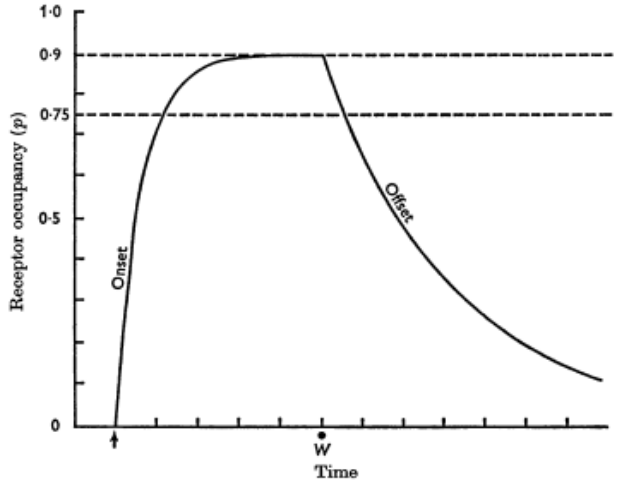


Fig. 9. Relationship between twitch height and degree of receptor occlusion by a competitive blocking agent. Ordinate: twitch height as % of normal. Abscissa: fractional receptor occupancy. Lines connect points from the same animal.



. 12. Calculated 'onset' and 'offset' of neuromuscular block by a competitive king agent; 'dose' of agent such that occupancy at equilibrium will be 0·9. inate: fractional occupancy. Abscissa: time in arbitrary units. Time constant of t of occupancy is 0·1 that of offset. Competitive agent 'administered' at arrow washed out at W. Horizontal interrupted lines at $y' = 0{\cdot}9$ and $p = 0{\cdot}75$ esent occupancies associated with threshold and deep block in a typical cat cle. Reduction in twitch height proceeds more slowly than recovery.

Paton and Waud 1966

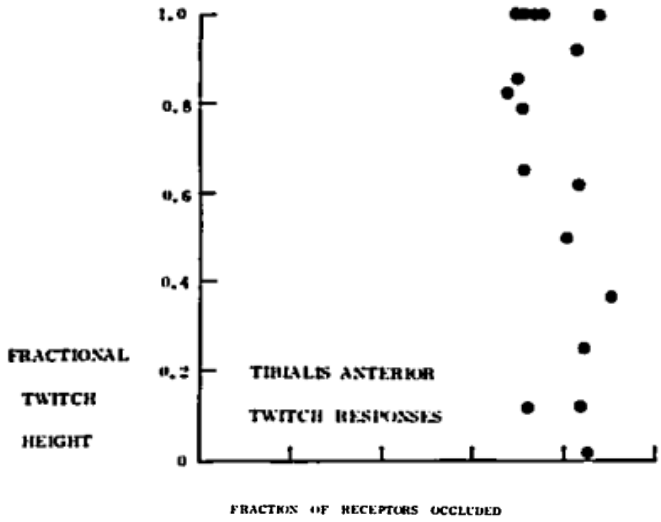


FIG. 6. Relation between twitch response or tetanic fade and receptor occlusion. Top left panel: twitch response plotted against receptor occlusion. When 20–25 per cent of the receptors become free the twitch response returns to normal. Remaining panels, tetanic responses. Bottom left: tetanic fade at 30/sec recovered at the same range of receptor occupancy at which the twitch recovered. Right-hand panels: tetani at 100/sec are not well-maintained until half the receptor pool becomes available, while tetani at 200/sec are not normal until two-thirds of the receptors are free.

Waud and Waud 1971

Add:

This notion of the margin of safety and it's mythical 75% - speculation from the work of Paton and Waud and then Waud and Waud on cats. They were prompted initially by these thoughts:

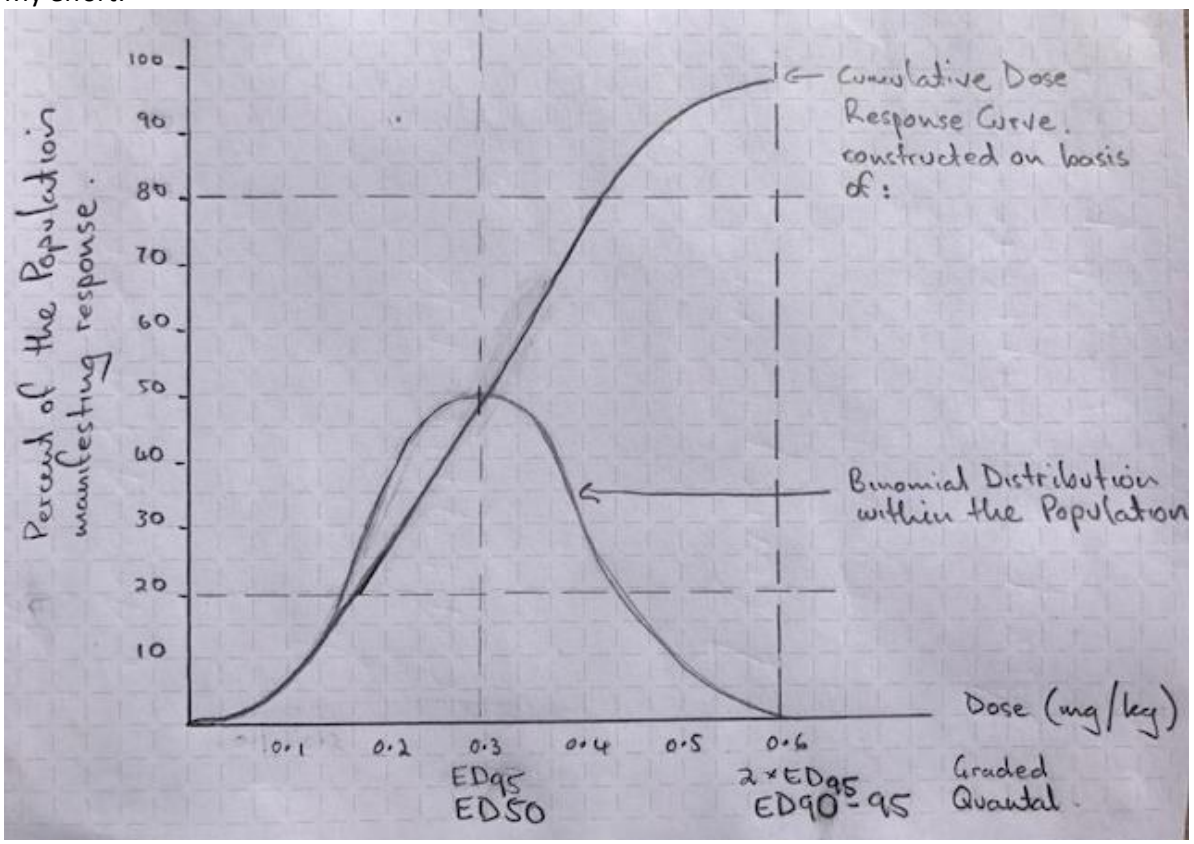
- teleological considerations indicate that neuromuscular transmission would not be borderline i.e. more receptors would be available than those barely necessary for transmission of signal
- the 'spare receptor' theory – a modification of receptor theory Stephenson RP (1956)

Paton WDM Waud (1966) The margin of safety of neuromuscular transmission J Physiol 91: 59 – 90

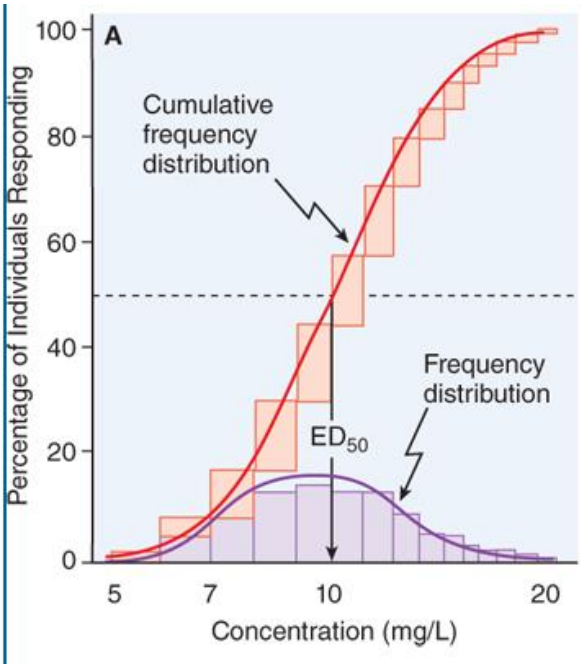
To determine the degree of receptor occlusion, the 'dose ratio' method (Gaddum, Hameed, Hathway & Stephens, 1955) was used. The principle consists of finding the ratio in which the dose of a stimulant must be increased in the presence of an antagonist in order to match a control response. In general, occupancy is equal to the dose ratio divided by the (dose ratio - 1), provided that parallel log-dose response curves are obtained; this requires either that the occupancy required by the stimulant is low, or that complete equilibrium between receptors, antagonist and stimulant is achieved

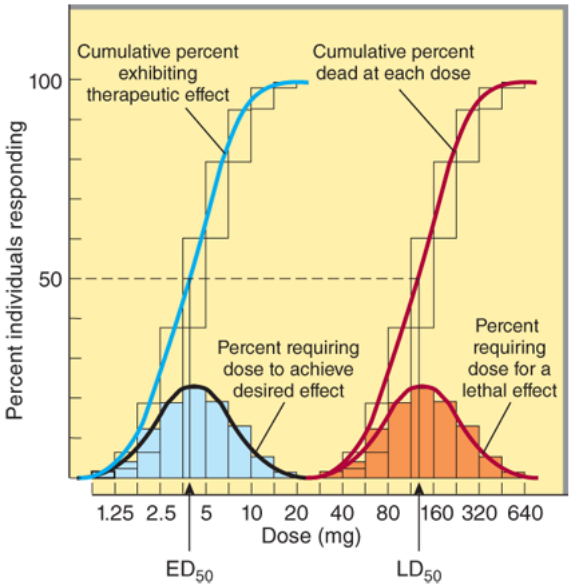
To produce threshold block to indirect stimulation once every 10 sec, a fractional occupancy by the antagonist of 0-76 + 0.05 (S.D.) was required;

Making a distinction on the other iteration of this question:
Draw and explain a QUANTAL dose response curve for rocuronium
My effort:



Based on:
Goodman and Gillmans and Katzung and Trevor:





Katzung:

- *For most drugs, the doses required to produce a specified quantal effect in individuals are lognormally distributed; that is, a frequency distribution of such responses plotted against the log of the dose produces a gaussian normal curve of variation*
- ***the quantal dose-effect curve and the graded dose-response curve summarize somewhat different sets of information, although both appear sigmoid in shape on a semilogarithmic plot***

NB.

Evers and Maze:

- Graded responses can be quantized.
- The cumulative fraction of subjects that respond at a given dose (i.e., responding at that dose or lower) appears as a sigmoid curve on semilogarithmic axes.
- It is important to note that the shape, particularly the slope, of cumulative dose–response relationships derived from quantal data **reflects the heterogeneity of the population studied rather than the underlying physiology of drug action**
- Note that the nomenclature for quantal (ED50) and graded (ED_{50}) dose-response curve differs, with the subscript numeral only used for graded data

Factors associated with potentiation of ND-NMBDs

- Neonatal state
- Neuromuscular diseases
  - Myasthenia gravis
  - Muscular dystrophies
- Drugs
  - Inhalational anaesthetics
  - Local anaesthetics
  - CCBs
  - Antibiotics
  - Steroids
  - Diuretics
  - Immunosuppressants
  -
- Electrolytes disorders
  - Hypokalaemia
  - Hypocalcaemia
  - Hypernatraemia
  - Hypermagnesaemia
- Respiratory acidosis

Factors associated with resistance to ND-NMBDs

- Presence of extra-junctional receptors
  - Burns
  - Trauma
  - UMN and LMN lesions
  - Demyelinating lesions
- Prolonged immobilization
- Drugs
  - Xanthine derivatives: aminophylline, theophylline
  - Phenytoin
  - corticosteroids

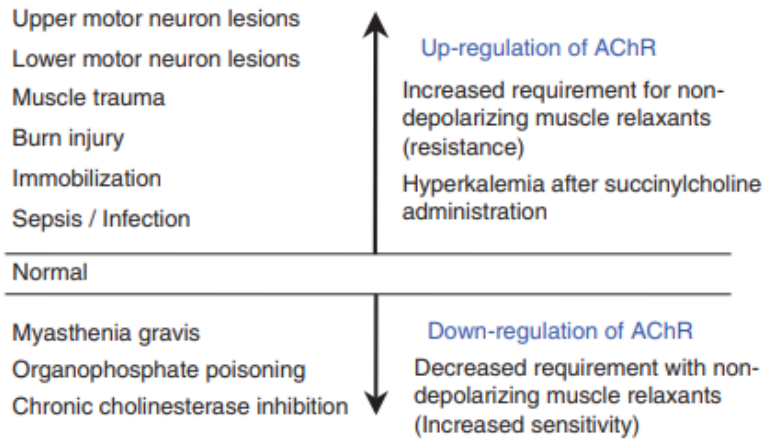


Figure 38.8. Conditions with altered acetylcholine receptor (AChR) expression.