Possibly the most important source of biostatistical variation in a biological response to a drug are the numerous relatively small and usually indefinite errors 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 "intrinsic 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, e.g. to test its acute toxicity, and the % mortality in each group is recorded—obviously if all the animals were 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 a sigmoid curve which has been stated by J. E. Warren to be the characteristic curve for the particular species and drug. Obviously then the distribution of individual lethal doses (I.D.), though in this type of experiment each I.D. is not measured, and hence the distribution of resistance to the drug is not Gaussian. This is really not surprising as
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 at 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 the log x to be normally distributed, as putting \( f(x) = \log x \) we have \( \frac{dx}{df(x)} = x \). This is very likely the case in practice of log x.

and hence that the response is plotted against log x, a symmetrical sigmoid curve is obtained. This is shown to approximate to an integrated normal distribution curve by the plotting point method as the response metamer to the "probit" which is related to P - fracture response (i.e. of response/100) thus:
\[
P = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{c} e^{-\frac{1}{2}x^2} dx
\]

is the normal probability integral, in which c corresponds to the normal equivalent deviation and the probit = NED + 0.5 (to avoid negative deviations). On plotting this against log x, a straight line is usually obtained indicating that the log x 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 Belurman in 1921 and by de la Hand van Wijnhoven in 1926 (using lateral and jugular in cat). These results were of the type indicated above and demonstrated the futility of the "physiological" units which were in use at that time for histological standards (as definition of the feng unit of chip et. cetera as the...
let be done per gram 7F frog - it is now obvious that the 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 Student for intrajet administration of depot thiocyanate for von der Ein.

This type of variation may also be seen sometimes when measuring produced responses as the contraction of a muscle - his utricular - response to histamine - perhaps because the IED's for such cell of the muscle are logarithmically distributed. However, it is much more common to find that the dose response curve is approximately hyperbolic, suggesting a chemical type receptor equilibrium of the type derived by Langmuir for adsorption of a gas onto polished metal, viz. 

\[ R_x = \frac{y}{100 - y} \]

where \( R_x \) is the dissolved gas content and \( y \) is the stimulus 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 - as the degree of inhibition of frog's ventricle by structurally non-specific depressants.

In addition to the above, there are numerous factors which affect the response. The hyperactivity and hypoactivity of individual units tolerance are dealt with above - such individuals are those in the tails of the distribution curve.

Idiopathic 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 hyperactive responses which are), eg. the causing of asthma by aspirin, of allergies to the pyrazolones, chloramphenicol, sulphonamides, thiourea derivatives (as the thiocyanates) and solid salts.
Chlorpromazine can also produce aplastic anemia and thrombocytopenia, sulfoximmines can cause leukocyte anemia and certain antibiotics can cause agranulocytosis. These responses are all probably idiosyncratic in nature - such responses are often allergic or anaphylactoid in nature as "drug fever", urticaria and conjunctivitis, eczema and occasionally more serious dermatitis or exfoliative dermatitis.

Tolerance to a drug may either be acquired or acquired. An acquired tolerance may be a true cellular tolerance e.g. to morphine, ethanol, heroin or it may be a so-called pseudo-tolerance due to decreased absorption (e.g. codeine), increased rate of excretion (morphine addicts mean an excitable intestine normal) or increased rate of excretions. Tolerance to barbiturate agents, in particular the polyanhydrides polyethylene-co-existence carrier may be due to sensitization of circulating precursor agent by the functional desensitization produced.

Drugs to which tolerance is acquired often cause habituation or addiction (with a physical dependence on drug and withdrawal symptoms when it is dropped).

The weight (or probably more correctly the surface area) of a person will affect his response to a given dose. Hence dosages are often expressed "per kg body weight".

The amount of body tissue which affects such drugs as are rapidly taken up by it as thiopentone.

Age will affect the response - The proportion of the adult dose can be estimated from

\[
\text{dose} = \frac{\text{wt. in lb. (female)}}{150} \times \text{age} + \text{years}
\]

or age next birthday (continuing) - This mostly gives (as results

over to age 12 and it is probably better to use average weight as index of dose as above, however children
9) Specific antagonism by $\alpha$-methyl tyrosine effects
- Action by blocking $\alpha$-adrenergic receptors
  - Receptor competition - or by in situ

It may also be non-competitive eg. dibenamine
(phenylisopropylamine) which
forms strong probably could weak with
adrenergic receptor, not easily exercised
by sympathomimetics.

Other factors which must be taken into account are
species variation (often very large eg in case of
norepinephrine blocking effects), route of administration
($\mathrm{Ca}^{++}$ not absorbed from GI tract - i. e. exert local GI
effects orally but systemic effects (quite different in
case of $\mathrm{Ca}^{++}$) potentently. Also distribution in body,
bioconversion and excretion must be considered.

Sex - chloroform in male rats
27) a) In the previous question, it was defined that the definition of an effective dose (ED) corresponds to the 50% response level. Here, the dose-response relationship is given as a percentage of the maximum response. The ED50 is the dose at which 50% of the maximum response is achieved.

<table>
<thead>
<tr>
<th>Dose</th>
<th>Percentage</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5</td>
<td>-2</td>
<td>3</td>
</tr>
<tr>
<td>16.6</td>
<td>-1</td>
<td>4</td>
</tr>
<tr>
<td>50</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>83.4</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>97.5</td>
<td>2</td>
<td>7</td>
</tr>
</tbody>
</table>

As explained, when the dose is plotted against the response rate and a regression line is fitted, the regression equation can be calculated. The influence of curvature and variance in the data can be modelled relatively easily. The model equation is the slope of the regression line, which can be seen as the standard error (S.E.) of the mean log ED. The standard error can be calculated and used in the equation to predict the dose at which a certain percentage of the maximum response is achieved. This is known as the IC50, representing the dose causing 50% of the maximum response.

b) Graded response. This is the type of response when the variable response changes over a range - e.g. the weight of a person, the height of a person, the efficiency of a machine, or the change in blood pressure from an activity. It falls in the category of a continuous variable.
assumption that the response is not really continuous variable but that the methods of measurement are insufficiently sensitive to detect the individual "quantum" responses, or most components of the hypothetic type which then published as log dose because standard is sufficient if its length to allow calculations to be made or for bio-assays purposes.

\[ y = 100 - x^N \]

\[ x = 100 - \frac{y}{N} \]

- The fact that the logarithmic absorption equation often describes the data very well cannot be taken as proof of any physical-chemical process as it would involve assuming 1) that all receptors are equally accessible to the drug and 2) the response was proportional to the number of receptors occupied - neither of which is very probable.

c) Sympathetic mimetic - implies a drug which mimics the action of the sympathetic nervous system. In theory this could be done by stimulation of central sympathetic centres (this is a minor action of various amine and ether) by selectively stimulating sympathetic ganglion (but no known drugs does this) or most important, by combining with the hypotensive adrenergic receptors in 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 in more usually known as sympathomimetic, as, unlike the rest of post-ganglionic sympathetic nerve endings
these inverting the vector glands have rather than sympathetic (which is more considered to consist usually about 80% noradrenaline + 20% adrenaline and is the usual transmitter at the junction between postganglionic sympathetic and the target gland these inverts). As there appear to be various types of adrenergic receptors eg. excitatory (e) and inhibitory (p) it is not surprising that different sympathomimetic drugs show a and p effects to different degrees e.g. noradrenaline mostly a, isoproterenol mostly p).

1. Aside 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 another condition.

2. Biologically standardisation is a method using being utilized at maintaining constancy of production of a product which cannot be analysed chemically (of very large molecules, as the pure chain structure is unknown, or mixture of similar drugs or very small quantities). This involves a standard is used to prepare an accurate laboratory reagent standard against.
which subsequent batches of the drug were standardized using the one of the type of response maintained previously. When the dose response relation is work

unravel by the methods described the accuracy of the

and its error can be calculated.