PROFESSOR DANIEL: I would like to say something about this biopsy business. Suppose it had turned out to be a medulloblastoma. It would have responded to radiotherapy but it would have killed the boy in a year or less, though he could, perhaps, have been saved for that time by radiation. As it is, I am sure that there is astrocytomatous material throughout the whole neuraxis. You can't tell this without a biopsy, and you must confirm whether it is treatable or not.

DR BRIMBLECOMBE: Would Professor Tizard just sum up the whole thing?

PROFESSOR TIZARD: I was influenced towards the diagnosis of a granuloma here because of the possibilities of treatment. I have taken too simplistic a view of astrocytomata. The reason I had put astrocytomas on one side was that I was under the impression that astrocytomata of field origin ran a pretty rapid course, but that discrete astrocytomata might be relatively benign. There is evidently an inbetween situation here, but it must be very rare to have one which presents with midline tumour, which is much more characteristic of medulloblastoma. Finally, I do not think any of our deliberations have explained these fluctuations. The intermittent obstruction and hydrocephalus may explain some of the features, but one wonders if there is a vascular component or cerebral oedema, which the steroids might have dealt with, or if he has one of the patchy leucoencephalopathies associated with tumours elsewhere. This was a most fascinating and instructive case.

PS. I should have believed in the mother's diagnostic acumen!

This conference was recorded and transcribed by Dr W F Whimster.

APPOINTMENTS OF SPEAKERS

(1) Dr F S W Brimblecombe, FRCP, DCH, paediatrician, Royal Devon and Exeter Hospital Heavitree, Exeter EX1 2ED.
(2) Professor J P M Tizard, FRCP, DCH, professor of paediatrics, University of Oxford.
(3) Professor P M Daniel, FRCP, FRCPATH, neuropathologist, Institute of Psychiatry, London SE5 8AF.
(4) Dr R D Hoare, FRCR, MRCP, consultant neuroradiologist, The Hospital for Sick Children, London WC1N 3JH.
(5) Mr K Till, MB, FRCS, neurological surgeon, The Hospital for Sick Children, London WC1N 3JH.
(6) Professor J F Soothill, MB, FRCP, professor of immunology, Institute of Child Health, London WC1.
(7) Dr J Wilson, PHD, MRCP, neurologist, The Hospital for Sick Children, London WC1N 3JH.
(8) Dr J H H MacRae, MB, CHB, London SW6 2LA.
(9) Dr C H Stewart-Hess, FRCP, FRCGP, general practitioner, Crediton, Devon.

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Today's Treatment

Diseases of the cardiovascular system

Hypertension—I

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When to treat

The Framingham study has shown that the risk of cardiovascular "events" rises in proportion to the height of the blood pressure, systolic or diastolic, with no discernible critical level.[1] Such evidence has been taken to suggest that an active reduction of blood pressure is desirable. The Framingham study and much life insurance information, however, is concerned with the natural history of a population with a wide range of blood pressures. These studies offer minimal, if any, information about the effects of antihypertensive treatment.

The outstanding evidence for the beneficial effects of drug treatment comes from carefully controlled Veterans Administration studies.[2-5] In men with sustained diastolic blood pressure readings above 110 mm Hg (phase 4*) antihypertensive treatment resulted in a reduction of severe morbid events associated with hypertension, such as congestive cardiac failure, renal failure, and stroke. Unfortunately no reduction in the complications of coronary artery disease was shown. In women other than with severe hypertension the influence of hypotensive treatment has not been clearly established. At diastolic blood pressures below 110 mm Hg (phase 4) the case for treatment is not proved, and large-scale multicentre trials are in progress to determine the effects of reduction of blood pressure in patients with mild hypertension and in the elderly. In such patients the decision to start treatment should not be based on a solitary high reading, systolic or diastolic. The blood pressure should be measured on at least three separate occasions at weekly or two-weekly intervals, as a significant fall in blood pressure readings occurs without drug treatment over this period if the measurement is made under similar circumstances by the same observer. Ideally a profile of casual, lying or sitting (3-5 min), standing (1-3 min), and post-exercise blood pressure levels should be obtained on each occasion, preferably at different times of day. The diastolic end-point should be recorded as phase 4 or phase 5 or both. Care to eliminate factors that may distort the measurement must also be taken.[6] For example, the width and length of cuff for the sphygmomanometer varies in relation to the size of the arm (childhood or obesity), and the rate of deflation of the cuff should be steady and slow (2-3 mm/s fall in the column of mercury).

*Phase 4, distinct, abrupt muffling of sound; phase 5, disappearance of sounds.

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The decision to start treatment—for example, in a 40-year-old man with a sustained lying blood pressure of 165/100 mm Hg (phase 4)—is also weighted by proved "risk" factors, such as raised lipid values, cigarette smoking, glucose intolerance, and electrocardiographic evidence of left ventricular hypertrophy.[1] A strong family history of cardiovascular events or features thought to be associated with sustained high blood pressure such as cardiac hypertrophy, renal damage, or fundal changes are further indications that treatment should be started, even though the benefits of antihypertensive treatment at this level of blood pressure in a 40-year-old man have to be proved. In women, who appear to tolerate raised blood pressure levels better than men, or in obese or older patients, the arguments for active treatment at a level of 165/100 mm Hg are much weaker. Only enthusiastic believers in the benefits of active reduction of minor increases in blood pressure would initiate treatment.

The decision to treat is also influenced by the presence of underlying causes of hypertension. Examples include concurrent drug treatment such as oral contraceptives or corticosteroids, primary aldosteronism, coarctation of the aorta, Cushing's syndrome, and phaeochromocytoma. Age, occupation, and personality of the patient also affect the decision.

Clearly a rigid policy not to treat any patient with casual, lying, or standing baseline levels below 110 mm Hg is untenable. Similarly critical examination must be made of exhortations to start treatment in all patients with a diastolic level above 90 mm Hg. Indeed, such a casual diastolic blood pressure may be found in 20-30% of adults.

What to use

Mild and moderate levels of hypertension are usually symptomless at diagnosis. Patients will persevere with lifelong treatment only if it does not interfere too much with their daily activities. In clinical practice most grades of hypertension may be treated satisfactorily with a limited number of drugs—at most six—chosen from the 90 preparations marketed in Britain. These can be used alone or in various combinations.

Diuretics

Diuretics (23 preparations) and diuretic combinations (25 preparations) are widely used for all grades of hypertension. There is no evidence of a clear superiority of any individual benzothiadiazine diuretic. The mode of action of thiazides in long-term treatment is uncertain. An effect on vascular smooth muscle, perhaps mediated through a reduction in intracellular sodium and water, has been suggested. The onset of hypotensive action is within two to three days but may not be fully developed even after four weeks of treatment. The once-daily dose required (say bendrofluazide 5 mg/day) is below that needed to produce a troublesome diuresis, and the use of high-potency diuretics such as frusemide or bumetanide offers no advantage. Longer-acting diuretics such as chlorthalidone or aldosterone antagonists such as spironolactone are also effective. The mean reduction in sustained lying and standing blood pressures obtained with bendrofluazide 5 mg/day under controlled conditions is 15-20 mm Hg systolic and 5-10 mm Hg diastolic. Combined treatment with other agents such as beta-blockers or methyldopa is rational as an increased hypotensive effect is obtained.

The principal adverse reactions to thiazide diuretics include rashes, mild gastrointestinal symptoms, hypokalaemia, impairment of glucose tolerance, raised serum urate levels, and aggravation of renal insufficiency. Potassium supplements are seldom required in patients on a normal daily diet containing over 70 mmol (mEq) potassium if low doses of thiazide diuretics are used—such as bendrofluazide 5 mg/day. In potassium-losing states or when there is doubt about the dietary intake and in patients with impaired liver function or receiving concurrent treatment with digoxin, corticosteroids, or carbenoxolone, potassium supplements (24-32 mmol/day) or a potassium-sparing or retaining diuretic are indicated. Diabetes mellitus is not an absolute contraindication to thiazides. Alterations in antidiabetic treatment, diet, and exercise may counteract any adverse effect of the diuretic on glucose tolerance. Newer agents, such as metolazone, are reputed to cause less deterioration in glucose handling. Allopurinol may be prescribed in patients who develop hyperuricaemia secondary to thiazide treatment, although other antihypertensive agents such as beta-blockers may be preferred. Photosensitivity and thrombocytopenia are among other adverse effects that have been reported. Raised plasma renin levels have been associated with an adverse prognosis in hypertension, although the evidence is controversial. Thiazides raise renin levels, and their use in hypertension has been questioned on theoretical grounds.

Beta-adrenoceptor antagonists

Eight proprietary beta-blockers (six drugs) are marketed in Britain. The use of beta-blockers as first-choice treatment either alone or in combination with other agents is increasing. Possession of partial agonist (intrinsic sympathomimetic), cardioselective, or local anaesthetic (quinidine-like or membrane-stabilising) activity has not been shown to confer antihypertensive superiority.

Differences occur in the handling of different beta-blockers —for example, absorption (propranolol, almost complete; oxprenolol 70-100%); protein binding (propranolol 90-95%; metoprolol 12%); volume of distribution (practolol 1·6, propranolol 3·6, metoprolol 5·6 l/kg); formation of active metabolic products and urinary excretion of unchanged drug (oxprenolol 22-29%; propranolol 1-4%). In addition, wide inter-individual variations in response complicate the interpretation of the effects of single and repeated fixed doses of beta-blockers such as propranolol. Throughout the dosage range the mode of action in reducing blood pressure remains controversial. Speculation continues about the relative contributions of the fall in cardiac output (variable), fall in peripheral resistance (variable), and central and baroreceptor influences as well as the effects of the renin-angiotensin axis (variable reduction in renin release).

The optimal starting and maintenance doses and the time of onset of hypotensive action of beta-blockers are not clearly established. Higher and less frequent initial oral doses—for example, 40 or 80 mg propranolol or oxprenolol two or three times a day—are now being recommended than when beta-blockers were introduced over 10 years ago. A reduction of pressure within four hours with such doses may occur, but with continued fixed-dose treatment the hypotensive effect probably becomes evident within 24-72 hours. No further reductions in blood pressure occur after two weeks on a fixed dose, and a two-fold increase in dose is usually recommended. A twice-daily dosage regimen appears to be satisfactory with some agents—for example, propranolol and oxprenolol. About a fifth of the patients do not respond to conventional doses of beta-blockers (say, propranolol 240-320 mg/day). In such non-responders alternative hypotensive treatment may be added or substituted, although some workers have increased the dose of beta-blockers to 2-5 g/day, at which levels a central mode of action may assume an increased importance. The mean reduction in supine and erect blood pressure under controlled conditions in a randomly selected group of patients is about 20/10 mm Hg with propranolol 120—240 mg/day. Once such a reduction has been obtained, doubling the dose of beta-blocker—for example, atenolol (above 200 mg/day) or oxprenolol—may not cause further significant reduction. Combination treatment with other drugs such as thiazides is effective.

The predictable pharmacological actions of beta-blockers imply that their use is contraindicated in patients with asthma, moderate and severe heart failure, conduction defects (2° and 3°), metabolic acidosis, and prolonged fasting. Relative contraindications quoted by some manufacturers include chronic

obstructive lung disease, severe cardiomegaly, mild cardiac failure, pregnancy, allergic rhinitis, diabetes mellitus, and sinus bradycardia. In these instances the potential benefits of beta-blockade must be weighed against the disadvantages.

Many adverse reactions have been associated with beta-blockers. Nausea, anorexia, and vomiting may be reduced by taking them before food. A rise in blood urea levels and deterioration in renal function have been reported as with other hypotensive agents. On the other hand, successful use of beta-blockers and a reduction in the plasma half life of propranolol have also been described in renal failure. The avoidance of high doses (say, over 400 mg propranolol or oxprenolol daily) may reduce the occurrence of symptoms of mild fatigue, lassitude, light-headedness, ataxia, anxiety, mental confusion, hallucinations, insomnia, vivid dreams, and a hypertensive response, which have been reported in some patients. In cold climates cold extremities, aggravation of Raynaud's phenomenon, and symptoms of peripheral vascular disease may be troublesome. Rashes have been reported with most agents. Several minor adverse reactions have also been described. In severe ischaemic heart disease withdrawal of beta-blockers should not be abrupt, as deaths from cardiac arrhythmia and myocardial infarction have been reported. The principal adverse drug interaction concerns antidiabetic treatment. Signs of hypoglycaemia may be masked and the hypoglycaemic effects of concurrent treatment increased.

A validated case of the oculomucocutaneous syndrome associated with practolol treatment has not yet been reported with any other beta-blocker. Careful monitoring of patients on beta-blockers, particularly the newer agents, is required. The cause of the reaction has not been determined.

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Statistics at Square One

XI—The t tests

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Previously we have considered how to test the null hypotheses that there is no difference between the mean of a sample and the population mean, and no difference between the means of two samples. We obtained the difference between the means by subtraction, and then divided this difference by the standard error of the difference. If the difference is 1·96 times its standard error, or more, it is likely to occur with a frequency of only 1 in 20, or less. The probability attached to other ratios of the difference divided by the standard error appeared in table 7.1.

But with small samples, where more chance variation must be allowed for, these ratios are not entirely accurate. Some modification of the procedure of dividing the difference by its standard error is needed, and the technique to use is the *t* test. Its foundations were laid by W S Gossett under the pseudonym "Student,"[1] so that it is sometimes known as Student's *t* test. The procedure does not differ greatly from the one used for large samples, but it is preferable when the number of observations is fewer than about 60, and certainly when they amount to only 30 or less.

The application of the *t* distribution to four types of problem will now be considered:

(1) The mean and standard deviation of a sample are known (or can be calculated). What is the probability that the population mean, which is unknown, lies within a certain range of the sample mean?

(2) The mean and standard deviation of a sample are known (or can be calculated) and a value is postulated for the mean of the population. How significantly does the sample mean differ from the postulated population mean?

(3) The means and standard deviations of two samples are known (or can be calculated). How significant is the difference between the means?

(4) Paired observations are made on two samples (or in succession on one sample). What is the significance of the difference between the means of the two sets of observations?

In each case the problem is essentially the same—namely, to establish multiples of standard errors to which probabilities can be attached. These multiples are the number of times a difference can be divided by its standard error. We have seen that with large samples 1·96 times the standard error has a probability of 5% or less, and 2·576 times the standard error a probability of 1% or less (table 7.1). With small samples these multiples of standard error are larger, and the smaller the sample the larger they become.

(1) Where does population mean lie?

A rare congenital disease, Everley's syndrome, generally causes a reduction in concentration of blood sodium. This is thought to provide a useful diagnostic sign as well as a clue to the efficacy of treatment. Little is known about the subject, but Dr Pink, who is director of a dermatological department in a London teaching hospital, is known to be interested in the

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