in asthma are therefore likely to be complex and depend on the balance between the proinflammatory and the anti-inflammatory effects of prostanoids produced by various cell types under different circumstances. A better understanding of this issue might be achieved by direct functional studies with airway tissues from asthmatic patients, but these are notoriously difficult to obtain.

L PANG

Division of Respiratory Medicine,
City Hospital,
Nottingham NG5 1PB,
UK
linhua.pang@nottingham.ac.uk

1 Pang L, Pitt A, Petkova D, *et al*. The COX-1/COX-2 balance in asthma. *Clin Exp Allergy* 1998;**28**:1050–8.
2 Broide DH, Lotz M, Cuomo AJ, *et al*. Cytokines in symptomatic asthma airways. *J Allergy Clin Immunol* 1992;**89**:958–67.
3 Cembrzynska-Nowak M, Szklarz E, Inglot AD, *et al*. Elevated release of tumour necrosis factor-alpha and interferon-gamma by bronchoalveolar leukocytes from patients with bronchial asthma. *Am Rev Respir Dis* 1993;**147**:291–5.
4 Mitchell JA, Belvisi, MG, Akarasereenont P, *et al*. Induction of cyclo-oxygenase-2 in human pulmonary epithelial cells: regulation of dexamethasone. *Br J Pharmacol* 1994;**113**:1008–14.
5 Newton R, Kuitert LM, Slater DM, *et al*. Cytokine induction of cytosolic phospholipase A_2 and cyclooxygenase-2 mRNA is suppressed by glucocorticoids in human epithelial cells. *Life Sci* 1997;**60**:67–78.
6 Pang LH, Knox AJ. Effect of interleukin 1β, tumour necrosis factor-α and interferon-γ on the induction of cyclo-oxygenase-2 in cultured human airway smooth muscle cells. *Br J Pharmacol* 1997;**121**:579–87.
7 Belvisi MG, Saunders MA, Haddad E-B, *et al*. Induction of cyclo-oxygenase-2 by cytokines in human cultured airway smooth muscle cells: novel inflammatory role of this cell type. *Br J Pharmacol* 1997;**120**:910–6.
8 Endo T, Ogushi F, Sone S, *et al*. Induction of cyclooxygenase-2 is responsible for interleukin 1β dependent prostaglandin E_2 synthesis by human lung fibroblasts. *Am J Respir Cell Mol Biol* 1995;**12**:358–65.
9 Pang LH, Knox AJ. PGE_2 release by bradykinin in human airway smooth muscle cells: involvement of cyclo-oxygenase-2 induction. *Am J Physiol* 1997;**273**:L1132–40.
10 Fong CY, Pang LH, Holland E, *et al*. $TGF\beta_1$ stimulates PGE_2 release, cyclooxygenase-2 induction and IL-8 release from human airway smooth muscle cells. *Am J Physiol* 2000;**279**:L201–7.
11 Demoly P, Jaffuel D, Lequeux N, *et al*. Prostaglandin H synthase 1 and 2 immunoreactivities in the bronchial mucosa of asthmatics. *Am J Respir Crit Care Med* 1997;**155**:670–5.
12 Sousa AR, Pfister R, Christie PE, *et al*. Enhanced expression of cyclo-oxygenase isoenzyme 2 (COX-2) in asthmatic airways and its cellular distribution in aspirin sensitive asthma. *Thorax* 1997;**52**:940–5.
13 Taha R, Olivenstein R, Utsumi T, *et al*. Prostaglandin H synthase 2 expression in airway cells from patients with asthma and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000;**161**:636–40.
14 Redington AE, Meng Q-H, Springall DR, *et al*. Increased expression of inducible nitric oxide synthase and cyclo-oxygenase-2 in the airway epithelium of asthmatic subjects and regulation by corticosteroid treatment. *Thorax* 2001;**56**:351–7.
15 Pavord ID, Tattersfield AE. Bronchoprotective role for endogenous prostaglandin E_2. *Lancet* 1995;**345**:436–8.
16 Gardiner PJ, Collier HOJ. Specific receptors for prostaglandins in airways. *Prostaglandins* 1980;**19**:819–41.
17 Armour CL, Johnson PRA, Alfredson ML, *et al*. Characterisation of contractile prostanoid receptors on human airway smooth muscle. *Eur J Pharmacol* 1989;**165**:215–22.
18 Hardy CC, Robinson C, Lewis RA, *et al*. Airway and cardiovascular responses to inhaled prostacyclin in normal and asthmatic subjects. *Am Rev Respir Dis* 1985;**131**:18–21.
19 Gavett SH, Madison SL, Chulada PC, *et al*. Allergic lung responses are increased in prostaglandin H synthase-deficient mice. *J Clin Invest* 1999;**104**:721–32.
20 Belvisi MG, Saunders M, Yacoub M, *et al*. Expression of cyclo-oxygenase-2 in human airway smooth muscle is associated with profound reduction in cell growth. *Br J Pharmacol* 1998;**125**:1102–8.
21 Pang LH, Holland E, Knox AJ. Role of cyclo-oxygenase-2 induction in interleukin-1β induced attenuation of cultured human airway smooth muscle cell cyclic AMP generation in response to isoprenaline *Br J Pharmacol* 1998;**125**:1320–8.
22 Pang LH, Holland E, Knox AJ. Impaired cAMP production in human airway smooth muscle cells by bradykinin: role of cyclooxygenase products. *Am J Physiol* 1998;**275**:L322–9.
23 Pang LH, Knox AJ. Bradykinin stimulates IL-8 production in cultured human airway smooth muscle cells: role of cyclooxygenase products. *J Immunol* 1998;**161**:2509–15.

Thorax 2001;**56**:336–339

Sarcoidosis: old and new treatments

G J Gibson

2001 marks the 50th anniversary of the first reports of the successful treatment of sarcoidosis with cortisone[1 2] and ACTH.[3] In an early report of treatment with corticosteroids, Siltzbach[4] highlighted one of the problems of evaluating the results when he wrote:

> "The aetiology of sarcoidosis still eludes us, as does the definitive treatment. Part of the difficulty stems from the unpredictability of spontaneous remissions. This accounts for the many transitory successes reported at one time or another with such agents as calcium salts, gold, arsenicals, potassium iodide, chaulmoogra oil, antileprol and tuberculin."

It is somewhat depressing that no better therapeutic agents than steroids have emerged over the subsequent 50 years, and the sceptic might well conclude that little has changed! While the approach to treatment may have become more rational and the choice of effective agents has increased, it is at best suppressive rather than curative. Happily, as Siltzbach pointed out, in most patients the natural tendency of pulmonary sarcoidosis is towards spontaneous resolution. The therapeutic challenges remain the recognition of those patients in whom remission and resolution are less likely, and determination of the optimum treatment to minimise permanent organ damage.

Several uncontrolled and controlled studies, as well as common clinical experience, have amply confirmed the suppressive effect of steroids.[5–11] In pulmonary sarcoidosis the most common indication for treatment is symptomatic, usually troublesome breathlessness and sometimes cough. Most commonly, prednisolone is started at a dose of 30–40 mg daily with later reduction titrated against symptoms, respiratory function, and radiographic appearance. Once started, treatment is usually continued for at least 1 year but patients may require more prolonged treatment if dose reduction is accompanied by recrudescence of disease activity. Whether or not steroid treatment reduces long term pulmonary damage due to fibrosis has proved difficult to determine. Common experience shows that in many cases pulmonary fibrosis is not prevented by steroids as, not infrequently, patients are seen with advanced destructive fibrosis even after their continuous use for several years. Most of the controlled studies which have attempted to assess the long term outcome of steroid treatment have been criticised on one or more counts—in particular, inclusion of patients with bilateral hilar lymphadenopathy without pulmonary shadowing, which has a good prognosis for spontaneous resolution, and the introduction of steroids at the time of presentation often in relatively asymptomatic patients in whom most clinicians would normally adopt a "wait and see" policy before embarking on treatment. The importance of the latter approach was apparent in the recent BTS controlled study[11] where 50% of patients who presented with pulmonary shadowing but

did not require immediate treatment to control symptoms showed spontaneous radiographic improvement over a 6 month observation period. The BTS study[11] concentrated on patients with pulmonary shadowing in whom spontaneous improvement had not occurred over such a period. Subjects were then allocated to receive either a prolonged course of steroids ("long term" treatment) or to remain under observation with treatment later only if required because of troublesome symptoms or deteriorating respiratory function ("selective treatment"). After an average follow up of 4 years, patients in whom long term treatment was given had a significantly better outcome than those in whom the policy of selective treatment was adopted. This better outcome was reflected in symptoms, respiratory function, and radiographic appearances, although the differences between the two groups at the end of the study were modest. In practice it is impossible to perform a controlled study of the long term effects of steroids in severe pulmonary sarcoidosis as virtually all such patients receive appropriate treatment with steroids for symptomatic relief.

It was also noteworthy in the BTS study that, of a further group of more severely affected patients who required early steroids for symptomatic benefit, approximately half were still taking the treatment after 5 years, most frequently because of deterioration in symptoms when dose reduction or withdrawal was attempted.[11] This tendency to relapse following dose reduction has been recognised for many years[12 13] and has been emphasised in two recent studies.[14 15] The potential disadvantages of long term steroid treatment are, of course, widely recognised in patients with sarcoidosis, as in other conditions. More specifically, in sarcoidosis the question has been raised as to whether steroids may delay resolution of granulomatous inflammation, thereby contributing to prolongation of the disease. In a retrospective study Gottlieb *et al*[14] showed that, of 103 patients who achieved complete remission of sarcoidosis while taking steroids, the disease subsequently relapsed in as many as 76 when steroids were discontinued. On the other hand, of 118 who showed spontaneous remission, only 10 subsequently relapsed. The authors suggested that "corticosteroids contributed to the prolongation of the disease by delaying resolution". However, the study was retrospective and, inevitably, the untreated patients had milder disease; furthermore, the population studied was different from that found in Europe with the majority being African Americans (in whom the disease is usually more aggressive) and most had been treated for non-respiratory sarcoidosis. The authors considered the alternative explanation that "severe presenting symptoms portend a protracted and recurrent course" to be less likely. While the hypothesis that steroid treatment may delay resolution of sarcoidosis is intriguing, to date no prospective study has been performed to test it.

These recent studies of steroids in sarcoidosis therefore have implications for long term treatment which potentially conflict. In particular, the BTS study[11] is a little more favourable towards long term treatment than earlier studies, whereas the analysis by Gottlieb *et al*[14] suggests the need for caution with too liberal use of these agents. The decision whether or not to treat has to be made on an individual basis and relative contraindications (such as hypertension and obesity), together with the likely need for prolonged treatment, have to be balanced against the need to control symptoms or the possibility of reducing lung scarring. In practice, the indication for treating pulmonary sarcoidosis with steroids in most cases remains the relief of uncomfortable or disabling symptoms.

If steroids are to be used, many authorities favour alternate day treatment once a "maintenance dose" has been established. The limited available data[16] suggest that, at a similar total dose, this policy is as effective as daily treatment but information on long term adverse effects is lacking. Some recent data have suggested that an alternative steroid, deflazacort, may have similar efficacy with fewer adverse effects, particularly on bone mineral density.[17] However, experience to date is limited and similar claims for earlier alternative steroids have not stood the test of time. A recent placebo controlled study[18] of the third generation bisphosphonate, alendronate, in patients with sarcoidosis reported better preservation of bone density with less evidence of steroid induced bone resorption in those receiving alendronate. Additional calcium supplementation was not included in this study and is probably best avoided in view of the known effects of sarcoidosis on calcium metabolism and the tendency to hypercalciuria and occasionally hypercalcaemia.

The problems associated with oral steroid treatment in patients with sarcoidosis have inevitably led to use of other agents. Inhaled steroids have been the subject of several studies with somewhat mixed results. Following an early open study of inhaled budesonide which showed apparent benefit,[19] three controlled studies have been reported. Zych *et al*[20] compared inhaled budesonide with prednisolone, 10 mg daily, over a 12 month period as maintenance treatment following induction with larger doses of prednisolone. The outcome was similar in the two groups but no placebo or treatment group was included. In a second double blind placebo controlled study of previously untreated patients Milman *et al*[21] found no difference in outcome after 12 months compared with placebo. However, only 21 patients were included and some had no pulmonary shadowing. In a third controlled study of 47 patients inhaled budesonide was again compared with placebo over a 6 month period.[22] An unknown number of patients presenting with "severe symptoms" was excluded and no preliminary observation period was used. Thirteen of the patients had no pulmonary shadowing. The results showed that, compared with placebo, patients taking inhaled budesonide had a significantly lower overall symptom score after 6 months of treatment. There was also a significantly greater increase in vital capacity in the treated patients but, surprisingly, there were no accompanying differences in forced expiratory volume in 1 second, carbon monoxide transfer factor, or radiographic appearance. Moreover, the relatively small numbers of subjects requiring introduction of oral steroids for symptomatic relief during the study period were not significantly different in the two groups. In the most recent study Pietinalho *et al*[23] compared two groups of patients treated for a total of 18 months with either prednisolone for 3 months followed by inhaled budesonide for 15 months or 3 months of placebo tablets followed by 15 months of placebo inhaler. Again, no preliminary observation period was used and a proportion of the patients had bilateral hilar lymphadenopathy only. Radiographic improvement was seen in the active treatment group at 3 and 6 months but the difference was not sustained. In the subgroup of patients with pulmonary shadowing the improvement in carbon monoxide transfer factor at 18 months was greater than in the placebo group. The authors concluded that initial treatment with prednisolone followed by long term inhalation of budesonide was more effective than placebo in this subgroup of patients, but the better outcome may of course have been due to the initial oral steroid rather than the subsequently inhaled drug. Other studies have suggested that inhaled budesonide has a definite effect on the activity of sarcoidosis as judged by bronchoalveolar lavage findings.[24] Its role in clinical practice, if any, is likely to be as maintenance treatment after an initial course of oral steroids in patients with relatively mild pulmonary disease.

Many of the alternative oral agents which have been used for treatment of pulmonary sarcoidosis have been found unsatisfactory. Drugs such as cyclosporin A,[25] chlorambucil,[26] thalidomide,[27] and cyclophosphamide[28] are either too poorly effective or too toxic (or both) to recommend other than in exceptional circumstances. One recent uncontrolled report[29] suggested that pentoxifylline, which has an inhibitory effect on tumour necrosis factor alpha (TNFα), may benefit some patients but further experience is required before it can be recommended.

Azathioprine, methotrexate, and the antimalarial agent chloroquine remain as viable alternatives or adjuncts to steroid treatment, most commonly as steroid sparing agents. Unfortunately, neither azathioprine nor methotrexate has been the subject of a controlled trial. Azathioprine is usually reserved for severe refractory cases and has occasionally been reported to be effective in sarcoidosis apparently resistant to steroid treatment.[30] In a recent study azathioprine combined with prednisolone was reported to induce remissions in a small number of patients with chronic relapsing pulmonary disease.[31] Rather more experience has been reported with the use of the folate antagonist methotrexate, albeit largely from one group of investigators.[32 33] Their observational data on prolonged treatment in more than 100 patients suggest functional improvement and the ability to reduce or withdraw chronic steroid treatment in a significant proportion. The drug is given orally once a week in a usual dose of 10 mg. The most significant complication of methotrexate is hepatotoxicity and guidelines for monitoring liver toxicity, including the possible need for liver biopsy, have been published.[34] Methotrexate also occasionally causes pulmonary toxicity, which obviously may present diagnostic confusion in patients with pulmonary sarcoidosis.

Other than corticosteroids, the drug with the best controlled evidence in sarcoidosis is chloroquine. It has been widely used by dermatologists treating cutaneous sarcoidosis, but relatively little by respiratory physicians, although a seminal controlled study was published by the Research Committee of the British Tuberculosis Association as long ago as 1967.[35] This compared chloroquine (600 mg daily for 8 weeks followed by 400 mg daily for 8 weeks) with placebo in patients known to have radiographic pulmonary shadowing for at least 6 months and previously untreated with corticosteroids. There was clear evidence of greater radiographic improvement in the chloroquine group at the end of the treatment period (4 months) and again at 6 months, although the difference between the two groups was no longer evident at 12 months. A resurgence of interest in chloroquine has been occasioned by the recent study of Baltzan *et al*[36] who reported the effects of treatment in 23 patients with chronic pulmonary sarcoidosis, known to have been present for between 2–18 years (mean 6.2). Most had been treated with high dose oral steroids without sustained symptomatic or functional improvement. Initially, all subjects received chloroquine for 6 months starting with a relatively high dose (750 mg daily for 2 months, 500 mg daily for 2 months, 250 mg daily for 2 months). At the end of this open treatment period the subjects were randomised to either an observation group or a maintenance group who continued to receive chloroquine in a dose of 250 mg daily. The rate of decline in respiratory function was then followed until "relapse" which was defined as a reduction in the relevant functional index to a value less than that recorded at the start of the open treatment period. The patients showed symptomatic improvement during the initial run in period and a significantly diminished rate of decline in respiratory function during maintenance with chloroquine compared with placebo. These results therefore suggest that chloroquine has a useful therapeutic role, even in patients with advanced chronic disease, particularly when corticosteroids are poorly effective or are causing significant side effects. The greatest concern about the use of chloroquine has been its potential toxic effects on the eye. These are of two types: corneal deposits, which are almost universal, asymptomatic and reversible, and a much rarer, but potentially irreversible, retinopathy. Ophthalmological assessment before treatment and every 6 months during treatment is recommended[37] and the side effects are, to some extent, dose dependent. There has been a natural reluctance to use chloroquine because of these effects, but an interesting parallel is the use of ethambutol in tuberculosis where most respiratory physicians are well used to the care required and the need to warn patients to report any visual disturbance.

Of non-pharmacological treatments, the only recent therapeutic development relevant to pulmonary sarcoidosis is lung transplantation for which advanced pulmonary disease is now an accepted indication. Recurrence of the disease in the transplanted lung has been reported on several occasions[38] but the long term implications are not yet clear.

The findings reported with pentoxifylline and chloroquine suggest that other agents inhibiting TNFα might usefully be subjected to controlled trial. In the meantime, corticosteroids remain the mainstay of treatment, as they have been for the last 50 years. Of the alternatives, in refractory cases or when steroid sparing is desirable, chloroquine (or hydroxychloroquine), methotrexate, and azathioprine are currently the "best buys".

G J GIBSON

Department of Respiratory Medicine,
Freeman Hospital,
Newcastle upon Tyne NE3 1LX,
UK
G.J.Gibson@ncl.ac.uk

1 Siltzbach LE, Posner A, Medine MM. Cortisone therapy in sarcoidosis. *JAMA* 1951;**147**:927–9.
2 Sones M, Israel HL, Dratman MB, *et al*. Effect of cortisone in sarcoidosis. *N Engl J Med* 1951;**244**:209–13.
3 Galdston M, Weisenfeld S, Benjamin B, *et al*. Effect of ACTH in chronic lung disease. *Am J Med* 1951;**10**:166.
4 Siltzbach LE. Effects of cortisone in sarcoidosis. A study of thirteen patients. *Am J Med* 1952;**12**:139–60.
5 James DG, Carstairs LS, Trowell J, *et al*. Treatment of sarcoidosis. *Lancet* 1967;ii:526–8.
6 Israel HL, Fouts DW, Beggs RA. A controlled trial of prednisone treatment of sarcoidosis. *Am Rev Respir Dis* 1973;**107**:609–14.
7 Selroos O, Sellergren T-L. Corticosteroid therapy of pulmonary sarcoidosis. A prospective evaluation of alternate day and daily dosage in stage II disease. *Scand J Respir Dis* 1979;**60**:215–21.
8 Harkleroad LE, Young RL, Savage PJ, *et al*. Pulmonary sarcoidosis. Long-term follow-up of the effects of steroid therapy. *Chest* 1982;**82**:84–7.
9 Eule H, Weinecke A, Roth I, *et al*. The possible influence of corticosteroid therapy on the natural course of pulmonary sarcoidosis. Late results of a continuing clinical study. *Ann NY Acad Sci* 1986;**465**:695–701.
10 Zaki MH, Lyons HA, Leilop L, *et al*. Corticosteroid therapy in sarcoidosis. A five-year, controlled follow-up study. *NY State J Med* 1987;**87**:496–9.
11 Gibson GJ, Prescott RJ, Muers MF, *et al*. British Thoracic Society sarcoidosis study: effects of long term corticosteroid treatment. *Thorax* 1996;**51**: 238–47.
12 Hoyle C, Smyllie H, Leak D. Prolonged treatment of pulmonary sarcoidosis with corticosteroids. *Thorax* 1967;**22**:519–24.
13 Johns CJ, Zachary JB, Ball WC. A ten-year study of corticosteroid treatment of pulmonary sarcoidosis. *Johns Hopkins Med J* 1974;**134**:271–83.
14 Gottlieb JE, Israel HL, Steiner RM, *et al*. Outcome in sarcoidosis. The relationship of relapse to corticosteroid therapy. *Chest* 1997;**111**:623–31.
15 Rizzato G, Montemurro L, Colombo P. The late follow-up of chronic sarcoid patients previously treated with corticosteroids. *Sarcoidosis Vasculitis Diffuse Lung Dis* 1998;**15**:52–8.
16 Spratling L, Underwood GH, Requa RK. Daily vs alternate day prednisone therapy for stage II sarcoidosis. *Chest* 1985;**88**:687–90.
17 Rizzato G, Riboldi A, Imbimbo B, *et al*. The long-term efficacy and safety of two different corticosteroids in chronic sarcoidosis. *Respir Med* 1997;**91**: 449–60.
18 Gonnelli S, Rottoli P, Cepollaro C, *et al*. Prevention of corticosteroid-induced osteoporosis with alendronate in sarcoid patients. *Calcif Tissue Int* 1997;**61**:382–5.
19 Selroos O, Lofroos A-B, Pietinalho A, *et al*. Inhaled budesonide for maintenance treatment of pulmonary sarcoidosis. *Sarcoidosis* 1994;**11**:126–31.
20 Zych D, Pawlicka L, Zielinski J. Inhaled budesonide vs prednisone in the maintenance treatment of pulmonary sarcoidosis. *Sarcoidosis* 1993;**10**:56–61.

21 Milman N, Graudal N, Grode G, *et al*. No effect of high-dose inhaled steroids in pulmonary sarcoidosis: a double-blind, placebo-controlled study. *J Intern Med* 1994;**236**:285–90.
22 Alberts C, van der Mark Th W, Jansen HM and the Dutch Study Group on Pulmonary Sarcoidosis. Inhaled budesonide in pulmonary sarcoidosis: a double-blind, placebo-controlled study. *Eur Respir J* 1995;**5**:682–8.
23 Pietinalho A, Tukiainen P, Haahtela T, *et al*. Oral prednisolone followed by inhaled budesonide in newly diagnosed pulmonary sarcoidosis: a double-blind, placebo-controlled multicenter study. *Chest* 1999;**116**:424–31.
24 Spiteri MA, Newman SP, Clarke SW, *et al*. Inhaled corticosteroids can modulate the immunopathogenesis of pulmonary sarcoidosis. *Eur Respir J* 1989;**2**:218–24.
25 Wyser CP, Van Schalkwyk EM, Alheit B, *et al*. Treatment of progressive pulmonary sarcoidosis with cyclosporin A: a randomized controlled trial. *Am J Respir Crit Care Med* 1997;**156**:1371–6.
26 Israel HL, McComb BL. Chlorambucil treatment of sarcoidosis. *Sarcoidosis* 1991;**8**:35–41.
27 Carlesimo M, Giustini S, Rossi A, *et al*. Treatment of cutaneous and pulmonary sarcoidosis with thalidomide. *J Am Acad Dermatol* 1995;**32**:866–9.
28 Baughman RP, Lower EE. Steroid-sparing alternative treatments for sarcoidosis. *Sarcoidosis* 1997;**18**:853–64.
29 Zabel P, Entzian P, Dalhoff K, *et al*. Pentoxifylline in treatment of sarcoidosis. *Am J Respir Crit Care Med* 1997;**155**:1665–9.
30 Pacheco Y, Marechal C, Marechal F, *et al*. Azathioprine treatment of chronic pulmonary sarcoidosis. *Sarcoidosis* 1985;**2**:107–13.
31 Muller-Quernheim J, Kienast K, Held M, *et al*. Treatment of chronic sarcoidosis with an azathioprine/prednisolone regimen. *Eur Respir J* 1999; **14**:1117–22.
32 Lower EE, Baughman RP. Prolonged use of methotrexate for sarcoidosis. *Arch Intern Med* 1995;**155**:846–51.
33 Baughman RP, Lower EE. A clinical approach to the use of methotrexate for sarcoidosis. *Thorax* 1999;**54**:742–6.
34 Kremer JM, Alarcon GS, Lightfoot RW, *et al*. Methotrexate for rheumatoid arthritis. Suggested guidelines for monitoring liver toxicity. *Arthritis Rheum* 1994;**37**:316–28.
35 British Tuberculosis Association. Chloroquine in the treatment of sarcoidosis. A report from the Research Committee of the British Tuberculosis Association. *Tubercle* 1967;**48**:257–72.
36 Baltzan M, Mehta S, Kirkham TH, *et al*. Randomized trial of prolonged chloroquine therapy in advanced pulmonary sarcoidosis. *Am J Respir Crit Care Med* 1999;**160**:192–7.
37 Zic JA, Horowitz DH, Arzubiaga C, *et al*. Treatment of cutaneous sarcoidosis with chloroquine. *Arch Dermatol* 1991;**127**:1034–40.
38 Kazerooni EA, Jackson C, Cascade PN. Sarcoidosis: recurrence of primary disease in transplanted lungs. *Radiology* 1994;**192**:461–4.

Thorax 2001;**56**:339–340

Good respiratory practice in primary care

C P van Schayck

It is estimated that approximately 85% of all patients with asthma or chronic obstructive pulmonary disease (COPD) in the UK[1] and in the Netherlands[2] are treated by a general practitioner (GP). This underlines the importance of providing good medical respiratory care in general practice. Strangely enough, guidelines for the diagnosis and treatment of asthma and COPD have mainly been written by national or international thoracic societies. Of course, the GP has many diseases to deal with other than asthma and COPD alone, so one could argue that it is the chest physician who is the specialist and should therefore be the one to produce these guidelines. However, the patients seen by chest physicians often differ from those seen by GPs in the severity of their disease and consequently in their treatment. It would therefore seem logical to include primary care experts in asthma and COPD guideline panels in order to improve respiratory practice in primary care.

Research has shown that currently there are deficiencies in respiratory practice related to primary care. For example, delays in diagnosis are common[3] and lead to inappropriate treatment being given while, in other cases, the severity is underestimated with the result that preventive treatment is underused.[4 5] One study showed that 74% of those admitted to hospital with severe asthma could have had the admission prevented by different primary care.[6] Surveys of deaths from asthma have shown that nearly 90% of cases involve avoidable factors.[7] This does not always mean that the GP is to blame. It might also be related to the patient who does not present his symptoms to the GP. Underdiagnosis has been shown to be mainly due to underpresentation of bronchial symptoms by the patient to the GP, and this seems to be associated with a poor perception of asthma symptoms by the patient.[8]

The improvement of respiratory practice in primary care starts with making clear guidelines for primary care. In the Netherlands the first national guidelines on the diagnosis and treatment of asthma and COPD in general practice were published in 1992 by the Dutch College of General Practitioners.[9] In 1997 these guidelines were updated on the basis of new literature and re-evaluation of the 1992 guidelines.[10] As it is known that publication of guidelines alone will not change the actual care provided by physicians,[11] a large study was undertaken to investigate the best strategy for implementing these guidelines.[12] Two intervention groups and one control group of general practices were formed: a small education group (17 GPs with 210 patients), a monitoring and feedback group (24 GPs with 299 patients), and a control group (17 GPs with 223 patients). The actual health care provided for asthma and COPD by the intervention groups was compared with the health care given by the control group. The outcome was measured in terms of structure and process parameters (knowledge and skills of GPs, presence of equipment, and pharmacological and non-pharmacological treatment) and patient outcomes (symptoms, smoking habit, exacerbation rate, and asthma specific quality of life). In the education group the intervention consisted of an interactive group education and peer review programme (four sessions of 2 hours), while in the monitoring/feedback group the intervention consisted of monitoring the intake procedure, regular follow up, and feedback on lung function, smoking habits, use of medication, and compliance. In the education group the only significant difference from the control group was in the skills of the GP. In the monitoring/feedback group, however, there were clear improvements in knowledge, skills, presence of peak flow meters, and adequate pharmacological treatment compared with the control group. This led to the conclusion that monitoring and feedback results in a significant change in the care provided for asthma and COPD. Improving care by implementing guidelines appears to be most successful when physicians are directly confronted with the specific health care results of their patients. It therefore seems that feedback of information to health professionals about their care can lead to an alteration in their behaviour. Audits alone in general practice may only give negative feedback when the care provided is compared with the optimal care displayed in guidelines. When the care provided is compared with the care given by peers, and subsequently discussed with these peers, both negative and positive feedback are given and the best (social) learning situation is created for obtaining clear