THE UNIVERSITY OF LEEDS

NAME *(in Block Letters, Surname first)* COCQUHOUN, D.

SUBJECT OF EXAMINATION Pharmacology

ROOM

No. of SEAT (1)

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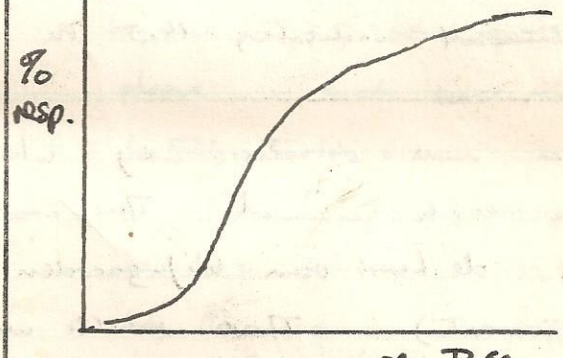
1

Possibly the most important source of ~~biology~~ variation in a biological response to a drug are the numerous relatively small and usually indefinable error causing variations in the biological test object which remain after as many as possible of the factors mentioned below have been eliminated, and usually described as "innate biological variability". Such variations are generally able to be treated by statistics. An illustration of this variability is seen when groups of say 20 or 30 animals are each given doses of a substance, eg to test its acute toxicity, and the % mortality in each group is recorded - obviously if all the animals are exactly the same there would be an exact lethal dose and all the animals receiving less than this would survive, all receiving more would die. This, of course, is not so and different numbers will die in each group.

If the % response is plotted against the dose the curve obtained is an asymmetric sigmoid curve which has been stated by JW Trevan to be the characteristic curve for the particular species and drug.



- Obviously then the distribution of individual lethal doses (IED), though in this type of experiment each IED is not itself measured, and hence the distribution of resistance to the drug, is not Gaussian. This is really not surprising as

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the effect of each small error-producing cause must be independent of the value of, in this case, x, the dose. if the distribution is to be normal and biologically this is unlikely. Hence we must transform x to $f(x)$ such that if the effect of each small error-producing cause on $f(x)$ is independent of $f(x)$ - which will then be normally distributed. The effect on x itself will then be proportional to the "Reaction" $\frac{dx}{df(x)}$

and biologically it is likely that any small effect will be proportional to x itself, and hence we would expect $\log x$ to be normally distributed as putting $f(x) = \log x$ we have $\frac{d\log_e x}{dx} = x$. This is very often the case in practice and hence when % response is plotted against $\log x$, a symmetrical sigmoid curve is obtained. This is shown to approximate to an integrated normal distribution curve by ~~plotting the point~~ taking as the response metameter the "probit" which is related to P = fraction response (i.e. % response /100) thus :-

$$P = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{c} e^{-1/2 c^2}$$

ie the normal probability integral, in which c corresponds to the normal equivalent deviation and the Probit = NED + 5 (to avoid negative deviations). On plotting this against log dose a straight line is usually obtained indicating that the log ~~dose~~ IED is normally distributed.

This is also illustrated in a more obvious way when the actual IED is measured in each animal. This was done by Behrens in 1921 and by de Kind van Wijngaarden in 1926 (using lethal dose of digitalin in cats). These results were of the type indicated above and demonstrated the futility of the "physiological" units which were in use at that time for biological standardisation (as definition of the frog unit of digitalin as the ~~exact response~~

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lethal dose per gram of frog — it is now obvious that this quantity will be extremely variable from one frog to another and also depending on the season, less being required in winter. This led to the introduction of standard preparations of the type used by Ehrlich for histological standardisation of diphtheria antitoxin for von Behring.

This type of variation may also be seen sometimes when measuring graded responses eg the contraction of a guinea pig's uterus in response to histamine — perhaps because the ED_{50}s for such cell of the muscle are lognormally distributed. However, it is much more common to find that the dose/resp. curve is approximately hyperbolic, suggesting a chemical drug-receptor equilibrium of the type derived by Langmuir for adsorption of gas onto polished metal. viz $kx^n = y/100-y$ where x = dose, k and n are constants and y = % of max. response.

This type of curve is converted to a straight line over the central portion by plotting resp. vs log dose.

Sometimes the dose response relationship is linear — eg the degree of inhibition of frog's ventricle by structurally non-specific depressants.

In addition to the above there are numerous other factors which can affect the response. ~~The~~ Hypersensitivity and hyposensitivity or individual natural tolerance are dealt with above — such individuals are those in the tails of the distribution curve".

Idiosyncrasy may occur. This is a totally unpredictable response which is not a normal response to the drug however big the dose, in most people (as opposed to hypersensitive responders which are) eg. the causation of Asthma by aspirin, (esp. amidopyrine) of agranulocytosis by the pyrazolones, chloramphenicol, sulphonamides, thiourea derivatives (eg the thiouracils) and gold salts.

meaning?

Direct mitotic poison?

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Chloramphenicol can also produce aplastic anaemia and thrombocytopenia, sulphonamides acute haemolytic anaemia and gold salts thrombocytopenic purpura. These responses are all probably idiosyncratic in nature - Such responses are often allergic or anaphylactoid in nature eg 'drug fever', urticaria and angioneurotic oedema and occasionally more serious destructive eg exfoliative dermatitis.

Tolerance to a drug may / natural, as above, or acquired. An acquired tolerance may be a true cellular tolerance eg. to morphine, ethanol, Heroin or it may be a so called pseudo-tolerance due to decreased absorption (i case of EtOH), increased rate of catabolism (morphine addicts break down amphetamine faster than normal) or increased rate of excretion. Tolerance to ganglion-blocking agents, in particular the polymethylene bistrimethylammonium series may be due to sensitisation to circulating pressor agents by the functional denervation produced.

are these the same?

Drugs to which tolerance is required often can cause habituation or addiction (with a physical dependence on drug and withdrawal syndrome when it is stopped.).

The weight (or probably more correctly the surface area of a person will affect his response to a given dose - hence doses are often expressed "per kgm body weight"

The amount of fatty tissue will affect such drugs as are rapidly taken up by it as their reservoir.

Age will affect the response - The proportion of the adult dose can be estimated from $\frac{\text{Wt. in lb.}}{150}$ (Clark), $\frac{\text{Age}}{\text{Age}+12}$ (Young)

or $\frac{\text{age next birthday}}{24}$ (Cowling) - This mostly gives too results over to age of 12 and it is probably better to use body weight as index of dose as above. However children

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3) Specific antagonism eg of the muscarinic effects of ACh by atropine by blocking of ACh receptors
- Receptor competition - or by substrate competition eg delaying, of destruction of ACh by inhibition of ChE with eserine,
It may also be non-competitive eg diphenyline (NPhenoxyisopropyl Phenoxy) Bchlorobetylamine) which forms strong probably covalent bonds with adrenoceptors, not ~~only~~ reversible by competitive kinetics.

- Other factors which must be taken into account are species variation (often very large eg in case of neuromuscular blocking agents), route of ~~administration~~ admin (Mg^{++} + streptomycin not absorbed from GI tract - ∴ exert local not effects only but systemic effects (quite different in case of Mg^{++}) parenterally. Also distribution in body, biotransformation + excretion must be considered.

Eg — chloroform in male rats

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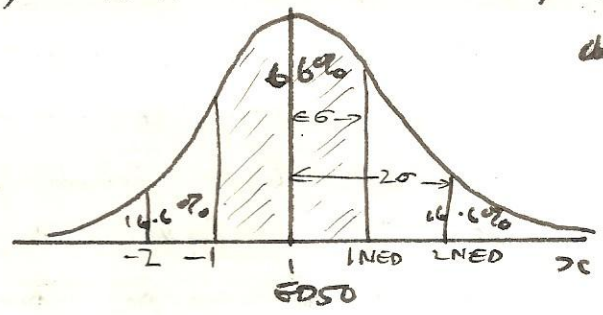
2) c) Probits have been defined in the previous question. – this definition is illustrated opposite – The ~~probit is the area of~~ NED corresponds to the % of area under the curve below it as explained hence



%	NED	Probit
2.5	−2	3
16.6	−1	4
50	0	5
83.4	1	6
97.5	2	7

As explained when the probit is ~~taken~~ of the response metameter + plotted against log dose, then if the NED is normally distributed, regression is linear and hence calculations can be made relatively easily. The regression equation of probit on log dose would be calculated and ~~the~~ b – the slope of the regression line stated. It can be seen that $1/b = \lambda$ = S.D. of mean log NED. The standard error can be calculated and hence, using the distribution of t, the fiducial limits for the ED50 (or LD50), or ~~EC~~ for the potency ratio if there are two ~~dose response~~ lines representing drugs A different potency one of which is being standardised against the other.

4) Graded response. This is the type of continuously variable response described above – eg the weight of ash in bones, the height of contraction of an isolated muscle, or of changes in blood pressure of an animal, or fall in blood sugar level after insulin.

As before the dose response relationship may be linear, of the quantal type (though this really involves the

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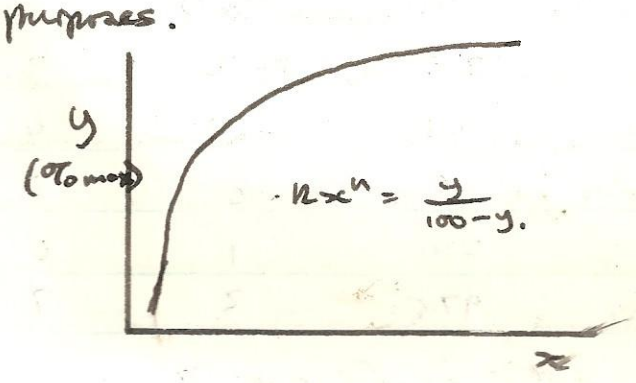
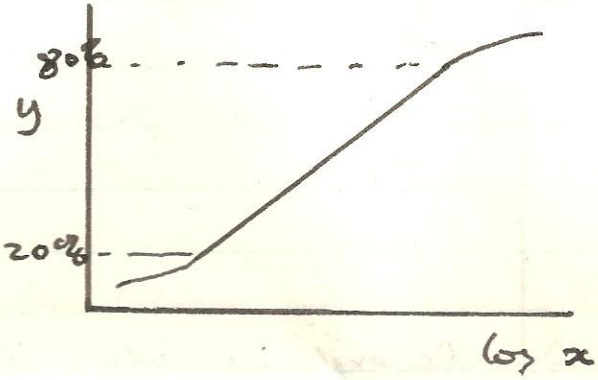
assumption that the response is not really continuously variable but that the methods of measurement are insufficiently sensitive to detect the individual "quanta" of response), or most compounds of the hyperbolic type which show positive as log dose becomes straight over sufficient of its length to allow calculations to be made eg for bio-assays purposes.





- the fact that the Langmuir adsorption isotherm often describes the data very well cannot be taken as proof of any physico-chemical process as this would involve assuming 1) that all receptors were equally accessible to the drug and 2) the response was proportional to the ~~number~~ of receptors occupied - neither of which is very probable.

c) Sympathomimetic. - implies a drug which mimics the actions of the sympathetic nervous system. In theory this could be done by stimulation of central sympathetic centres (this is a minor action of various drugs as either), by selectively stimulating sympathetic ganglia (but no known drug does this) or most important, by combining with the hypothetical adrenergic receptors on organs which are innervated by post-ganglionic sympathetic nerves. (However the sweat glands fall into this category but are not stimulated by drugs such as adrenaline is more usually known as sympathomimetic, as, unlike the rest of post ganglionic sympathetic nerve endings

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those innervating the sweat glands have ACh as transmitter rather than sympathetic (which is now considered to consist usually about 80% Noradrenaline + 20% adrenaline and is the usual transmitter at the junction between post. symp. fibres and the tissue which they innervate.)

As there appear to be various types of adrenergic receptors eg excitatory (α) and inhibitory (β) it is not surprising that different sympathomimetic drugs show α and β effects to different degrees (e.g. Noradrenaline mostly α, Isoprenaline mostly β).

d) A Side Action is simply an action of the drug other than the action which is considered to be the useful or pharmacotherapeutic action in any particular case. Thus an action which is useful for treating one condition may be a side effect in treating another.

e) Biological standardisation is a method using living material of maintaining constancy of potency of a product which cannot be analysed chemically (eg very large molecules, or those whose structure is unknown, or mixtures of similar drugs or very small quantities). An international standard is used to prepare an accurate laboratory secondary standard against

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which subsequent batches of the drug are standardized using the one of the type of responses mentioned previously. When the dose-response relation is made known by the methods described the potency of an and its error can be calculated.