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Clinical trials in asthma

A great deal of medical research depends on the recruitment of patients into clinical trials. Little attention has been paid, however, to patients' attitudes to such research and their reasons for giving their informed consent. Cassileth *et al*[1] recently investigated these attitudes in patients with cancer and heart disease and in 107 members of the general public. The three groups gave similar answers, over 70% believing that patients should be willing to take part in research. When asked what would be their main reason for their personal participation 52% said that it would be to help them to get the best medical care. This expectation of some medical benefit outside the trial re-emphasises how careful investigators must be adequately to protect their patients in the design of and recruitment for such studies. Ethical committees and researchers should remember the Declaration of Helsinki, which states: "Clinical research cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject."[2]

The much vaunted double blind randomised crossover trial of treatments relies on patients entering each limb of the trial with their disease in the same baseline state. Trials of conditions which show spontaneous fluctuations may, therefore, be frustrating. In asthma this very variability is used as a defining characteristic of the disease,[3] while the responses to bronchodilating and bronchoconstricting stimuli are closely related to the initial airway calibre.[4] All trials in asthma should have adequate control for the placebo responses that often occur, and investigators should also be "blinded," since any suggestion of the expected effects of a treatment may itself modify the changes produced.[5] The accepted method of dealing with baseline variability in asthma trials is to ensure that before all treatments the measurements of a feature such as the forced expiratory volume in one second (FEV_1) are within 15% of each other.[6] Even this does not guarantee an equivalent physiological state, since other tests of lung function such as total lung capacity may change significantly without changes in FEV_1.[7] Such changes in lung volume are particularly likely to occur during recovery from acute exacerbations of asthma—a time when trials are often performed on the "captive" hospital population.[6]

The problems caused by varying baselines may lead to particular varieties of asthmatic patients being selected for research studies. Clearly the findings may then not be applicable to other groups of patients. The patients most suitable for study are those with mild and stable asthma, reliable enough to keep peak flow records and diary cards at home and with social and occupational commitments which allow their regular attendance for laboratory tests. Such individuals are very different from the patients who are inadequately controlled on their current treatment who may be most in need of any new drug.

Many drug trials in asthma may be divided broadly into those that assess a bronchodilator response and those that look at induced bronchoconstriction alone or in association with bronchodilatation. Pure bronchodilator trials have several drawbacks. Other bronchodilator drugs, and possibly other prophylactic treatments, need to be withdrawn for some time before the assessment. Withdrawal of the patient's usual treatment may precipitate an acute exacerbation of asthma, and some patients will be unable to stop their routine treatment even for a short period. Once the test drug is given there may be further problems such as a paradoxical bronchoconstrictor response or specific adverse effects. Most bronchodilators given by inhalation in conventional doses produce very few adverse effects, but mild side effects may occur in 40% or more of patients given conventional oral[8] or parenteral[9] treatments. Reproducible bronchoconstriction has recently been reported with the inhalation of the anticholinergic agent ipratropium bromide,[10] and this was attributed to an adverse reaction to bromide. The vehicles used in pressurised bronchodilator aerosols when given alone regularly produce slight narrowing of the airways detectable by sensitive respiratory function tests.[11] Occasionally these vehicles (or contaminants from the canister or valve apparatus) may provoke more severe bronchoconstriction,[12,13] as may dry powder preparations such as sodium cromoglycate.[14,15] Asthmatic patients stable enough to withdraw their routine medication for a short time, however, are very unlikely to have substantial problems with such bronchodilator studies.

Provocation of bronchoconstriction with agents such as methacholine or histamine is widely used in some countries as part of the diagnostic assessment of asthma. Provided that patients who already have airflow obstruction are excluded, this is a safe technique. Induction of narrowing of the airways with antigens and industrial agents may be more hazardous because of poorer standardisation of the challenge material, the variability of the response, and the occurrence of late reactions some hours after exposure. Such provocation tests should be carried out only in laboratories equipped to deal with any problems and with facilities to keep patients under observation during the time of a possible late reaction. Once again they should not be performed in the presence of any degree of airflow obstruction and should be limited to one exposure each day because of the unpredictable late response. Aas's laboratory

has carried out over 20 000 such tests without encountering bronchoconstriction that was not easily reversible with appropriate treatment.[16]

Induced bronchoconstriction may be much more difficult to reverse when it occurs after beta blockade. After non-cardioselective agents such as propranolol large doses of isoprenaline and salbutamol may be ineffective.[17 18] Deaths have occurred during treatment of asthmatic patients with such agents,[19] and single conventional doses of oxprenolol[20] and nadolol[21] have produced near fatal exacerbations. Some recent studies administering propranolol to asthmatic patients fit uncomfortably into Claude Bernard's dictum, "Among the experiments that may be tried on man, those that can only harm are forbidden; those that are innocent are permissible; and those that may do good are obligatory."

The sudden fluctuations in airflow obstruction characteristic of asthma mean that acute exacerbations will occur whether or not patients are included in clinical trials at the time. In these circumstances patients may be reluctant to upset research studies by adjusting their treatment, so they must be told exactly what they should do. They should also be able to get in touch with one of the trial organisers at once for further advice.

The alternatives to the use of asthmatic patients in clinical trials are animal studies and the use of normal people. Many animal systems have been used, but none provides a really satisfactory model of human asthma. Normal people are used less often than they might be to look for bronchodilator responses. Changes in values such as FEV_1 are small, but useful information can be obtained by measuring airways resistance in the body plethysmograph or by observing the effects of bronchodilators on induced bronchoconstriction.[22] In normal individuals there is no danger of precipitating severe bronchoconstriction if the dose of the provoking agent is increased in a steady stepwise fashion, and the problems of varying baselines and other interacting treatments are also avoided. Some research workers have been fortunate enough to have their own personal hyperreactive airways to use for preliminary studies.[23]

Although such normal people might be used more often, the introduction of new treatments and the development of existing ones will continue to depend on assessment of responses in asthmatic patients. We must ensure that the information sought by the trials is important enough to justify any inconvenience and risk to the patient. The patients must be carefully chosen, the trial adequately controlled, and the measurements appropriate. Poorly controlled trials or those which allow baseline fluctuation are very unlikely to be of any scientific value and waste the time of patients, investigators, and subsequent readers. Large open studies of the use of drugs in hospital outpatients or general practice are very unlikely to provide more than additional advertising material for pharmaceutical companies.

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Classifying lupus

Treatment for patients with systemic lupus erythematosus remains largely symptomatic and non-specific and will probably do so until we know more about its aetiology and pathogenesis. Yet it is important for a patient to be aware that her (or, occasionally, his) doctor knows the dimensions of her particular disease and the prognosis. In particular, are the clinical subgroups, such as mixed connective tissue disease (MCTD),[1] realistic divisions or do they merely represent a clustering of problems, which is inevitable in a disorder protean in its manifestations and transgressing subspecialty boundaries? And what part does measurement of the immunological features play in assessing prognosis?

The first of these questions is readily answerable, for we now know that the individual prognosis depends more on the degree of end organ dysfunction than on the range of manifestations.[2] We also know that measurement of the concentrations of complement (C3, C4, CH_{50}) and, to a less extent, of immune complexes may be helpful in prognosis but have only a limited application to the individual, unless the estimations are done serially and frequently.[3–5] It is in diagnosing and categorising patients that clinical immunology is providing most new information. For a quarter of a century we have known of the strong association between systemic lupus erythematosus and antibodies against nuclear components,[6] the touchstone for which has been the demonstration by immunofluorescence of antinuclear antibody (antinuclear factor). The preliminary criteria for the classification of systemic lupus erythematosus suggested by the American Rheumatism Association in 1971 included the presence of