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Dynamic Approach to Asthma

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A clinical trial, with historical controls, as of a way of conceptualizing labile asthma, which in my experience has proven useful in planning long term ambulatory management, in communicating with and enlisting the support of referring physicians, and in enlisting patient confidence and cooperation in home monitoring and medical management of changes in disease activity is reported.

INTRODUCTION

Asthma is most simply defined as reversible obstructive pulmonary disease. Morbidity and hospital utilization statistics[1] and an estimated mortality approximating 8 per million population per year[2] suggest that satisfactory reversal is frequently not achieved. The present study is a test of the hypothesis that incomplete asthma control is often not the result of a lack of adequate diagnostic and therapeutic technology, but of lack of a concept or model of the disease in terms of which the specialist, the primary physician and the patient and/or family can anticipate and prepare for changes in the activity of the disease and cooperate in applying already existing therapeutic modalities for its control.

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DYNAMIC MODEL OF ASTHMA

A dynamic process is suggested by the 1962 definition of asthma by the Committee on Diagnostic Standards for Nontuberculous Respiratory Diseases of the American Thoracic Society[3]:

> "Asthma is a disease characterized by an increased responsiveness of the trachea and bronchi to various stimuli and manifested by a widespread narrowing of the airways that changes in severity either spontaneously or as a result of therapy."

"Widespread airway narrowing," can be acutely life-threatening. "Changes in severity either spontaneously or as a result of therapy," imply a need to monitor closely. "Increased responsiveness of the trachea and bronchi to multiple stimuli," suggests that attacks will not always be possible to prevent, or even to predict. It is beyond the scope of this paper to review experimental

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evidence supporting a pathophysiologic model compatable with these dynamics. It will instead be summarized briefly, and justified by its utility in reversing this reversible disease.

Three phenomena are usually regarded as *primary* pathophysiologic changes in asthma: bronchoconstriction, hypersecretory activity of bronchial mucus glands, and bronchial mucosal edema. The locus of principal obstruction varies in different patients and sometimes at different times in the same patient, but the process usually involves bronchi between 0.5 and 8 mm diam. Bronchoconstriction, increasing resistance to airflow, is the major pathophysiologic process affecting the larger bronchi within this range, which have more circumferential smooth muscle. Their larger ratio of x-sectional area to circumference also makes them less susceptable to obstruction by a similar degree of volume incursion per unit circumference by mucus production and mucosal edema. Obstruction in small airways is principally via closure, by relatively lesser degrees of bronchospasm, of the lumens of bronchi already significantly narrowed by intraluminal mucus plugs and mucosal edema. I would suggest that bronchospasm is the primary physiologic change, and that mucosal edema and mucus hypersecretion comprise a partially inflammatory process of reactive hyperactivity of normal bronchial clearing mechanisms. These are a response to chronic or recurrent obstruction located slightly more centrally in the tracheobronchial tree. The aggregate response behaves as a biological amplification mechanism, and manifests a characteristic common to many such mechanisms: At low levels of stimulus activity (bronchoconstriction) the response depends on continuous presence of the stimulus which elicits it. At higher levels, however, the obstruction produced by the reaction, itself, can become self-perpetuating. At the cellular level these dynamics reflect the normal presence in bronchial mucosa of only limited numbers of mast cells, and relative mucosal impermeability to irritant and allergic stimuli. The chemical mediators of inflammation released following activation of mast cells in the mucosa increase mucosal permeability to both allergens and non-specific irritants, however, and also attract and activate much larger numbers of reactive cells, so that at high enough levels of activity the inflammatory process becomes self-sustaining.

What I have defined, above, in terms of "system" behavior, is a positive feedback loop: A transient stimulus, without causing any direct irreversible change, induces a persisting alteration or adaptation in the state of the system. Positive feedback loops are not inherently bad—they are operative in embryogenesis, the development of adaptive immunity, in many other process of physiologic adaptation, and in learning and memory. However when the process of which such a loop is a part is maladaptive, as in many disease processes mediated by inflammation, optimal management depends on dissecting and defining the positive feedback loops involved in the pathophysiology of the particular disease process in question, to look for weak links, which may vary from patient to patient.

The dynamic pathophysiology of asthma I have outlined above can be represented as a nest of positive feedback loops (1)–(3) in Figure 1. A fourth loop is suggested by recent work of Bergquist et al.[4,5]: Intrathoracic pressure changes caused by airway obstruction in asthma, transmitted to the gastrointestinal system, facilitate gastroesophageal reflux. Reflexes originating in the esophagus and/or aspiration of small amounts of gastric contents then increase bronchospasm.

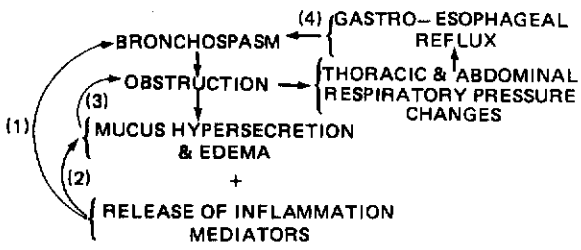

Figure 1. Positive feedback loops in asthma.

I suggested that bronchospasm is the primary change, at least in acute exacerbations or increases in disease activity. If bronchoconstriction can be controlled within the range in which inner loops (2) and (3) are not yet operative, by removal or control of external precipitating factors and/or by treatment with bronchodilators or other drugs which interrupt loop (1) (this may be the effect of inhibition of mediator release by sodium cromolyn, for example), any inflammatory changes associated with that exacerbation can be expected to regress by themselves. If inner loops (2) and (3) are sufficiently active, however, the patient will not respond without intensive direct anti-inflammatory therapy, which, in the pharmacopoeia of 1983, means high dose steroids. Appreciation of the positive feedback nature and dynamic behavior of the process being treated is necessary if the toxicity of this therapy is to be minimized. The earlier and less developed the steroid-requiring inflammatory process at the time of treatment, the shorter the course of intensive steroid therapy necessary for its reversal. Also, in the steroid-dependent patient in whom these inner loops are continuously active and require chronic suppression, as the inflammation responds to treatment with decreasing amounts of feedback activity the amount of steroid suppressive therapy can be correspondingly reduced.

Patients and families, both in my office and in community asthma education programs, and primary care and emergency physicians in CME programs, often seem to grasp the concept of the dynamic behavior of asthma when it is explained in terms of the mechanical model in Figure 2: The primary problem in labile asthma is not that the patient's bronchoconstrictor tone and inflammatory activity are increased, represented graphically by displacement of the cart downward on its track, as most of the time they are not. The problem is that they are unstable, like a cart so heavy that if any force P arises to push it slightly down the hill, natural stabilizing forces W and L plus chronic maintenance therapy T_0 will not pull it back, and it keeps rolling down even

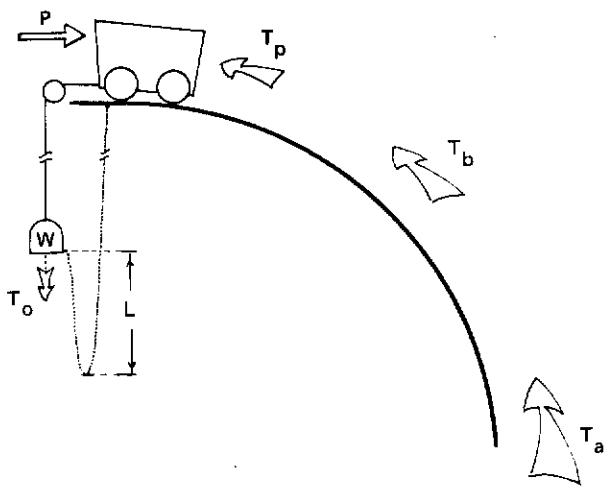

Figure 2. Mechanical analogue of bronchomotor tone.

if P is removed. Because the farther it rolls down hill the stronger the force of additional treatment necessary to bring it back and the longer the time during which it may have to be applied, both of which increase the risk of adverse effects of treatment, and because of the more significant morbidity and risk of mortality associated with these exacerbations, optimal management depends on early recognition of minimal perturbations of this unstable equilibrium. Additional treatment T_b sufficient to restore equilibrium should be applied promptly, before sufficient displacement has occured to result in significant morbidity and require longer, stronger and potentially more toxic T_a. Once equilibrium is restored, lesser treatment T_p may be substituted for T_b and should be continued to balance destabilizing force P, which may be a viral respiratory infection, an unavoidable increase in exposure to aeroallergens, climatic, or other environmental stress, etc., as long as P persists. When steroids or other drugs which are either costly or entail significant risks of adverse side effects are required as a part of chronic maintenance therapy T_0, the mechanical model is useful to explain to patients that if T_0 is strong enough to keep the cart from ever moving off center no matter how strong the P, most of the time they are probably receiving more treatment than they need. The goal of maintenance therapy in labile asthma is not

to keep the cart at the top of the track all of the time, but to keep it there most of the time and provide enough T_0 so that with systematic monitoring of disease activity, which I have termed, "anticipatory management" (AM), exacerbations can be recognized before they result in significant morbidity, and be reversed by the timely application of well tolerated short courses of T_h and appropriate T_p.

APPLICATION OF DYNAMIC MODEL TO "ANTICIPATORY MANAGEMENT" (AM)

Home Acute Management Protocols

Because positive feedback destabilizing mechanisms are involved, promptness in initiating treatment is paramount if bronchomotor homeostasis is to be restored with minimum morbidity and minimum exposure to side effects of treatment. Patients subject to recurrent acute exacerbations should therefore always have medications available, at home, and, depending on rapidity of onset, possibly at school or at work as well, for early initiation of treatment upon identification of signs of a developing exacerbation. Patients or families should have individualized guidelines for seeking reevaluation between "maintenance" office visits and also for when to telephone the responsible physician for emergency management. Some patients are best instructed to call any time an exacerbation appears to be developing, prior to taking emergency medications. For others, prudence dictates that they begin prescribed acute treatment (which may include bursts of high dose steroids) and then call. Some patients can be optimally managed with instructions to call any time an exacerbation fails to resolve within a specified period of time in response to an individually prescribed acute treatment protocol. Some patients may be instructed to seek advice any time that more than a specified number of inhalations of long acting metered dose adrenergic or home treatments with nebulized adrenergic are needed within a specified period of time, or to schedule an appointment for reevaluation any time that more than a specified number of extra doses of prednisone, given according to a protocol for specified indications, are needed in a single month. Any patient or family with a history of severe acute exacerbations should be encouraged to telephone the responsible physician at any time that the disease does not appear to be responding adequately to that patient's prescribed acute management protocol.

Pulmonary Function Monitoring

The temporal variability in both disease activity and necessary intensity of treatment argue in favor of repeated monitoring with simple, relevant, and inexpensive measures of pulmonary function. Peak expiratory flow rate (PEFR) is a simple quantitative measure of "large airway function" which correlates well with acute asthma activity. Two inexpensive PEFR measuring devices, the Armostrong mini-Wright Peak Flowmeter* and the Vitalograph Pulmonary Monitor† are available by prescription, covered by most major medical insurance, and sufficiently accurate[6] and reproducable‡ to facilitate routine home monitoring. More than 60 patients with labile asthma in my practice routinely monitor their PEFR every day before morning meds, before supper, and to document the response of any acute attacks to their individual acute treatment protocols. The utility of home PEFR monitoring in the early recognition of impending acute exacerbations has been reported[7] and routine home monitoring also permits the safe downward titration of steroid dose and withdrawal of other added meds between physician visits, after acute exacerbations have been brought under control by intensive short term therapy.

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†Vitalograph Medical Instrumentation, 8347 Quivira Rd, Lenexa, KS 66215; phone 800-266-6626.

‡Personal experience, unpublished.

The maximum midexpiratory flow rate (MMEF of $FEF_{0.25-0.75}$), calculated manually or electronically from spirometry, is generally accepted as a measure of small airway function, and is probably the least expensive and least invasive small airway function measurement. A random measurement of MMEF may be interpreted as a measure of small airway function resulting from currently active external precipitating factors plus the sum of activity present in all four positive feedback loops. A similar measurement following treatment with injected or nebulized adrenergic bronchodilator or when the patient is already receiving maximum tolerated nonsteroid therapy, when compared to previous measurements to adjust for any impairment resulting from emphysema or other irreversible pathology, is clinically useful as a measure of potentially steroid-responsive inner loop activity. A low random or post-bronchodilator MMEF in a patient who is free of acute symptoms and has a normal PEFR suggests increased loop (2) and (3) activity, resulting in increased feedback stimulation of bronchospasm via loop (1). This destabilizes bronchomotor homeostasis by decreasing the amount of additional stimulation necessary to exceed that patient's threshold for PEFR-detectable and clinically significant bronchoconstriction.

Maximizing Control of Inflammation

For the patient with labile steroid-dependent asthma who has never had a normal MMEF, or not had one in recent years, the only way to determine the 'normal" of "inflammation-free" level of small airway function is with an intensive course of high dose steroid anti-inflammatory therapy until either spirometric improvement stabilizes or an arbitrary limit of 2 to 3 weeks is reached. A spirogram which improves within 7 days on high dose steroid therapy but does not improve further following an additional 4–7 days continuing treatment may be regarded as already maximal. Frequently the achievement of an individual patient's inflammation-free baseline permits major reduction in dose or even total withdrawal of steroids when this would not have been possible prior to control of loops (2) and (3). In each patient the risks of up to 3 weeks intensive steroid therapy must be weighed against the value of obtaining a spirometric endpoint correlating with maximal loop (2) and (3) suppression and the advantages of potentially decreased maintenance therapy needs once maximal loop (2) and (3) control has been obtained. My schedule for intensive steroid therapy with oral prednisone is 1 mg/kg body weight twice a day up to a maximum dose of 70 mg twice a day in males and 60 mg twice a day in females. For treatment of acute exacerbations the first two doses are 1 mg/kg irrespective of body weight. Treatment with steroid "burst" therapy according to this schedule was effective in halting disease progression in 154 cases and in effecting quantitative reduction in asthma activity within 6–8 hr of initiation in 153 of 154 cases studied. All of these observations involved patients with established patterns of predictable progression to increased severity in the absence of this therapy.[7]

REDUCTION IN HOSPITAL (H) AND EMERGENCY ROOM (ER) UTILIZATION

Reduction in H and ER utilization on anticipatory management (AM) was calculated for all patients presenting to my practice during a 14 month period in 1981–1982 who satisfied the following criteria:

1. History of two or more H and/or ER in the 12 months prior to coming under my care.
2. At least 2 months subsequent follow-up.
3. Age at presentation greater than 24 months, because of inaccuracies inherent in the projection of anticipated rates of H and ER based on a 12-month historical control period prior to age 1 yr.

A total of 32 patients (11 male, 21 female) met these criteria, and each patient or family was oriented in the principles of AM at the time of presentation. At the end of 16 months (14 months for entry + 2 additional months to complete follow-up), they had been followed for a total of 26.83 patient-years (pt-yr). Age range at presentation was 2–85 yr, with a mean of 23.28 yr. Patient characteristics, frequencies of H and ER for asthma in the 12 months prior to presentation, and selected characteristics of subsequent care are listed in Table 1. Extrapolation of each patient's rate of H and ER for the preceding 12 months permits calculation of expected H and ER for comparison with observed utilization data during AM based on the dynamic model. Patient 14, for example, was hospitalized six times for asthma during the 12 months prior to beginning AM, and would thus contribute an expected 4.5 H during her subsequent nine months on the AM protocol. Expected totals are the sum of expected H and ER similarly calculated for all 32 patients during their respective periods of follow-up on AM:

exp (H) = 49.0 = 1.82/pt-yr,
exp (ER) = 142.08 = 5.29/pt-yr,
obs (H) = 1 = 0.037/pt-yr,
obs (ER) = 1 = 0.037/pt-yr.

The single instances of H and ER both represent breaks in the AM protocol. Each involved a child whose asthma had been under unprecedentedly good control during a period of several months on AM, and whose parents had understandably become relatively complacent. In each case a parent telephoned the office the day before the evening ER and early morning H. Each was advised to bring the child to the office that day, but was busy, and because the child did not seem to be too sick, chose to try to wait until the next day.

The subsequent course of the 10 year old girl seen in the ER was uneventful. The hospitalized child was a developmentally retarded 3 yr old boy who, at that time, had not yet learned to use a home PEFR monitoring device. His acute exacerbations characteristically involved early activation of positive feedback loop (4), such that initial symptoms of lower respiratory congestion were rapidly followed by dyspnea and vomiting with intolerance of oral medications. He was subsequently found to be responsive to nebulized metaproteranol solution followed by chest physiotherapy. A small ultrasonic nebulizer was then prescribed for home use, and two exacerbations since this unit has been in the home have been controlled with the above treatment, followed immediately by the beginning of a short prednisone burst, with repetition of nebulized metaproteranol and/or bronchial drainage as needed. This family's acute home treatment protocol specifies giving the first nebulizer treatment and steroid dose *before* trying to telephone me because of the explosive progression of their child's symptoms in the absence of early intervention. Total steroid use is closely monitored, and has been less since the institution of this protocol than prior to the beginning of AM. This child's very patient mother is now working to teach him to use a home PEFR monitor, which, once mastered, should facilitate earlier recognition and easier treatment of future exacerbations.

Seven of the 32 patients in the series have never required treatment with steroids, 10 require steroids intermittantly, and 15 require chronic steroid therapy, either orally on alternate mornings or by inhalation. Seventeen patients had significant skin test reactivity to a panel of common inhalant aeroallergens; three had reactivity that may possibly be clinically significant, and two, who were tested, lacked significant reactivity. Ten patients have not been skin tested. Of the 17 patients identified as having significant allergic components to their asthma and/or coexistent rhinitis, nine are presently receiving immunotherapy. One additional patient previously received it from another physician, and I have not felt it to be indicated in the other seven.

Office follow-up evaluation is recommended at 3 month intervals for most patients with significant recent asthma

Table 1. Patient Characteristics

NO. PATIENT	NO. mo FOLLOWED	AGE AT ENTRY	SEX	PRIOR 12 mo H	PRIOR 12 mo ER	PRESENT STEROID[a]	HOME PEFR[b]	HOME NEB[c]	ALLERGIC[d]	IT[e]	FOLLOW-UP (mos)	CONTROL[f]
1.	14	3	M		6	0				prev.	as needed	
2.	11	3	M	6	8	I	+	+	+		3	
3.	15	11	M		2	C	+		+	+	3	
4.	11	5	F	4	12	C	+		+		3	
5.	10	58	F		4	I	+		+		6	
6.	14	40	F	6	12	C	+	+	±		3[g]	*i*[g]
7.	10	4	F	2	5	C	+		±		3	
8.	14	12	M		4	0					as needed	
9.	16	28	F	1	6	C	+	+	+	+	2	*u*[h]
10.	16	12	F	1	8	I	+		+	+	3	
11.	2	26	F	1	1	C	+		−		moved	
12.	12	11	F	1	6	C	+		+	+	3[i]	*i*[i]
13.	11	4	F	2	2	I			+		as needed	
14.	9	64	F	6		C	+	+	+	+	3	*i*[k]
15.	15	6	M		2	0			−		as needed	
16.	2	5	M		8	0			+		as needed	
17.	13	8	M		12	I	+		+	+	3	
18.	12	38	F	12	12	C	+				as needed	
19.	2	2	F		8	0					as needed	
20.	9	8	F		3	0					3	
21.	9	11	F	1	2	I	+		+		as needed	
22.	9	6	M		3	C	+		+		3	
23.	14	9	F	1	1	I	+		+	+	3	
24.	8	85	F	3	1	C	+	+			2	*i*[k]
25.	8	62	F	2		C	+		+		2	
26.	8	74	F	2	4	C	+				3	
27.	7	2	M	2	15	I			±		as needed	
28.	15	10	M	1	2	I	+		+	+	3	
29.	2	60	M		3	C					moved	
30.	15	10	F		6	I	+		+	+	3	
31.	5	65	F		2	C	+				3	
32.	4	3	F		2	0					as needed	

[a]0, none; I, intermittant; C, continuous inhaled or alternate day oral.

[b]+, Home monitoring two times per day and as needed for symptoms, and to follow acute response to home treatment.

[c]+, Ultrasonic or pump driven nebulizer prescribed for as-needed home treatment with nebulized adrenergics.

[d]+, probably significant; −, probably not significant; ±, indeterminate; no mark, not skin tested.

[e]Aeroallergen immunotherapy: +, present; prev, previous but not present.

[f]Overall asthma control satisfactory where not marked. *i*, satisfactory control on investigational drug; *u*, control not satisfactory.

[g]On investigational treatment with metered dose ipatropium bromide (Atrovent ®) to reduce steroid need; treatment protocol requires more frequent follow-up visits than every 3 mo needed for asthma management.

[h]Overall control unsatisfactory because of significant Cushingoid changes at steroid doses required for satisfactory asthma control.

[i]On investigational treatment with ketotifen (Zatiden®) to reduce steroid need; treatment protocol requires more frequent follow-up visits than every 3 mo needed for asthma management.

[k]On investigational treatment with nebulized methylprednisolone (Solu-Medrol®) to reduce systemic steroid side effects.

morbidity who require chronic medications but with them maintain good control. Recommended follow-up interval may be shorter or longer, depending on difficulty of control, presence of other conditions complicating treatment, and individual indications to attempt to titrate maintenance steroid therapy downward to minimize long term complications of treatment. Patients referred from long distances, if clinically well with a full range of normal activities for age while taking no medications other than well tolerated doses of theophyllines, long-acting oral and metered dose inhaled adrenergics and cromolyn are told they may be followed by their local physician and need not return for further specialty care as long as they continue to experience excellent control on these drugs. Patients requiring no medications other than infrequent, short term treatment with the same drugs are equipped to give it at home when needed, and instructed to return if such episodes increase in either frequency or severity. The average frequency of scheduled follow-up for the 30 patients who remain in my referral area is now 2.9 office visits per pt-yr. Unscheduled additional visits, for care of acute exacerbations and for patients followed as needed only, approximate one per pt-yr. Four patients are receiving treatment with investigational drugs, in each case to decrease the dose of systemic steroids necessary for control, and the care of one additional patient is judged less than fully satisfactory because of significant Cushingoid changes caused by the steroid doses needed for asthma control. H and ER use in this population of former heavy users has been reduced by a factor of 96, with fully satisfactory and uncomplicated reversal of this reversible disease in 97% of 32 patients, on an AM program involving scheduled + unscheduled office care at 55% of the previous frequency of H + ER.

SUMMARY

Morbidity, need for H and ER, and, presumably, risk of mortality have been reduced to near zero in a cohort of asthma patients previously dependent on frequent H and ER. These improvements followed, and are attributed to, the planning of therapy, instruction of patients, and orientation of interested referring physicians in an anticipatory management protocol based on a dynamic model of asthma.

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Outcome summary for prior yr 2 or more ER &/or hosp admissions for asthma:

1) 98.9% reduction in frequency of hospital & ER visits for asthma.
2) 97% of patients reported total control of asthma as a limiting condition in their lives.
3) Cost of asthma health care reduced by ~50%