

# Control of asthma

JERRY DOLOVICH, MD, FRCP[C]  
FREDERICK E. HARGREAVE, MD, FRCP[C]  
WILLIAM M. WILSON, MD, FRCP[C]  
JOSEPH GREENBAUM, MD, FRCP[C]  
A.C. PETER POWLES, MB, FRCP[C]  
MICHAEL T. NEWHOUSE, MD, FRCP[C]

Developments of the past decade have greatly improved the likelihood that patients can control their asthma. Inhaled medications are basic to a regimen that may include bronchodilators only, or bronchodilators along with cromoglycate and steroid to the extent required to achieve and maintain control. The regimen is modified for the individual and designed to control symptoms while avoiding an overdose of any one agent and overuse of inhaled bronchodilators (a sign of their lessening effectiveness). The regimen outlined emphasizes controlling asthma day to day and providing effective intervention early to prevent attacks from becoming severe.

Les découvertes de la dernière décennie ont grandement amélioré la probabilité qu'un patient puisse maîtriser son asthme. Les médicaments en inhalation sont fondamentaux au traitement, qui peut comprendre des bronchodilatateurs seuls, ou des bronchodilatateurs en association avec le cromoglycate et le stéroïde de façon suffisante pour obtenir et maintenir les symptômes sous contrôle. Le régime thérapeutique est ajusté individuellement et il est établi de façon à maîtriser les symptômes tout en évitant le surdosage d'un ou l'autre des agents et l'abus des bronchodilatateurs en inhalation (signe d'une perte d'efficacité). Le régime thérapeutique décrit vise à contrôler l'asthme jour après jour et à procurer une intervention efficace immédiate afin de prévenir l'aggravation des crises.

The 1950s saw the introduction of convenient, but easily abused, inhalers containing metered doses of such potent bronchodilator medications as isoproterenol for the control of asthma, and patients and their physicians began to rely on these aerosols as the mainstay of treatment. At that time physicians were reluctant to prescribe systemic therapy with adrenocortical steroids, even for short periods, to control asthma. Often the attacks were so severe that patients had to be admitted to intensive care units, where efforts to resuscitate them were not always successful. In the 1960s increases in the number of deaths associated with overuse of inhaled isoproterenol were documented in Great Britain and

Australia.<sup>1,2</sup> A fear of prescribing metered-dose inhalers persists.<sup>3</sup>

In the 1970s methods of treatment that controlled asthma had so improved that respiratory failure because of an acute asthma attack became infrequent in patients with largely reversible airway obstruction. These improvements included:

- Development of a therapeutic strategy that often incorporated several agents, each at dosages within the individual's limit of tolerance for that agent.

- Use of inhaled cromoglycate<sup>4,6</sup> and inhaled beclomethasone<sup>7</sup> for maintenance treatment — that is, for the control of asthma and the prevention of acute attacks.

- Recognition of the relative safety of short-term therapy with ingested prednisone.<sup>8,9</sup>

- Introduction of selective therapy with longer-acting sympathomimetic bronchodilators ( $\beta_2$ -agonists), recognition that there were choices in the route of administering these agents and recognition that the frequency with which they were used had to be strictly limited.<sup>10,11</sup>

- Confirmation of the usefulness of therapy with ingested theophylline.<sup>12</sup>

- Recognition that an isolated cough or wheeze, or breathlessness was an early sign that an acute attack might occur, and thus was an important signal that steps to prevent the attack should be started.<sup>13,14</sup>

- Recognition that such secondary and circumstantial factors as emotional upset, cold air, exercise and hyperventilation are stimuli with secondary effects that are operative during the increased nonspecific bronchial responsiveness in asthma.<sup>15</sup>

- Recognition that asthma associated with occupational exposure is a major problem and that frequently patients have to avoid a workplace where they are so affected.<sup>16,17</sup>

- Development of a portable peak-flow meter to assist patients in assessing their condition and then adjusting their therapy to the minimum required to control their asthma.<sup>18</sup>

## Patterns of asthmatic response

In bronchial provocation tests for the analysis of asthma, inhalation of an allergen aerosol induces different patterns of airway response in different individuals with allergic asthma.<sup>19</sup> An initial response lasting an hour or two, termed the early asthmatic response, may be followed by a late asthmatic response, so that there

From the chest and allergy units, St. Joseph's Hospital and McMaster University Medical Centre and the departments of pediatrics and medicine, McMaster University, Hamilton

Reprint requests to: Dr. Jerry Dolovich, Department of pediatrics, McMaster University, 1200 Main St. W, Hamilton, Ont. L8N 3Z5

is a dual asthmatic response in which the early airway obstruction is relieved but then recurs and is often maximal 8 to 12 hours after allergen inhalation. In some individuals antigens may elicit an isolated late asthmatic response during which the airway may not become obstructed until 3 to 4 hours after the initial provocation.

In patients with increased bronchial responsiveness the antigen-induced early asthmatic response is mimicked by the response to emotional upset, cold air, exercise, hyperventilation, inhaled histamine and inhaled particles. The predisposition to this response relates directly to the patient's level of nonspecific bronchial responsiveness. The antigen-induced late asthmatic response can be mimicked by the response to inhaled industrial chemicals, such as toluene diisocyanate, and endotoxins and by ingested acetylsalicylic acid.

### Objectives of treatment (definition of control)

Treatment of patients in whom generalized airway obstruction is completely or almost completely reversible can achieve the following:

- Prevent severe attacks.
- Allow the individual to function normally most of the time.
- Prevent chronic and troublesome symptoms, such as coughing or breathlessness in the night, in the early morning and after exertion.
- Avoid systemic side effects from medications.

### Methods of controlling asthma

Exposure to some substances, such as airborne allergens and chemicals encountered in industry, can increase nonspecific bronchial reactivity, and avoidance of such exposure may reduce responsiveness to a variety of stimuli.<sup>20-22</sup> However, although such avoidance is important and may even be crucial, it may not obviate the need for medication.

#### *Avoid offending substances*

*Substances in the home:* If there is a pet in the home, sensitization to the animal may be demonstrated by the patient's history or by allergy skin tests or both. The patient with respiratory symptoms and a positive reaction to an animal as indicated by the result of a skin prick test almost invariably improves when the pet is removed. The presence indoors of pollens and mould spores that originate outdoors can be reduced by installing an air-conditioner so that windows can be kept closed.<sup>23</sup> Even a window model in the bedroom is effective. The patient should be instructed to keep the vent option closed. The use of electrostatic air cleaners may be unwarranted, as they are ineffective in reducing the indoor count of mould spores and pollen if windows are kept open, and unnecessary if windows can be kept closed, as indoor counts would then be almost zero. Indeed, such cleaners, if poorly serviced, may be detrimental: they may aggravate asthma by generating excessive ozone.<sup>24</sup> Such aggravation is only suspected. Nevertheless, owners of these cleaners should be encouraged to clean the plates regularly to reduce the release of ozone. Steps to control other indoor irritants,

such as dust, sometimes helps, but a major disruption of the home is generally not productive.<sup>25-27</sup> Cigarette smoke generated by the affected person or others is a major irritant that can be avoided in the home. Exposure to volatile substances, such as those emitted by new carpets or paint, can be reduced by restricting home renovations to the summer months, when good ventilation is feasible.

*Substances in the workplace:* The list of airborne substances known to induce asthma that are encountered in the workplace is long and getting longer.<sup>16,17</sup> Often, as in most cases of toluene diisocyanate-induced asthma, there may be no demonstrable allergic (immunologic) basis for the patient's asthmatic reaction. Proof of the cause of such a reaction in an individual case rests on measures of the pulmonary responses to exposure to the substance in the workplace or in a laboratory under conditions simulating occupational exposure.<sup>17</sup> Even trace quantities of substances such as diisocyanates can cause severe asthma. Such attacks can usually be prevented by strict avoidance of exposure. However, even complete avoidance will sometimes fail to completely reverse airway hyperresponsiveness once asthma has developed.

*Drugs:* A number of drugs, including  $\beta$ -blockers such as propranolol and the newer "selective" blockers, are well known to exacerbate asthma. Nonsteroid analgesics can worsen asthma in many individuals. In asthma patients intolerant of acetylsalicylic acid, life-threatening attacks can also develop following ingestion of other analgesics, including indomethacin, phenylbutazone and ketoprofen, because of their effect on prostaglandin synthesis. Thus, caution is required with *all* of these agents in the acetylsalicylic acid-intolerant patient.

#### *Take medications*

The amount of control patients have of their asthma often depends on their ability to decide on the type and amount of treatment their present condition requires. For some, control can be achieved by ingesting or inhaling bronchodilators. Others may need to use inhaled cromoglycate powder, either alone or in combination with bronchodilators. The next levels of treatment are the use of inhaled steroids, followed by the ingestion of steroids. When attacks can no longer be prevented or relieved with these measures, treatment in hospital with oxygen, hydration and the addition of parenteral medications becomes necessary. Handouts outlining appropriate treatment choices for patients can help them to make these decisions. Patients should understand that effective intervention at an early stage can prevent an attack from becoming severe.<sup>28</sup> Once patients have achieved control at a certain level of treatment — for example, with ingested steroids — they can usually begin to gradually adjust to a lower level of treatment — for example, with inhaled medications only.

Many of the medications used to control or relieve asthma produce side effects that vary between individuals. Patients should be monitored to ensure that the doses they take are within their limits of tolerance. Therapy should be designed so that asthma patients take the minimum amount of medication at the lowest

level of treatment that will enable them to control their condition and prevent acute attacks.

*Agents that bronchodilate and reduce bronchial hyperresponsiveness:* Bronchodilators are much more effective in reversing early asthmatic responses than late ones. The two main categories of such agents are the  $\beta_2$ -agonist sympathomimetics and the methylxanthines.

The sympathomimetics generally used at present can be administered by inhalation (salbutamol [Ventolin] and fenoterol [Berotec]), by ingestion (orciprenaline [Alupent], salbutamol and terbutaline [Bricanyl]) and by injection (epinephrine). Tests comparing topical use (inhalation) with systemic (ingestion or injection) show that topical therapy is invariably advantageous; inhaled medication produces greater bronchodilation with fewer side effects<sup>10,11,29</sup> and reduces bronchial hyperresponsiveness.<sup>10,30</sup> However, it has been theorized, though not yet proved, that for patients in whom airway obstruction is already marked systemic medication could reach the small airways more easily and thereby have a greater effect. Nevertheless, it is clear that it is generally preferable to inhale than to ingest these agents, at least for maintenance therapy. The advantages of topical therapy are enhanced by the relatively selective activity of  $\beta_2$ -agonists such as salbutamol and fenoterol.<sup>31</sup>

The technique with which patients use a metered-dose inhaler is an important determinant of its efficacy. The correct method should be demonstrated to patients during their first and subsequent visits to the physician's office.<sup>32</sup> While shaking the canister vigorously the patient should exhale gently and hold the head back. With the canister base pointed up and the plastic mouthpiece about 3 cm from the wide-open mouth the patient should slowly inhale while directing a single spray toward the back of the throat. The inhalation should continue for about 5 seconds and then, if possible, the breath should be held for 5 to 10 seconds. If the patient requires more than one spray, each should be inhaled separately.

Routinely,  $\beta_2$ -agonists can be inhaled up to four times daily. As a preventive measure these agents can be inhaled 10 to 15 minutes before an event known to induce symptoms, such as exercising or inhaling cromoglycate.

Patients should be cautioned about, and their treatment should be reviewed for, possible side effects. If two sprays of bronchodilator induce a side effect the dose should be reduced to one spray. In a few patients, however, even a single spray of salbutamol or fenoterol can produce tremor, tachycardia, agitation, sleeplessness or headache, or raise the blood pressure. Such patients can reduce the amount they inhale below that inducing the side effect by holding the inhaler sufficiently far from the mouth that some of the inhalant is lost.

A reduced response to inhaled bronchodilators is an early signal that additional treatment with other modalities is needed immediately, as is the need to use the inhaler more than four times daily on a regular basis or more than six times daily at any time.<sup>33,34</sup> If the patient is already receiving adequate doses by mouth of the bronchodilator theophylline, adrenocortical steroid may

be required. Prescriptions for bronchodilators that specify "Use no more than four times daily" and "Renewals no more than once every 3 or 4 weeks" may remind patients to watch for these signals. In most patients overuse of the inhaler is not a sign of "habituation" or "thrill-seeking" but indicates that normal use is not controlling their asthma sufficiently. The patient uses the inhaler increasingly for temporary relief of symptoms, yet the asthma becomes more refractory. To extricate patients from this vicious cycle the physician should provide additional treatment early.

When taken to control asthma, methylxanthines are ingested, usually in the form of theophylline (in either the short-acting or the newer sustained-release form) or oxtriphylline (65% theophylline by weight). These agents provide steady maintenance treatment that usually is sufficient only for those whose asthma is mild. Patients should start by taking a low dose, then gradually increase the dose to an amount that will control their asthma without causing side effects.<sup>35</sup> The maintenance dose of theophylline for adults varies from 100 to 300 mg taken up to four times daily.<sup>36</sup> The starting daily dose for children under 9 years of age should be about 14 mg/kg or 280 mg in total, whichever is less, given in four doses. This can be gradually increased to a daily dose of 20 mg/kg in those who tolerate it. In older children the initial dose should be proportionately less, so that in those over 16 years the initial daily dose is 10 mg/kg or 600 in total, whichever is less; any increase should be gradual and dependent on the patient's tolerance.<sup>37</sup> Patients can take the total daily dose of sustained-action preparations in two rather than four doses.<sup>38</sup> As the appropriate dose of theophylline varies markedly from person to person, serum theophylline measurements can help physicians establish this dose. Such measurements are required in the use of high-dose therapy intended to produce plasma levels of theophylline in the range of 10 to 20  $\mu\text{g/ml}$ . However, doses that produce plasma levels in this range can cause side effects; such an occurrence indicates that the dose should be reduced or the treatment stopped. Common side effects in children include behavioural changes, hyperactivity and sleeplessness. Others are heartburn, nausea, vomiting, diarrhea, rash, arrhythmias and seizures. Gastric irritation can be reduced by ingesting the medication with food.

*Preventive agents:* Sodium cromoglycate (Intal) is taken as an inhaled powder supplied in a 20-mg capsule. It is likely to be available in Canada soon for use in a metered-dose inhaler. It can prevent both early and late asthmatic responses and can be taken in conjunction with bronchodilators by patients whose asthma is not controlled by bronchodilators alone. Cromoglycate is especially useful in the maintenance treatment of asthma in young and allergic patients.<sup>46</sup> It can be taken alone or in combination with other medications before patients exercise or if they know they will be exposed to an allergen that worsens their asthma. The usual dose is the contents of a capsule up to four times daily. Patients who usually take less can increase the dosage to four capsules daily when symptoms appear. However, when asthma is sufficiently severe, inhalation of the powder can induce coughing or

wheezing and the patient may have to stop taking cromoglycate until the asthma has been controlled — generally by taking an adrenocortical steroid. The tendency to cough or wheeze may be reduced if the patient inhales a  $\beta_2$ -agonist 5 or 10 minutes before inhaling the cromoglycate. The record for safe use of cromoglycate is excellent, although in rare cases reversible hypersensitivity reactions have occurred.

**Steroid agents:** The use of steroids as basic preventive treatment is not recommended, as these agents do not produce bronchodilation or inhibit antigen- or exercise-induced early asthmatic responses. However, they can prevent or reverse late asthmatic responses.<sup>19</sup> Therapy with inhaled steroids is almost invariably combined with regular bronchodilator therapy. In children, both cromoglycate and bronchodilators are often used with inhaled steroids. The efficacy of the simultaneous use of steroids and  $\beta_2$ -agonists appears to reflect the fact that steroids restore and probably maintain airway responsiveness to  $\beta_2$ -agonists.<sup>33,34,39</sup> For inhalation, beclomethasone dipropionate (Beclivent, Vancril) is recommended.<sup>7</sup>

In general, inhaled steroids are used regularly for control, but for patients who do not require them on a regular basis they can be added to the regimen during exacerbations. The usual starting dose is two sprays four times daily, a dose that most patients tolerate without serious systemic side effects, although a reduction in morning plasma cortisol levels has been observed.<sup>40</sup> The dosage may be increased to six inhalations four times daily if required. Some patients may benefit from taking the total daily dose at shorter intervals during the morning rather than at longer, evenly spaced intervals four times daily.<sup>41</sup> Patients whose asthma is aggravated by inhaling steroids can first inhale a  $\beta_2$ -agonist. A fairly common side effect of steroid inhalation is pharyngitis, a condition that may not be recognized as a complication of therapy in patients who are otherwise susceptible to upper respiratory tract symptoms. Dysphonia can occur in up to 50% of patients. Steroid inhalation can also cause pharyngeal candidiasis, but rarely is the condition severe or disabling.<sup>42</sup> These local side effects can be reduced by modifications in the technique of using the inhaler. As with bronchodilator inhalers, holding the canister outside the mouth reduces the amount of steroid deposited in the mouth and throat. Using the inhaler before meals and rinsing the mouth and throat with water after inhalation reduce the residual steroid in the throat. A holding chamber into which the medication is sprayed before being inhaled has proven to be effective, experimentally, in reducing the frequency of side effects.

For ingestion the steroid of choice is prednisone in tablet form. It is added to the treatment regimen when the agents already described, taken either alone or in combination, have failed to provide control. Such therapy is effective and generally safe for a short period. During acute attacks the best dosage for a particular patient is one that has previously been found effective. If this dosage is not known a reasonable initial dose is 30 to 40 mg for an adult or 1 mg/kg for a child. Such a dose may be repeated once or twice the day that symptoms first worsen, then may be taken after break-

fast once daily until the asthma is controlled. For patients who are not dependent on steroids for regular control the dose can then be decreased daily or on alternate days until the drug is discontinued. The latter approach permits therapy to continue while it minimizes adrenal suppression. The injection of adrenocortical steroids in depot form is not recommended, as such therapy does not make more steroid available than ingestion of prednisone and commits patients to prolonged continuous exposure to these drugs without the possibility of varying the dose according to individual needs.

**Combination therapy:** Bronchodilators, cromoglycate and steroids can be taken simultaneously, as they are complementary. Bronchodilators can prevent or reduce early asthmatic responses, cromoglycate can prevent both early and late responses, and steroids can prevent or reduce late responses.

**Allergen injection treatment (immunotherapy, hypo-sensitization)**

Allergen injection treatment can reduce patients' responsiveness to particular antigens. Such treatment has been demonstrated to be efficacious for patients with allergic rhinitis caused by pollens.<sup>43</sup> Although data on this treatment in asthma patients remain rather scant, reductions in airway responsiveness to the antigen have been demonstrated.<sup>44</sup> However, in some patients asthma can be aggravated by injections and is improved when they are stopped. As the alternatives for treatment have greatly improved in recent years, most of us (except W.M.W.) do not regard asthma as a condition that indicates allergen injection treatment. For patients with asthma who are receiving such treatment the following guidelines should be observed:

- If the injections aggravate the asthma the dose should be reduced or the injections stopped.
- If symptoms are present medication must be given in sufficient doses to control the asthma.
- When symptoms have been stable for 2 years, whether or not they have lessened, the injections should be stopped to observe the results.

**Understand the nature of asthma**

Patients may be better able to cooperate with physicians in controlling their asthma if they and their families understand the following about their condition:

- Asthma is probably not the result of anything the patient or family has done or not done.
- Asthma is not due to an emotional or personality disorder.
- Asthma does not cause permanent lung damage, such as emphysema.
- Asthma does not leave the heart weakened.
- Asthma is a disorder that fluctuates in severity. Even in those who have undergone treatment for extended periods there can be marked improvement that considerably reduces their need for such treatment. Conversely, even patients whose mild asthma has been well controlled for long periods may have sudden severe exacerbations that require an immediate and significant increase in the amount of treatment.
- It is not only safe but also, for some patients, more

effective if the various medications are taken simultaneously.

- If immediate side effects can be avoided, the medications presently used are generally well tolerated for years.

- Early intervention prevents severe attacks. Decisions made at home are important in ensuring that additional treatment, when necessary, is started early. Most patients can be taught to recognize that their condition is deteriorating and to institute appropriate therapy, including ingested steroids.

- Improved understanding and new medications provide more reason for optimism now than at any time in the past.

### Asthma in young children

The treatment of asthma in young children presents some special challenges.<sup>45</sup> Because the history is provided by a second party, a parent, it may be less reliable. A parent's use of such terms as recurring bronchitis, pneumonia and recurring bronchiolitis may delay the physician's recognition that a child has asthma. Measurements of pulmonary function are virtually impossible, and therapy with metered-dose inhalers often cannot be administered effectively. Nevertheless, control can be maintained in most cases. Theophylline can be ingested, and other bronchodilators and steroid from metered-dose inhalers can be tried. If ingested steroid must be used repeatedly to control attacks, the preferred method is regular inhalations with the use of a compressor in the home. Treatment with salbutamol (Ventolin Respirator Solution, Berotec Inhalant Solution) and cromoglycate (the powder from an Intal capsule or the solution from a single-dose vial being introduced into the nebulizer containing salbutamol and saline) can be reliable. This treatment, one to four times daily, often provides excellent prophylaxis without causing side effects.<sup>46</sup> Ingested theophylline, inhaled beclomethasone and, if necessary, ingested prednisone — preferably on alternate days — can be added to the regimen.

### The severe attack

Preoccupation with the concept of "status asthmaticus" is now outdated, as it is possible to intervene with effective, carefully monitored treatment long before the patient reaches the stage of being unresponsive to sympathomimetics. In severe attacks, including any episode requiring admission to hospital, systemic therapy with adrenocortical steroid must be given without delay. In milder but potentially more severe situations a convenient rule of thumb is that evidence that breathing has not returned to normal within 1 hour after the start of treatment with bronchodilators and possibly other measures, such as oxygen inhalation and increased hydration, constitutes an indication for immediate steroid therapy. If symptoms develop rapidly, the steroids should be ingested or infused intravenously rather than inhaled.

Patients should be thoroughly assessed to exclude other conditions, such as aspiration of a foreign body or pneumonia, and complications, such as atelectasis, pneumothorax or pneumomediastinum.

Once the attack has become acute the patient should be given oxygen — 28% or more — without delay, either before or with the bronchodilator, since use of the latter alone can worsen existing hypoxemia.<sup>47</sup> Treatment with a solution of salbutamol or fenoterol nebulized by compressed oxygen can be started shortly after the patient enters an emergency unit, and is preferred during a severe attack of asthma since synchronization of oxygen inhalation with the use of a metered-dose inhaler may be difficult. A reasonable dose of a 5 mg/ml salbutamol solution is 0.25 to 0.5 ml for an adult and 0.005 to 0.01 ml/kg for a child. If this dose is ineffective and tachycardia has not been induced, it can be repeated in 15 to 30 minutes. Inhalations can be repeated as often as once every 2 hours during the acute phase and until the steroids have taken effect. The frequency can be decreased and the dose sometimes reduced as the response to therapy increases in magnitude and duration.

If the patient has not been undergoing maintenance treatment with ingested theophylline, this drug can be provided. Any addition to the regular dose should be monitored by measuring the plasma theophylline concentration. However, the results of these measurements are not usually immediately available. Moreover, shifts in theophylline distribution during acidemia<sup>48</sup> and during reduced renal clearance because of respiratory tract infections<sup>49</sup> add to the risk of emphasizing the use of theophylline during severe attacks.

Marked airway obstruction, as indicated by shock, retention of carbon dioxide, pulsus paradoxus, clouding of consciousness or other evidence that this is a life-threatening attack, is an indication for immediate intravenous therapy with steroid<sup>8,9</sup> in addition to appropriate bronchodilators. Hydrocortisone, 200 to 400 mg for an adult or 4 mg/kg for a child, or methylprednisolone, 50 mg for an adult or 0.5 mg/kg for a child, can be infused as a bolus over 5 minutes. The initial effect — restoration of the efficacy of sympathomimetics — may be evident within 1 to 2 hours.<sup>50</sup> If there is no improvement this dose should be repeated every 2 hours until benefit is apparent. During attacks of this severity the patient requires admission to hospital and repeated blood-gas measurements. If the attack is unremitting the patient may require intubation and controlled ventilation. The extent to which treatment is scaled up or down during an acute attack depends on the response of the patient to the present level of treatment.

Once a patient's condition has stabilized following a severe attack, treatment should be gradually scaled down to the medication or combination of medications that, along with avoidance of offending substances, allows the patient to regain and then maintain control of the asthma.

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### Home remedies for asthma

*Get a Mexican hairless (chihuahua) dog, but not someone else's, and keep it nearby. The asthma will go from you to the dog.*

*Sleep in sand pits containing small amounts of uranium. Get a muskrat skin and wear it fur side down over the lungs.*

*Sleep on sheep's wool that has recently been clipped. Do not clean or wash it. The asthma will be absorbed into the wool.*

*String a line of crickets on a silk string and wear it around your neck.*

—Reprinted from "The Book of Home Remedies and Herbal Cures" (a Jonathan-James book) by Carol Bishop, Octopus Books Ltd., London, Eng, 1979: 28