sweat electrolytes. Nevertheless, both the chloride and the sodium electrodes still pose problems, and not all infants in the first week of life can produce enough sweat fast enough for abnormalities in the sweat electrolytes to be detected reliably. The meconium and electrolyte-sensitive electrode tests are both about 85\% sensitive and 95-99\% specific.

A satisfactory screening test should be simple and rapid; non-traumatic; accurate and precise; sensitive and specific; with a cost commensurate with community resources and the likely benefits. While the tests available are reasonably accurate, collaborative trials and research could improve their efficiency still further. Early presymptomatic diagnosis by screening followed by appropriate treatment should reduce if not prevent the digestive problems and the progressive bronchopulmonary disease which affect most patients with cystic fibrosis sooner or later. Nevertheless, any screening test is presumptive only, and there must be an adequate back-up service with a specific validated diagnostic test.

For cystic fibrosis this means the classical iophoresis sweat test of Gibson and Cooke. Without exception, all babies with positive results from screening tests should be assessed with a minimum time interval between screening and the final diagnosis. "The screener is definitely advertising"—that is to say, that screening must have an adequate support programme of treatment and counselling.

Angina and aortic valve stenosis

Morgagni in 1761 gave us vivid descriptions of angina and sudden death in patients with aortic valve disease. He described a young woman who "had long been subject to a kind of paroxysm, which appeared in the following manner: on using quick exercise of the body, a kind of violent uneasiness came on, within the upper part of the thorax on the left side, joined with difficulty of breathing and a stupor of the left arm... In the year 1707... and being cheerful in her mind, beheld the same paroxysm returned: with which being seized and saying that she would die, she actually died on the spot." At necropsy he found "the semilunar valves which were in various places, hard together, with the beginnings of future bone."

Early surveys of patients with aortic stenosis showed an incidence of angina of roughly 22\%. More recent studies, which used the diagnostic criterion of peak systolic aortic valve gradient rather than clinical assessment, have shown a higher incidence of 47-77\%. Up to 48\% of patients who had undergone coronary arteriography had angina despite normal coronary arteries. Of equal importance was the presence of unsuspected coronary artery disease in patients with aortic stenosis but without angina—as high a proportion as 45\% in one series.8

Angina in aortic stenosis is due to an increased demand for oxygen combined with a reduced supply. Studies in which the heart has been stressed with isoprenaline\(^8\) have shown that lactate production occurs in patients with aortic stenosis with normal coronary arteriograms, a finding which shows that the myocardium becomes ischaemic. In patients with high pressure gradients coronary blood flow remained relatively fixed under stress,\(^9\) and, though oxygen extraction could have increased, anaerobic glycolysis supervened: the demand for oxygen exceeded its supply.

Myocardial oxygen consumption depends mainly on three variables: heart rate, contractility, and wall tension. In the present context the most important is the last. Laplace's law states that wall tension is directly proportional to the pressure in a lumen and its radius.\(^11\) In aortic stenosis increasing intra-ventricular pressure increases wall tension. The ventricular volume is usually normal, unless there is additional aortic regurgitation, when an enlarged volume further increases wall tension.\(^10\) The thicker wall reduces its stress,\(^10\) but the greater muscle mass increases myocardial oxygen consumption.\(^14\)

Aortic valve stenosis also reduces the supply of oxygen to the myocardium. Coronary flow is proportional to the mean aortic pressure, which may be low in these patients. The raised ventricular diastolic pressure will further reduce coronary perfusion, and a Venturi effect from the jet through the narrow valve orifice may actually reverse coronary flow in systole.\(^15\) The left ventricular ejection time is prolonged,\(^16\) and this reduces the time for coronary flow during diastole. Myocardial oxygen supply may be lowered still further by the presence of coronary artery disease or anaemia, and coronary embolism may occur from calcified fragments of the aortic valve.

These considerations are relevant to surgery of the aortic valve. Myocardial infarction during aortic valve replacement accounted for 80\% of deaths in a recent series.\(^17\) The various methods of coronary artery perfusion are necessarily unphysiological and may be jeopardised by coronary artery disease, the increased mass of muscle to be supplied, and anatomical variations of the coronary ostia. Coronary arteriography is therefore recommended before aortic valve replacement to delineate these lesions, and critical coronary artery stenoses may be amenable to saphenous vein bypass grafting.

These problems are influencing cardiac surgeons to use hypothermia\(^18\) and agents which affect the electrolyte balance of the myocardium\(^19\) in preference to coronary perfusion for myocardial preservation during aortic valve replacement.

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Correcting the calcium

Many medical articles include a statement that “the plasma calcium results were corrected for the plasma protein levels,” and numerous formulae have been proposed for carrying out the correction. Why is it necessary and how much does it matter?

The root of the problem is that only half the calcium in the plasma is ionised. Most of the rest is bound to proteins, principally albumin, while a little is complexed with citrate and other organic anions. The ionised and complexed fractions are together known as the “ultrafiltrable calcium.” For most purposes it is only ionised calcium which is physiologically relevant, and ideally this would be the fraction to be measured. Methods are available, but they require expensive or specially built apparatus and call for rapid anaerobic handling of the sample. The same is true of the measurement of ultrafiltrable calcium, and neither assay is suitable for general use. On the other hand, most laboratories have simple methods for estimating the total plasma calcium; these are readily automated and give good precision. So most clinicians have to assess disturbances in calcium metabolism from changes in the total calcium concentration.

Calcium binding to albumin is influenced by pH, but within the range found in clinical practice the proportion of calcium which is bound varies little. Clearly the most important factor affecting the total plasma calcium is the plasma protein concentration, so that many formulae have been proposed for predicting the ionised calcium value, or “correcting” the total calcium to an arbitrary “normal” protein value. Such formulae have been based on plasma total protein, or on plasma albumin, or on plasma specific gravity—which is largely a measure of total protein. Formulae based on albumin are preferable, since most protein-bound calcium is bound to albumin and albumin assays are now widely available on the same automated machinery used for plasma calcium.

Correction factors have been calculated from published data and, expressed as mmol/1 change in calcium for each 1 g/l change in albumin, include 0·018, 0·019, 0·020, 0·021, 0·022, 0·023, and 0·025. The similarity of these figures suggests that a simple routine correction of plasma calcium is a reasonable procedure. The chosen reference value for plasma albumin should be in the middle of the range for the method in use; for many current automated methods a value of 40 g/l is appropriate. The “correction” of the plasma calcium may then be simplified as follows: for every 1 g/l by which the plasma albumin exceeds 40 g/l 0·02 is subtracted from the total plasma calcium. A corresponding addition is made when the plasma albumin is less than 40 g/l. The reference range for plasma “corrected” calcium must be determined for each laboratory; it depends on the methods used for both calcium and albumin and on the formula employed.

However crude the mathematical manipulation used, some correction of the plasma calcium can relieve anxiety about those patients, particularly in surgical wards, whose low calcium concentration results from a low albumin and does not reflect a disorder of calcium metabolism. Spuriously high calcium values resulting from the prolonged application of a tourniquet may be corrected in the same way. In specialised units newer methods for ionised calcium assay may prove valuable, but for most of us the “corrected” plasma calcium is an adequate measure of ionised calcium on almost all occasions.

Long-term clinical trials

The scientific method is apt to be something of a Procrustean bed on which to lay patients. People with painful, distressing, and perhaps fatal diseases are in no condition to be treated heartlessly. Yet if their illness is to be studied objectively, as it must be for their own good as well as other sufferers, some kind of statistical analysis is often needed. Consequently the examination, treatment, and follow-up of every patient in a series may have to follow a carefully defined protocol if exact observations are to be made and valid conclusions drawn from them.

A most helpful guide to the design and analysis of clinical trials has now come from a group of British and American workers. It is concerned with trials of fairly long duration over several years. Though the report is addressed to the Medical Research Council’s Leukaemia Steering Committee, it will be of interest to clinicians carrying out a long-term trial in any specialty. Exceptionally clearly written, it is intended for non-statisticians, and its authors are clearly aware of the many ways in which the smooth course of a trial can be upset—for example, by failure of patients to receive treatment, exclusion of patients for some special reason, or loss of patients in follow-up. Some useful tests are described that demand no more than simple arithmetic for their performance, and statisticians will find fuller information on them in the appendices. Only one misfortune has befallen the pair of papers in which this report is presented: though they appear in successive parts of the British Journal of Cancer, these parts are in different volumes—1976 and 1977.

The need for more accurate statistical analysis was recently the painful lesson of a paper in the British Medical Journal, and this need is unlikely to be met by collaboration with trained statisticians, because there are too few of them. Consequently any doctor embarking on an objective clinical study will probably need some understanding of elementary statistical testing himself. For long-term trials this latest report offers invaluable guidance to clinicians.