

muscle that results in vasodilatation and a rapid fall in blood pressure. Again, it affects the arterioles more than the veins but we do not know the precise mechanism. If it antagonises the effects of calcium ions, as has been suggested, then its powerful vasodilator action could result from interference with the role of calcium in generating action potentials or in the release of calcium ions during the initiation of muscle contraction.

Several antihypertensive agents affect sympathetic nerves and adrenergic receptors. The constrictor action of noradrenaline, released from sympathetic nerves, on vascular smooth muscle can be antagonised by alpha-adrenergic antagonists such as phentolamine.

Pentolinium has an antihypertensive action by blocking transmission in sympathetic ganglia, but the drug is now seldom used. Adrenergic neurone-blocking drugs such as guanethidine, bethanidine, and debrisoquine are also used as antihypertensive agents. These act in a third way: after they are taken up into the adrenergic nerve terminal they prevent the release of noradrenaline.

BETA-ADRENERGIC ANTAGONISTS

Beta-adrenergic antagonists such as propranolol are of value for treating hypertension, and they may be given with vasodilators. The onset of the antihypertensive effect of propranolol is not immediate, and the mechanism of its action is still not clear, though its role in reducing the heart rate and the cardiac output is obviously important. Propranolol also affects the peripheral blood vessels, and lowers the plasma renin activity. The latter action would lower angiotensin levels, and since angiotensin contracts vascular smooth muscle, the result would be a reduction of the peripheral vascular resistance.

Two other possible mechanisms of propranolol are a change in the sensitivity of the baroreceptors of the carotid sinus and major arteries, so that their performance adjusts to the reduced cardiac output, and a direct effect on the central nervous system.

METHYLDOPA

Methyldopa also seems to have an antihypertensive effect by an action on the CNS. Methyldopa inhibits dopadecarboxylase, the enzyme which converts dopa (dihydroxyphenylalanine) to dopamine. This depresses the synthesis of dopamine, noradrenaline, and serotonin. The significance of this is being reconsidered, however, and a recent hypothesis is that methyldopa in the CNS is metabolised to alpha-methylnoradrenaline; this compound may exert an antihypertensive action through interaction with central alpha-adrenoceptors.

CLONIDINE

A drug often used in mild hypertension is clonidine, though initially it may increase the blood pressure. This may reflect the fact that clonidine, which is structurally similar to tolazoline, the alpha-adrenoceptor antagonist, has intrinsic alpha-adrenoceptor agonist activity so that a direct but transient peripheral vasoconstrictor action could occur. Its withdrawal may cause rebound hypertension.

The adrenoceptor agonist activity may be concerned also in its antihypertensive action if alpha-adrenoceptors in the CNS are activated so that the sympathetic nervous system is inhibited. This hypothesis is a difficult one to test but the action of clonidine does seem to result from effects in the CNS rather than at the periphery.

One cannot include here a discussion of the mechanisms of all the drugs that influence the activity of the cardiovascular system. Those which have been mentioned, however, do illustrate the extent to which the treatment of cardiovascular disorders has a sound pharmacological basis.

Statistics at Square One

VII—Statements of probability

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We have seen that when a set of observations have a "normal" distribution—as they commonly have in medicine and biology—multiples of the standard deviation mark certain limits on the scatter of the observations. For instance, 1.96 (or approximately 2) standard deviations above and 1.96 standard deviations below the mean ($\bar{x} \pm 1.96 \text{ SD}$) mark the points within which 95% of the observations lie.

Probability limits

We noted that Dr Green's 140 children had a mean urinary lead concentration of $2.18 \mu\text{mol}/24 \text{ h}$, with standard deviation 0.87. The 95% probability limits here are $2.18 \pm (1.96 \times 0.87)$, giving a range of 0.47 to 3.89. One of the children had a urinary lead concentration of just over $4.0 \mu\text{mol}/24 \text{ h}$. This observation is greater than 3.89 and so falls in the 5% beyond the 95% probability limits. We can say that the probability of each of such observations occurring is 5% or less. This probability is usually expressed as a fraction of 1 rather than of 100, and written $P < 0.05$.

Standard deviations (or standard errors, which behave in exactly the same way) thus set limits about which probability statements can be made. Some of these are set out in table 7.1. To use table 7.1 to estimate the probability that a certain observation, say a urinary lead concentration of $4.8 \mu\text{mol}/24 \text{ h}$, came

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TABLE 7.1—Probability related to multiples of standard deviations (or standard errors) for a normal distribution

Number of standard deviations	Probability of observation showing at least as large a deviation from the population mean
0.674	0.50
1.0	0.317
1.645	0.10
1.960	0.05
2.0	0.046
2.576	0.01
3.0	0.0027
3.291	0.001

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from the same population of observations as Dr Green's 140 children provided, we proceed as follows.

The mean of Dr Green's series was 2.18 $\mu\text{mol}/24\text{ h}$, and the standard deviation 0.87. How many standard deviations from the mean does the new observation lie? The distance of the new observation from the mean is $4.8 - 2.18 = 2.62$. How many standard deviations does this represent? Dividing the difference by the standard deviation gives $2.62/0.87 = 3.01$. This number is greater than 2.576 in the table but less than 3.291, so the probability of finding a deviation as large as this lies between 0.01 and 0.001, which may be expressed as $0.01 > P > 0.001$. In fact table 7.1 shows that the probability is very close to 0.0027. This probability is small, so the observation probably did not come from the same population.

Again, the mean number of times that Dr Green's 140 children saw a doctor in one year (table 4.2) was 3.25, with a standard deviation of 1.25. A child that Dr Green thought needed special study was seen by a doctor only once. Was this unusual? The difference between this one visit and the mean is $3.25 - 1 = 2.25$. How many standard deviations does this represent? $2.25/1.25 = 1.8$. Table 7.1 shows that 1.8 standard deviations correspond to a probability of between 0.1 and 0.05. This is more than 5%, and so fairly high. Therefore this child's one visit was not particularly unusual in relation to the numbers of visits to or from their doctors that the 140 children had as a whole.

To take another example, Dr White found the mean diastolic blood pressure of the printers to be 88 mm Hg and the standard deviation 4.5 mm Hg. One of the printers had a diastolic blood pressure of 100 mm Hg. The mean plus or minus 1.96 times its standard deviation gives the following two figures:

$$88 + (1.96 \times 4.5) = 96.8 \text{ mm Hg}$$

$$88 - (1.96 \times 4.5) = 79.2 \text{ mm Hg.}$$

Is there a simple test for sickle cell trait or disease which could be used quickly for screening before outpatient general anaesthesia?

The simple detection of sickle-cell haemoglobin is easy and there are several commercially available screening techniques which detect sickle-cell haemoglobin with reasonable reliability. These screening tests collectively come under the heading of "solubility tests"—the older and classic "sickling test" which uses an incubated preparation of whole blood cells being harder to interpret.

Three major difficulties occur in clinical practice. (1) Sickle-cell haemoglobin predominantly occurs in Black people (who probably originated in the sickle belt of Central Africa) and commonly comes to Britain via the West Indies. Sickle-cell haemoglobin, however, is more widely distributed and may also, albeit comparatively rarely, be found in inhabitants of the Mediterranean area, Middle East, and India. The finding of sickle-cell haemoglobin in an apparently pure Caucasian is not unknown and may merely suggest previous cultural mix. In clinical practice one would probably confine a screening programme to those of Negro extraction, among whom a sickle-cell carrier rate of about 10% is to be expected in Britain. (2) The detection of the presence of sickle-cell haemoglobin does not distinguish the common sickle-cell carrier from the uncommon patient with sickle-cell disease

We can say therefore that only 1 in 20 (or 5%) of printers in the population from which the sample is drawn would be expected to have a diastolic blood pressure below about 79 or above about 97 mm Hg. These are the 95% limits. The 99.73% limits lie 3 standard deviations below and 3 above the mean. The blood pressure of 100 mm Hg noted in one printer thus lies beyond the 95% limit of 97 but within the 99.73% limit of 101.5 ($= 88 + (3 \times 4.5)$). This sort of difference from the mean is commonly described as "significant." That is to say, it is significant at the 5% level because it is not within the 95% limits.

The means and their standard errors can be treated similarly. If a series of samples are drawn and the mean of each calculated, 95% of the means would be expected to fall within the range of two standard errors above and two below the mean of these means. This common mean would be expected to lie very close to the mean of the population. So the standard error of a mean provides a statement of probability about the difference between the mean of the population and the mean of the sample.

Confidence limits

Confidence limits provide the key to a useful device for arguing from a sample back to the population from which it came. For example, Dr White found in her sample of 72 printers a mean diastolic blood pressure of 88 mm Hg. The standard error of the mean was 0.53 mm Hg. The sample mean plus or minus 1.96 times its standard error gives the following two figures:

$$88 + (1.96 \times 0.53) = 89.04$$

$$88 - (1.96 \times 0.53) = 86.96.$$

These are called 95% confidence limits, and we can say that there is only a 5% chance or less that the mean of the population lies outside the range of 86.96 to 89.04 mm Hg. If we take the mean plus or minus three times its standard error, the range would be from 86.41 to 89.59. These are the 99.73% confidence limits, and the chance of the population mean lying outside those limits is 1 in 370 or less.

Exercise 7. A count of malaria parasites in 100 fields with a 2-mm oil immersion lens gave a mean of 35 parasites per field, standard deviation 11.6. On counting one more field the pathologist found 52 parasites. Does this number lie outside the 95% probability limits; what are they? *Answer:* No; 12.26 and 57.74.

What are the 95% confidence limits for the mean of the population from which this sample count of parasites was drawn? *Answer:* 32.73 and 37.27.

(such as sickle-cell anaemia, sickle-cell haemoglobin C disease, and sickle-cell β -thalassaemia). Patients with sickle-cell haemoglobin C disease, who may react badly to anaesthesia, might have no history of previous ill health and may indeed not even be anaemic on testing. In other words, a positive screening test requires further haematological investigations including electrophoresis. (3) Most patients with sickle-cell haemoglobin will be the simple sickle-cell carrier. It is a much repeated truism to say that the sickle-cell carrier requires the same careful anaesthetic management (with avoidance of hypoxia) as is also needed by the overweight middle-aged Caucasian. The tiny minority with sickle-cell disease pose both diagnostic and therapeutic problems beyond the scope of this reply.

A woman patient of mine aged 77 has just had chickenpox. Is the disease rare in the elderly?

I have never seen a case of chickenpox in the elderly though I suppose nothing is impossible. What I have seen more than once is a generalised chickenpox-like rash in an old person who presented with clinical herpes zoster. This, I think, is not uncommon in elderly people, who are those most likely to be affected by shingles.