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-cardio-selective 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 oxprenolol²⁰ and nadolol²¹ 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 FEV₁ 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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¹ Cassileth BR, Lusk EJ, Miller DS, Hurwitz S. Attitudes toward clinical trials among patients and the public. *JAMA* 1982;**248**:968-70.

² World Medical Association. Human experimentation: code of ethics of the World Medical Association. *Br Med J* 1964;iii:177.

³ Scadding JG. Definition and clinical categories of asthma. In: Clark TJH, Godfrey S, eds. *Asthma*. London: Chapman and Hall, 1977.

⁴ Benson MK. Bronchial responsiveness to inhaled histamine and isoprenaline in patients with airway obstruction. *Thorax* 1978;**33**:211-3.

⁵ Horton DJ, Suda WL, Kinsman RA, Souhrada J, Spector SL. Bronchoconstrictive suggestion in asthma: a role for airways hyperreactivity and emotions. *Am Rev Respir Dis* 1978;**117**:1029-38.

⁶ Paterson JW. Early assessment of a bronchodilator drug in man. *Br J Dis Chest* 1977;**71**:236-8.

⁷ Woolcock AJ, Read J. Lung volumes in exacerbations of asthma. *Am J Med* 1966;**41**:259-73.

⁸ Wolfe JD, Tashkin DP, Calvarese B, Simmons M. Bronchodilator effects of terbutaline and aminophylline alone and in combination in asthmatic patients. *N Engl J Med* 1978;**298**:363-7.

⁹ Hendeles L, Weinberger M, Bighley L. Disposition of theophylline after a single intravenous infusion of aminophylline. *Am Rev Respir Dis* 1978;**118**:97-103.

¹⁰ Patel KR, Tullett WM. Bronchoconstriction in response to ipratropium bromide. *Br Med J* 1983;**286**:1318.

¹¹ Sterling GM, Batten JC. Effect of aerosol propellants and surfactants on airway resistance. *Thorax* 1969;**24**:228-31.

¹² Bryant DH, Pepys J. Bronchial reactions to aerosol inhalant vehicle. *Br Med J* 1976;ii:1319-20.

¹³ Nolte D, Berger D, Forster E. Wirken treibgase von dosier-aerosolen bronchokonstriktorisch. *Dtsch Med Wochenschr* 1979;**104**:172-4.

¹⁴ Paterson JC, Grant IWB, Crompton GK. Severe bronchoconstriction provoked by sodium cromoglycate. *Br Med J* 1976;iii:916.

¹⁵ Serup J. Severe asthmatic reaction during long-term treatment with disodium cromoglycate powder inhalations. *Acta Med Scand* 1979;**205**:447-8.

¹⁶ Aas K. *The bronchial provocation test*. Springfield, Illinois: Charles C Thomas, 1975.

¹⁷ Tattersfield AE. Beta-blockers in asthma. *Br Med J* 1981;**282**:901.

¹⁸ Decalmer PBS, Chatterjee SS, Cruickshank JM, Benson MK, Sterling GM. Beta-blockers and asthma. *Br Heart J* 1978;**40**:184-9.

¹⁹ Gauld DR, Pain MCF, Rubinfeld AR. Beta-blocking drugs and airways obstruction. *Med J Aust* 1979;ii:88.

²⁰ Williams IP, Millard FJC. Severe asthma after inadvertent ingestion of oxprenolol. *Thorax* 1980;**35**:160.

²¹ Raine JM, Palazza MG, Kerr JH, Sleight P. Near-fatal bronchospasm after oral nadolol in a young asthmatic and response to ventilation with halothane. *Br Med J* 1981;**282**:548-9.

²² Smith AP, Orehek J, Charpin J. Bronchodilator drug tests in normal subjects. *Br J Dis Chest* 1977;**71**:234-6.

²³ Morrison-Smith J. The recent history of the treatment of asthma—a personal view. *Thorax* 1983;**38**:244-53.

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, CH₅₀) 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

LE cells.⁷ The revised criteria published in 1982⁸ added the alternatives of antibodies to native DNA or to the extractable nuclear antigen designated Sm (after a patient, as is the practice, with serologically identified antigens). Nevertheless, explicit in these criteria is the principle that the diagnosis of systemic lupus erythematosus does not depend on laboratory tests. Thus, despite the fact that over 90% of patients with systemic lupus erythematosus have antinuclear antibodies, diagnosis does not require that these should be present.

Is there anything different about those patients who do not have antinuclear antibody, given that this is a true finding and not due to poor laboratory technique? Several recent reports have documented the clinical and laboratory features of such patients.⁹⁻¹¹ Patients with a persistently negative antinuclear antibody test result with conventional substrates tend to have a different clinical spectrum of systemic lupus erythematosus.¹² They are more likely to be white; cerebritis and nephritis are less frequent and severe; photosensitive dermatitis is much more common, yet the deposition of immune complexes in unaffected skin (the lupus band test¹³) is less frequent. There is a similarity, therefore, with the intermediate clinical subset termed subacute lupus erythematosus.¹⁴ Patients with subacute lupus erythematosus are quite often antinuclear antibody negative yet do not have the exclusively dermal chronic discoid lupus.

Patients with systemic lupus erythematosus but no detectable antinuclear antibody have antibodies identifiable in other ways. An antinuclear antibody negative serum may react positively in immunodiffusion or immunoelectrophoresis against soluble extracts of cell lines such as WIL2.^{15,16} Most patients have antibodies directed against cytoplasmic antigens such as Ro or La, which have been shown to be immunologically identical with those originally described in patients with Sjögren's syndrome and called SSA and SSB respectively.¹⁷ These antibodies are also found in antinuclear antibody positive patients with systemic lupus erythematosus. This immunological evidence confirms the clinical evidence¹⁸ of the pivotal position of the sicca syndrome in autoimmune diseases.

Although the emerging picture is of a bewildering array of immunological niceties, these findings of clinical correlations justify the full investigation of a patient with signs and symptoms suggestive of lupus. The immunofluorescence antinuclear antibody test remains the most useful, made more so by the availability of different substrates such as WIL2, KB, or HEP₂ (which are also relevant for defining other disorders such as scleroderma and CREST syndrome.¹⁹ (The CREST syndrome is a variant of systemic sclerosis characterised by the presence of calcinosis, Raynaud's phenomenon, abnormal oesophageal motility, sclerodactyly, and telangiectasia.)

Antibodies against DNA are characteristic of systemic lupus erythematosus, though their relation to individual prognosis is still debatable.²⁰ Antibodies against the native DNA molecule are more restricted and more specific for lupus nephritis, but there are technical problems in ensuring that specificity in the commonly used binding assays, because of the appearance of single stranded sites during the preparation of the antigen.²¹ The use as a substrate in immunofluorescence of the

kinetoplast of *Crithidia luciliae*, which contains pure double stranded DNA,²² gets round this problem of specificity but the test is not readily automated.

There is a great deal more to understanding systemic lupus erythematosus than defining subgroups on clinical and serological grounds. Nevertheless, the practising physician needs some guidance to prognosis, and the recognition of these subsets is a help in this direction. Whether the pathogenesis of the disease will be understood better as a result remains to be seen.

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- ¹ Sharp GC. Mixed connective tissue disease. *Bull Rheum Dis* 1975;**25**: 828-31.
- ² Ginzler EM, Diamond HS, Weiner M, et al. A multicenter study of outcome in systemic lupus erythematosus. I. Entry variables as predictors of prognosis. *Arthritis Rheum* 1982;**25**:601-11.
- ³ Lloyd W, Schur PH. Immune complexes, complement, and anti-DNA in exacerbations of systemic lupus erythematosus (SLE). *Medicine (Baltimore)* 1981;**60**:208-17.
- ⁴ Abrass CK, Nies KM, Louie JS, Border WA, Glasscock RJ. Correlation and predictive accuracy of circulating immune complexes with disease activity in patients with systemic lupus erythematosus. *Arthritis Rheum* 1980;**23**:273-82.
- ⁵ Morrow WJW, Isenberg DA, Todd-Pokropek A, Parry HF, Snaith ML. Useful laboratory measurements in the management of systemic lupus erythematosus. *Q J Med* 1982;**202**:125-38.
- ⁶ Friou GJ, Finch SC, Detre KD. Interaction of nuclei with globulin from lupus erythematosus serum demonstrated with fluorescent antibody. *J Immunol* 1958;**90**:324-9.
- ⁷ Cohen AS, Reynolds WE, Franklin EC, et al. Preliminary criteria for the classification of systemic lupus erythematosus. *Bull Rheum Dis* 1971;**21**:643-8.
- ⁸ Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982;**25**:1271-7.
- ⁹ Fessel WJ. ANA-negative systemic lupus erythematosus. *Am J Med* 1978;**64**:80-6.
- ¹⁰ Gladman DD, Chalmers A, Urowitz MB. Systemic lupus erythematosus with negative LE cells and antinuclear factor. *J Rheumatol* 1978;**5**:142-7.
- ¹¹ Maddison PJ, Provost TT, Reichlin M. Serological findings in patients with "ANA-negative" systemic lupus erythematosus. *Medicine (Baltimore)* 1981;**60**:87-94.
- ¹² Maddison PJ. ANA-negative SLE. *Clin Rheum Dis* 1982;**8**:105-19.
- ¹³ Provost TT, Andres G, Maddison PJ, Reichlin M. Lupus band test in untreated SLE patients: correlation of immunoglobulin deposition in the skin for the extensor forearm with clinical renal disease and serological abnormalities. *J Invest Dermatol* 1980;**74**:407-12.
- ¹⁴ Sontheimer RD, Thomas JR, Gilliam JN. Subacute cutaneous lupus erythematosus. A cutaneous marker for a distinct lupus erythematosus subset. *Arch Dermatol* 1979;**115**:1409-15.
- ¹⁵ Alspaugh MA, Tan EM. Antibodies to cellular antigens in Sjögren's syndrome. *J Clin Invest* 1975;**55**:1067-73.
- ¹⁶ Akizuki M, Powers R, Holman HR. A soluble acidic protein of the cell nucleus which reacts with serum from patients with systemic lupus erythematosus and Sjögren's syndrome. *J Clin Invest* 1977;**59**:264-72.
- ¹⁷ Alspaugh MA, Maddison P. Resolution of the identity of certain antigen-antibody systems in systemic lupus erythematosus and Sjögren's syndrome: an interlaboratory collaboration. *Arthritis Rheum* 1979;**22**: 796-8.
- ¹⁸ Shearn MA. *Sjögren's syndrome*. Philadelphia: WB Saunders, 1971:104-24.
- ¹⁹ Fritzler MJ, Kinsella TD. The CREST syndrome: a distinct serologic entity with anticentromere antibodies. *Am J Med* 1980;**69**:520-6.
- ²⁰ Adler MK, Baumgarten A, Hecht B, Siegel NJ. Prognostic significance of DNA-binding capacity patterns in patients with lupus nephritis. *Ann Rheum Dis* 1975;**34**:444-50.
- ²¹ Ballou SP, Kushner I. Immunochemical characteristics of antibodies to DNA in patients with active systemic lupus erythematosus. *Clin Exp Immunol* 1979;**37**:58-67.
- ²² Aarden LA, de Groot ER, Feltkamp TE. Immunology of DNA. III. *Crithidia luciliae*, a simple substrate for the determination of anti-dsDNA with the immunofluorescence technique. *Ann NY Acad Sci* 1975;**254**:505-15.