THE YEAR BOOK *of* DRUG THERAPY 1972

EDITED BY
DALE G. FRIEND, M.S., M.D.

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The material covered in this volume represents literature reviewed up to October, 1971.

INTRODUCTION

The format of the 1972 YEAR BOOK has been changed from a straight alphabetical listing of individual topics to a grouping of articles of related interest in chapters. I hope this arrangement will be more convenient for the reader, who may have special interests, and facilitate the finding of articles for reference purposes.

There have been some exciting advances in therapy during the year, and an attempt has been made to reflect these by selecting the important articles with enough confirmatory material to insure that the reader is getting a good overview of these developments.

Paget's disease of bone, after being an untreatable condition for many years, has now been attacked vigorously with several different agents. These are rapidly changing the outlook for this formerly chronic, painful, progressive disease.

Intensive work is continuing on the action of L-dopa in Parkinson's disease. The action of L-dopa and other agents in this disease has brought considerable hope into a formerly discouraging and at times hopeless situation. Many interesting articles are appearing on the mechanism of action of L-dopa and amantadine, and an attempt has been made to reflect these developments.

Contraception is of prime importance in view of the world population. There have appeared numerous interesting articles in this field. The prostaglandins are creating much excitement, and at present work already done indicates they have a paramount role in controlling pregnancies. Prostaglandins may well replace the oral contraceptive pill.

The use of immunosuppressive agents in many heretofore intractable situations has opened up new vistas. In the treatment of skin conditions such as psoriasis they are proving highly useful. Other chronic, progressive, usually fatal diseases such as polyneuritis and Wegner's granulomatosis are often responding to immunosuppression.

The chapter on Drug Action has been retained in this edition. An attempt has been made to select those articles of practical significance and common interest. A few items have been included when they indicate what may develop in future therapy.

D.G.F.

CURRENT TRENDS IN DRUG THERAPY

by

DALE G. FRIEND

Many ingredients go into making a successful physician. One of the most important is the ability to instill confidence in his patients. Physicians since ancient times have been accepted by their patients as wise counselors in the treatment of disease. This existed long before specific agents were available even to treat or cure most diseases. It is fair to say that the patients' faith in their physicians undoubtedly led to many cures, which in turn fostered the patients' belief in the wisdom of their physicians.

In the brief period of two generations we have advanced from a therapeutic armamentarium of perhaps a half dozen highly specific agents to dozens of highly potent, effective and reasonably safe substances for the treatment of disease. Although it is still true that the patient's confidence in his physician plays an important role in the management of many problems, there are now agents available that can treat disease states not amenable to the patient's faith in the healing abilities of his physician—diseases which in the past led to serious damage or even death.

It is now more evident than ever before that the successful physician will not only be the one who generates the patient's faith in him but also the one who uses his therapeutic tools to the best advantage. Excellent care of patients now dictates that the physician must exert skill in the selection and use of drugs. He must acquire a comprehensive knowledge of the many drugs available to him. There is much room for confusion and even potential for harm unless the physician makes a determined effort to learn the essential details about the drugs he selects and learns how to use them skillfully.

The wise selection of drugs is predicated upon certain general principles. First, every physician should become familiar with a few well-chosen agents that will meet the needs for perhaps 80-90% of all conditions he will treat. This therapeutic list probably would not encompass more than 100-150 drugs at most; in fact, it is altogether probable that even less than 50 drugs will cover the actual needs of the wise therapist, especially if he has limited his practice to a special field. In limiting the number of drugs used to a select list, it then behooves the physician to learn everything possible about these agents, including the minor reactions. As familiarity with these drugs is acquired, confidence and skill in their use would also grow. Such knowledge and skill would lead to his obtaining the maximum benefit for his patient from the drug used and not infrequently lead to a therapeutic success when one with less knowledge and skill would fail.

As examples of how this reasoning could be applied, consider agents in just two categories, the cardiac glycosides and the antianginal drugs. There are many different cardiac glycoside preparations available, but, for most clinical purposes, the use of digoxin is satisfactory to cover at

least 98% or more of the physician's needs. In certain situations, such as in intensive care units, the use of ouabain can be helpful in a very limited situation where there is need to get quick action and quick recovery from drug effect. However, for most other uses, digoxin, which can be given intravenously, intramuscularly and orally would certainly meet the needs for a cardiac glycoside. Therefore, in selecting this one drug, one can eliminate all the other preparations that fall in this category.

For the treatment of angina pectoris there are also dozens of preparations available, but the wise physician knows that only two or possibly three or four really have any sound basis for use. Everyone agrees nitroglycerin is an effective agent for the acute relief from angina pectoris. For the drug to be successful, however, the physician must see to it that only active drug is used by his patient. A definite clinical response consisting of flushing, altered heart rate and slight dizziness must occur every time the patient uses the drug. Only in this way can the physician be assured that the patient is using an effective preparation. This simple check is often neglected, and patients are found to be using ineffective or weak drugs. For the long-continued treatment of angina pectoris, most people have come to the opinion that the use of propranolol has something definite to offer. The long-acting nitrites, for the most part, have not been proved to be effective, and usually end up as placebo therapy. Therefore, if a physician selects nitroglycerin and propranolol from the list of 60 or 70 agents available, he can concentrate on these two and be assured of getting a good therapeutic effect. He can do the same for many other therapeutic categories and, in this manner, cut down the amount of information with which he needs to be readily familiar.

At present, there is a great deal of controversy over the use of agents containing multiple ingredients. The Council on Drugs of the American Medical Association has long deplored the use of multiple-ingredient preparations, pointing out that it is difficult to formulate a multiple-ingredient agent that has equal effectiveness for each drug in the preparation. Such preparations tend to lead to fixed-dosage regimens, which in many instances could defeat the over-all benefit that might be obtained from the separate adjustment of doses of the various ingredients in the preparation. Currently, the FDA, acting upon the recommendations of the National Research Council Study, is taking steps to remove poorly balanced, multiple-ingredient preparations from the market. This has created controversy because there are many commonly used mixtures that have widespread acceptance with the physicians and their patients. Mixtures of antispasmodics, sedatives, cough preparations and various gastrointestinal and asthma preparations, to name a few, have become fixtures in medical practice. Efforts to bring about more rational therapy and to eliminate some of these preparations is bound to create opposition on the part of some who feel that such preparations have a well-established place in therapy and should be left alone. However, if one calmly analyzes the situation, there is room for improvement. When one looks into some of these preparations, there are little actual control data on their real efficacy as compared with the proper use of one or two of the ingredients given separately. Of course, soundly formulated mixtures are useful in treatment,

save the patient the effort of adjusting various doses and taking multiple tablets and, because of more simple dose regimen, lead to less medication error. They are also often less expensive than individual prescriptions for two or three different drugs. Therefore, properly compounded preparations can be used successfully and are needed in medicine.

There is growing concern on the part of patients, physicians, insurance companies and state and Federal governments about the cost of drugs. This anxiety has directed some attention toward the hope that the use of generic-termed rather than trade-marked drugs will reduce some of this cost. In certain instances this can certainly afford a saving, and in most preparations they will proye to be as active and as good as the trade-name variety. However, in critical situations, unless the generic-named drug has been shown to be as effective in clinical use, there will always remain a concern on the part of the physician until such data are afforded. He will in that case insist on using a preparation he knows to be effective and adequately documented.

However, this is only one aspect of the cost of drugs. The real factor that concerns me is the tremendous amount of money that is poured into drug advertising, which must surely come out of the pocket of the patient who is using the preparation. This advertising has for years been under serious criticism by the medical profession. Physicians are disgusted by the numerous mailed articles they receive, often 5,000-6,000 a year, most of which are rapidly delegated to the wastebasket. Also of concern is the enormous amount of money spent on drug advertisements in the many throw-away medical journals, which owe their existence to the advertising they receive from drug manufacturers and are, in effect, parasites on the drug industry. These journals add nothing to the over-all medical educational program in the United States that isn't already being supplied by the standard journals. It is doubtful if throw-away journals add anything to the physician's knowledge of drugs or, what is worse, are a source of any real benefit to the drug manufacturer. Furthermore, it is shocking to see the amount of money that is spent in extensive advertising programs by competing companies putting out the same drug under different trade names. There is also widespread advertising of over-the-counter drugs on television, which is now getting to resemble the medical shows of years ago. This tremendous expenditure of money must be borne by the patient, who has to pay high prices for his drugs.

As a physician, I am not aware of how much money is spent on advertising by the drug firms, but I venture to propose that the price of drugs could be lowered approximately 30% if all advertising was restricted to brief informational material to the physician.

Relaxing Effect of ACTH on Human Bronchial Muscle In Vitro. Many clinicians suggest that ACTH is often superior to corticosteroids in treatment of asthmatic conditions, but this has not been proved. To determine whether ACTH has a direct relaxing influence on human bronchi, Nils Svedmyr, Rolf Andersson, Nils P. Bergh and Rolf Malmberg[1] (Univ. of Göteborg) studied the effect of various ACTH preparations and other agents on tension changes in samples of bronchial smooth muscle obtained from 8 patients undergoing operation for lung tumors.

The muscle specimens were first suspended in buffer solutions at 37 C. for about 30 minutes to attain basal conditions. Addition of carbocholine (1.7×10^{-7} Gm./ml.) increased tension to ½-1½ lb. Addition of ACTH (0.1-1.2 I.U.) caused a relaxing action with increasing dose which began after a latent period of 20-30 seconds, reached a maximum in 1½-2 minutes and persisted at least 15 minutes. The threshold dose was 0.1 I.U./ml. and maximum relaxation occurred at 0.6-1.2 I.U./ml. The relaxing effect of ACTH was completely blocked by sotalol, an adrenergic β-receptor blocking agent (2.8×10^{-5} Gm./ml.).

Addition of theophylline (4×10^{-5} Gm./ml.) shifted the dose-response curve for ACTH markedly to the left. The most pronounced effect was in muscle from a patient with chronic bronchitis and mild respiratory tract obstruction in which the effect of ACTH was potentiated about 1,000 times. In patients without respiratory tract obstruction, potentiation was 10-40 times.

Adenosine-3′-5′-monophosphate (cyclic AMP) itself had no relaxing action. A derivative of cyclic AMP which is not hydrolyzed by phosphodiesterase, dibuturyl cyclic AMP, ($2\text{-}6 \times 10^{-7}$ moles/per ml.) had a pronounced relaxing effect on the bronchi. Isoprenaline ($4\text{-}15 \times 10^{-9}$ Gm./ml.) produced distinct relaxation which was blocked by sotalol (5×10^{-6} Gm./ml.).

The relaxing effect of four different synthetic ACTH polypeptides with human amino acid sequences was also tested. One with all 39 amino acids, in the same sequence as human ACTH, was most effective. Another with the first 28 amino acids in the same sequence as human ACTH was also more effective than porcine ACTH on human bronchial muscle. A synthetic polypeptide with the first 14 amino acids of ACTH was without effect.

The threshold concentration of ACTH which relaxed human bronchial musculature in vitro was far above the level normally reached in ACTH therapy. However, the potentiating effect of theophylline was so pronounced, and the threshold concentration of ACTH so lowered, that a direct bronchial relaxing effect of ACTH, especially in patients with bronchospastic pulmonary diseases, could be of therapeutic significance.

Additional in vitro experiments with bronchial muscle of reserpine-treated guinea pigs and with rabbit colon suggest that the effect of ACTH

(1) Scandinav. J. Resp. Dis. 51:171-176, 1970.

is a direct one, mediated by stimulation of the adenylcyclase-cyclic AMP system.

► [Another action of ACTH, which seems to be rather specific for the molecule. Its potentiating or synergistic effect with theophylline is interesting and perhaps of therapeutic significance. In acute bronchiospastic emergencies, ACTH or a readily available corticosteroid such as prednisolone is more rapidly acting than prednisone, which must be converted to the active prednisolone.—Ed.]

Rectal Aminophylline: Blood Levels with Concentrated Solutions. Aminophylline (theophylline with ethylenediamine) is one of the most useful drugs in management of bronchial asthma. M. S. Segal and E. B. Weiss[2] (Tufts Univ.), with the technical assistance of Cecilia Carta, studied the effectiveness of Somophyllin, an aqueous solution of theophylline monoethanolamine (60 mg./cc.), given rectally, in 11 patients, aged 31-69, with chronic stable bronchial asthma of varying degrees of severity. With a disposable plastic syringe and rectal top, Somophyllin, 5 cc. (300 mg.), was administered rectally over 1 minute. Immediately before and up to 6 hours thereafter, plasma was taken for ultraviolet spectrophotometric analysis of serum theophylline concentration.

Serum concentrations of theophylline rose rapidly, reaching a mean of 266.4 μg./100 ml. in 15 minutes, a peak mean of 560.5 μg./100 ml. at 1 hour and a mean of 360.6 μg./100 ml. at 6 hours. Comparative data from the literature (table) indicate that over a comparable time period for equivalent administered doses, concentrated rectal solutions are equivalent to the other preparations in rising to effective blood levels.

Suppositories of aminophylline are often unreliable because of variable absorption rates and toxicity, particularly in children. Aminophylline in solution is rapidly absorbed from the rectal vascular plexus blood stream,

COMPARISON OF THEOPHYLLINE ABSORPTION RATES

Reference†		Kw (μg% serum theophylline min/mg) x 10^{-2}	Actual Peak Level* (time)	Preparation	Total Administered Dose (mg)
This paper	adults	5.2	560.6 (1 hr)	Rectal Solution	300
4	adults	3.4	672 (2 hrs)	Rectal Solution	450
		5.2	900 (15 min)	IV	450
		1.5	369 (4 hrs)	Suppository	500
5	children	10.0	1171 (1 hr)	Rectal Solution	288 (> 11 mg/kilo)
		8.9	932 (1 hr)	Rectal Solution	285 (8-10 mg/kilo)
		6.8	660 (1 hr)	Rectal Solution	286 (< 8 mg/kilo)
6	adults	10.3	1231 (1 hr)	PO (Elixophylline)	400
7	adults	3.7	840 (3 hrs)	PO (Cardalin®)	300
		5.6	1285 (3 hrs)	PO (Cardalin®)	600
8	adults	8.0	600 (30 min)	IV	250 mg
		2.1	660 (2 hrs)	IM	500
		3.7	325 (1 hr)	IM	250
		0.26	390 (4 hrs)	Suppository	500
		2.6	260 (1 hr)	Oral, uncoated tablets	200

*μg./100 ml. serum.
†References: 4, Yunginger, J. W., *et al.*, 1966; 5, Jackson, R. H., *et al.*, 1964; 6, Bickerman, H. A., *et al.*, 1953; 7, Waxler, S. H., and Schack, J. A., 1950; 8, Barach, A. L., 1945.

(2) Ann. Allergy 29:135-138, March, 1971.

reaching the pulmonary circulation. It does not enter the upper gastrointestinal tract and short circuits the liver, thus avoiding some of the side effects observed after oral aminophylline: nausea, vomiting and abdominal distress. The dosages can be accurately controlled and easily changed from time to time by dilution with water. Rapidity on onset, peak blood level and persistence in the blood over 6 hours clearly indicate that effective therapeutic levels are achieved with rectal administration of this concentrated form of aqueous aminophylline in small volume.

► [Liquid theophylline by the rectal route is highly effective and will abort an acute attack of asthma. The liquid is far superior to the suppository, which in many instances is so slowly absorbed as to give poor blood levels. Patients can adjust the dose to their needs. Many a night call from an asthmatic patient will be prevented if he is instructed in the use of liquid theophylline.—Ed.]

Immediate Hypersensitivity Reaction to Aminophylline: Report of Case with Immunologic Confirmation by In Vitro Procedure. Toxic reactions to aminophylline are not uncommon and occasional deaths from this drug have been reported; immediate allergic reactions have not been described after therapeutic administration of the drug. Donald Wong, Alberto F. Lopapa and Zack H. Haddad[3] (Los Angeles County-Univ. of Southern California Med. Center) recently examined a patient who exhibited generalized pruritus and urticaria after aminophylline therapy.

Boy, 12, a known asthmatic since age 5, was fairly well controlled on sublingual isoproterenol, promethazine and theophylline-potassium iodide elixir. An acute asthmatic attack was treated with epinephrine and intermittent positive-pressure breathing with isoproterenol without much improvement. He had no known drug allergies. The white blood cell count was 9,200/cu. mm. with 6% eosinophils. Ephedrine was given, as well as 3 mg. aminophylline per kg. by intravenous push. Generalized pruritus and urticarial lesions on the trunk developed a few minutes after a dose of 120 mg. aminophylline. An intravenous dose of 5 mg. several hours later resulted in the same reaction. Diphenhydramine was then given. In the past, the symptoms had occurred about an hour after the patient took phenobarbital-ephedrine-theophylline tablets. Results of intradermal skin tests to several antigens were positive. Tests with aminophylline gave positive results but a scratch test was negative. Passive transfer of the immediate wheal-and-flare reaction was accomplished in a nonatopic recipient.

On testing serum by the rat mast cell degranulation technic, aminophylline gave significant degranulation but ephedrine and phenobarbital did not. Weeds, molds and anti-IgE also produced significant degranulation in the presence of the patient's serum.

This patient exhibited an immediate hypersensitivity-type reaction to a therapeutic dose of aminophylline and an identical reaction on challenge with a subsequent dose of the same drug by the intravenous route. Reactions of this type are mediated largely by immunoglobulin E. Aminophylline inhibits histamine release in the human basophil leukocyte system but does not inhibit rat mast cell degranulation; this may reflect a difference in these biologic systems.

► [An unusual reaction. Allergic patients receive repeated exposures to aminophylline, which offers ample opportunity for sensitization, but I have never seen an acute allergic response to it, caffeine or theobromine.—Ed.]

Amitriptyline and Asthma. Some evidence suggests that depression may be an important component of the emotional state of asthma patients. R. A. Meares, Jennifer E. Mills, T. B. Horvath, Judith M. Atkinson, Lan-

(3) J. Allergy 48:165-170, September, 1971.

Queen Pun and M. J. Rand[4] (Univ. of Melbourne), having noted improvement within a week in 8 consecutive asthmatics referred to a psychiatric outpatient clinic who were treated with 50 mg. amitriptyline 3 times daily, carried out a controlled clinical and experimental study.

The effect of 25 mg. amitriptyline intramuscularly on pulmonary function was studied in 12 asthmatics aged 17-54 years. No bronchodilator drugs were used on the day of the study. Guinea pigs receiving positive-pressure ventilation were given histamine, 5-hydroxytryptamine and acetylcholine intravenously to increase the intratracheal pressure and then were given tricyclic antidepressant drugs intravenously. Studies were also done on isolated bronchial smooth muscle.

In the 12 patients, no significant over-all change in forced expiratory volume in 1 second occurred with saline, but 11 patients showed a significant improvement after amitriptyline injection. The mean group improvement was 17%, a significant change. The amitriptyline effect was undiminished during 2 hours of observation. No significant changes in pulse rate were noted during the trial.

In guinea pigs, intravenous amitriptyline counteracted the bronchoconstrictor effects of histamine, 5-hydroxytryptamine and acetylcholine. The effect was especially marked with histamine. The effect was dose dependent in each instance. Doses that markedly counteracted bronchoconstriction had no effect on the blood pressure or heart rate. Amitriptyline counteracted the contracting effects of the same agents on isolated bronchial smooth muscle. It was particularly potent against histamine-induced contractions. Desipramine and imipramine were less potent than amitriptyline in reducing bronchoconstrictor responses in intact guinea pigs.

These findings indicate that amitriptyline may have a beneficial effect in asthmatics since it has a bronchodilator effect when bronchial smooth muscle tone is elevated. The effect is not likely to be due to potentiation of adrenergic mechanisms, anticholinergic activity or antidepressant effect. Amitriptyline may be concentrated in lung tissue and act there by antagonizing histamine and 5-hydroxytryptamine and possibly other bronchoconstricting substances. Also, it may have a role in management of asthma by permitting reduction of other medications.

► [A surprising effect from an old and useful drug. Most observers believe the antiasthmatic effect is secondary to the antidepressant action. Asthmatics, like other patients with chronic disabling diseases, become depressed. It is good to know that there is an unexpected dividend when amitriptyline is given.—Ed.]

Exanthem Due to Contact Allergen (Benzoin) Absorbed Through Skin is described by David A. Spott and Walter B. Shelley[5] (Univ. of Pennsylvania). Benzoin sensitivity has been described but in all allergic contact, eczema has been the major dermatologic manifestation. Patients who have allergic contact dermatitis may acquire secondary disseminated dermatitis. Data is presented on a patient with benzoin hypersensitivity in whom not only local allergic contact dermatitis occurred but in whom a generalized exanthem also developed.

Man, 22, sprained the right medial collateral ligament and had associated effusion into the knee joint. The entire right leg was painted with tincture of benzoin and a plaster cast was applied from above the ankle to just below the

(4) M. J. Australia 2:25-28, July, 3, 1971.
(5) J.A.M.A. 214:1881-1882, Dec. 7, 1970.

groin. After 23 days the skin beneath the cast began to itch and an eczematous rash was noted at the margins of the cast. When the cast was removed, a florid contact dermatitis limited to the cast area was revealed and 48 hours later a rash appeared on the chest, arms, face and back. The entire right leg showed an eczematous papulovesicular dermatitis. A patchy morbilliform eruption was present symmetrically on the upper arms, chest and back. The face had an erythematous and urticarial appearance that was especially marked about the eyelids. During treatment with the continuous application of saline-soaked gauze compresses covered with an impermeable plastic pad on the right leg, the generalized eruption became more prominent. The saline compresses were discontinued and betamethasone valerate without an occlusive bandage was applied to the right leg 3 times a day. Gradual improvement in both skin conditions was then noted. Patch tests revealed strong positive reactions for tincture of benzoin and the pure benzoin gum resin powder.

The total leg cast acted as a closed induction system, promoting percutaneous absorption of the benzoin with the resultant development of a localized and generalized hypersensitivity. The continuous compresses accentuated the problem by increasing the amount of antigen being absorbed. Had the benzoin exposure been generalized or had the patient been taking other drugs, the nature of the exanthemic element would have been obscured.

► [It is surprising that more cases of sensitivity to benzoin are not seen. The widespread use of this agent by topical application and in vaporizers must expose many patients to it. Sensitivity reactions probably are either ignored or misdiagnosed.—Ed.]

Hypothalamic-Pituitary-Adrenal Function in Asthmatic Patients Receiving Long-Term Corticosteroid Therapy. D. N. S. Malone, I. W. B. Grant and I. W. Percy-Robb[6] (Edinburgh) studied 6 men and 10 women, aged 31-66 years, taking 15.5 mg. prednisolone on 3 consecutive days per week (group A) and 5 men and 6 women, aged 26-75, taking 11.3 mg. prednisolone daily (group B). Group A patients had taken corticosteroids orally for 3-11 years and group B for 3-10 years. A control group of 9 men and 7 women, aged 26-78, with bronchial asthma severe enough to warrant consideration for corticosteroid therapy was also studied.

In groups A and B, blood samples were taken at 9-9:30 A.M. and 10:30-11 P.M. for measuring diurnal plasma 11-hydroxycorticosteroid (11-OHCS) concentration on days 1 and 4 after prednisolone withdrawal. In the control group, 11-OHCS levels were measured on 1 day only. Basal levels of plasma 11-OHCS and levels after hypoglycemia induced by insulin, 1 unit per kg. intravenously, were estimated in 5 patients each from groups A and B on day 4 after prednisolone withdrawal and in 5 controls. Blood samples were taken for glucose as well as 11-OHCS estimation at 30, 60, 90 and 120 minutes after insulin. Plasma 11-OHCS concentration was assayed by Mattingly's method. Blood glucose concentrations were assayed by glucose oxidase, using gum guaiacum as final indicator and an Auto-Analyzer.

In the 16 group A patients, mean plasma 11-OHCS concentration in the morning of day 1 was 4.4 μg./100 ml. and of day 4, 14.7 μg./100 ml. Evening values were 3.5 and 6.1 μg./100 ml., respectively. Both plasma 11-OHCS concentrations on day 1 were significantly lower than those in controls, but neither on day 4 was significantly different from those in controls. In the 11 group B patients, mean plasma 11-OHCS concentration in

(6) Lancet 2:733-735, Oct. 10, 1970.

the morning of day 1 was 3.3 μg./100 ml. and of day 4, 9.2 μg./100 ml., but evening values were 2.3 and 4.6 μg./100 ml., respectively. These values were significantly lower than plasma 11-OHCS values in controls in the morning and evening of day 1 and morning of day 4; no significant difference in values occurred in the evening of day 4. Blood glucose concentration fell to under 35 mg./100 ml. in every patient in which it was studied; in each case, this was a fall to below 50% of fasting concentration. In each group, 1 of 5 patients had normal responses to hypoglycemia in terms of plasma 11-OHCS; all 5 controls had normal responses.

The findings suggest that function of the hypothalamic-pituitary-adrenal axis in the unstressed state is less suppressed in patients on the intermittent corticosteroid regimen, but if subjected to stress, these patients are as much at risk as those given daily corticosteroid therapy.

► [Everything is relative. Perhaps we are not as safe as we thought when we give intermittent corticosteroid therapy. The lack or decrease in degree of the external signs, commonly associated with daily corticosteroid therapy, during intermittent therapy seems to be misleading. Maybe the benign appearance is masking a more fundamental defect.—Ed.]

Mechanism of Bronchoconstriction Due to β-Adrenergic Blockade: Studies with Practolol, Propranolol and Atropine. The β-receptor theory of bronchial asthma, holding that bronchial irritability is caused by diminished responsiveness of the β-adrenergic receptors of the bronchial glands, smooth muscle and mucosal vessels, has been used to explain the triggering of bronchoconstriction by a large variety of nonallergic stimuli. Michael H. Grieco and Richard N. Pierson, Jr.[7] (Columbia Univ.) defined the mechanism of bronchoconstriction after parenteral administration of β-adrenergic antagonists.

Study was made of 4 men and 2 women aged 35-59, all chronic asthmatics. Three were on maintenance prednisone therapy when studied. Respiratory measurements were made on two occasions with the patient supine. Ten-minute infusions of 25 or 50 mg. practolol or 10 to 20 mg. propranolol were delivered. In propranolol studies, aerosol atropine was administered for 10 minutes before the reinfusion of propranolol in the same dosage.

The control forced expiratory volume in 1 second (FEV_1) was reduced to an average of 31% of predicted normal. The Pao_2 was reduced only slightly and hemodynamic parameters were normal. Propranolol reduced the FEV_1 by 20% from control levels and reduced the Pao_2 and cardiac index insignificantly. Arterial pressure and heart rate did not change significantly.

Atropine markedly improved the FEV_1 and subsequent propranolol infusion did not reduce the expiratory volume. Practolol infusion did not reduce the FEV_1 or vital capacity.

Propranolol-induced bronchoconstriction in intact human asthmatics is reversed by atropine, suggesting that constriction is due to unopposed cholinergic impulses. Pulmonary receptors can be differentiated from cardiac β-adrenergic receptors by selective β_1-adrenergic antagonists such as practolol, which appear to spare the bronchial tree.

► [Rather convincing evidence. It is interesting to know that atropine can block the

(7) J. Allergy 48:143-152, September, 1971.

effect of propranolol on the bronchi because propranolol is occasionally needed even in the presence of asthma.—Ed.]

Effect of Disodium Cromoglycate on Seasonal Allergic Rhinitis was investigated by E. Holopainen, A. Backman, and O. P. Salo[8] (Helsinki) in 15 adults and 14 children. Criteria for selection were a known history of allergic rhinitis due to pollen, a positive skin test (scratch) and a positive nasal provocation test. The appearance of the nasal mucosa in each patient was assessed before and after the trial. At each examination, a nasal smear was taken and the nasal cytology was assessed.

The patients were divided at random into two groups. One group were given disodium cromoglycate and the other placebo for 4 weeks when the specific pollen was present in the atmosphere. Disodium cromoglycate, 10 mg., was administered with lactose, 10 mg., in a no. 3 capsule. Lactose, 20 mg., in a similar capsule was used as placebo. The contents of the capsule were insufflated into each nostril by means of a specific insufflator 4 times a day. Each patient was asked to record the degree of nasal symptoms (sneezing, rhinorrhea, nasal obstruction and itching) on a 0-3 scale. Also, each patient was asked to record the number of antihistamine tablets used per day.

Two patients were excluded from the analysis. Of the others, 13 received placebo and 14 the active drug. Disodium cromoglycate significantly reduced rhinorrhea and nasal obstruction. The difference in sneezing and itching between the two groups was not significant, but this is not surprising since sneezing is a variable symptom. Only 1 patient in the active group required a high dose of antihistamines, whereas 4 in the control group found it necessary to take antihistamines in any quantity; the difference between the groups was statistically significant. In 4 patients, the nasal state was considered to be worse at the end of the trial; all 4 had received placebo. Some patients in both the active and placebo groups were judged to have a swollen mucosa before entering the trial, and this condition was still present at the final examination.

This trial indicates that disodium cromoglycate affords effective prophylaxis in controlling the symptoms of seasonal rhinitis and reduces or even eliminates need for antihistamines in a proportion of patients.

► [Although the results look promising, they are not outstandingly so. In such a variable situation as allergic rhinitis there are so many elements introduced that it is difficult to be certain the drug is as good as it appears. I think more work should be done with this agent before it is made available for general use.—Ed.]

Disodium Cromoglycate in Hay Fever. Disodium cromoglycate is reportedly useful in asthma and rhinitis. In a double-blind trial, L. H. Capel and P. McKelvie[9] (Royal Nat'l Throat, Nose and Ear Hosp., London) assessed its value in the treatment of 28 men and 16 women with hay fever (grass pollen rhinitis). All patients had skin test results positive for grass pollen extract and symptoms for at least 2 hay fever seasons.

On rising, at noon and at 5 P.M., patients insufflated into each nostril 1 capsule of 10 mg. disodium cromoglycate mixed with 10 mg. lactose or a capsule of 20 mg. lactose. Chloropheniramine (4 mg. tablets) could also be taken if further help was needed. Treatment continued through 4 summer months. Patients were interviewed every 2 weeks.

(8) Lancet 1:55-57, Jan. 9, 1971.
(9) Ibid., pp. 575-576, Mar. 20, 1971.

Nine of the 22 patients taking disodium cromoglycate but only 1 of the 19 taking lactose felt that they were helped by treatment; 3 patients did not complete the trial.

The treatment is nonspecific. Insufflation 4 times daily would probably be better than the 3 times used in the study.

► [Not very impressive results. I have mixed feelings about cromoglycate; it is so erratic in its action. Some authors get good results, others get poor results. None get excellent results. Drugs that behave like this usually end up being of very limited value. —Ed.]

Effects of Isoprenaline plus Phenylephrine by Pressurized Aerosol on Blood Gases, Ventilation and Perfusion in Chronic Obstructive Lung Disease. A fall in arterial oxygen tension or saturation may be produced by intravenous aminophylline, subcutaneous adrenaline, isoprenaline inhalation, orciprenaline inhalation, salbutamol inhalation, papaverine and papaverine plus isoprenaline inhalation and subcutaneous atropine. Theoretically, this fall could be prevented by adding a pulmonary vasoconstrictor or a cardiac slowing drug to a β-adrenergic bronchodilator.

L. H. Harris[1] (Newsham Gen'l Hosp., Liverpool, England) used an aerosol of isoprenaline and phenylephrine to treat 17 men and 6 women, aged 37-67, with chronic obstructive lung disease known to be reversible by subcutaneous injection of 0.5 mg. adrenaline. Ventilation, blood gases, cardiac output and physiologic shunt and ventilation-perfusion were assessed after inhalation of inert propellant and 30 minutes after inhalation of 2 puffs of aerosol, each puff containing 0.16 mg. isoprenaline hydrochloride and 0.24 mg. phenylephrine bitartrate.

Only 13 of the 23 patients showed an increase in FEV_1 of 20% or more after the test. In these 13 patients, there were significant increases in FEV_1, carbon dioxide output and alveolar ventilation and a significant decrease in the physiologic dead space-tidal volume ratio, indicating an increase in effective ventilation. Expiratory volume and oxygen consumption changes were insignificant.

Arterial oxygen tension was significantly increased and arterial carbon dioxide tension significantly decreased, also indicating efficacy of the increased ventilation. There were no significant changes in arterial oxygen saturation or pH.

There was no significant change in either cardiovascular output or physiologic shunt, suggesting that any cardiovascular response was minimal. Over-all ventilation-perfusion ratios were significantly improved. There was no significant change in the alveolar-arterial oxygen gradient.

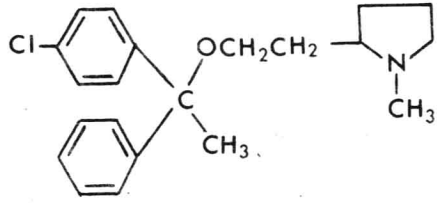
The addition of phenylephrine to isoprenaline probably prevents the increase of hypoxemia which may result from the disproportionate ventilation-perfusion ratio produced by sympathomimetics or xanthines used alone. The combination aerosol has a satisfactory bronchodilator effect and is safe if used by a severely hypoxic patient unaware of the seriousness of his condition.

► [A good point. Phenylephrine does seem to alter favorably the effect of isoprenaline. Further compromising of arterial oxygen can be serious in hypoxic patients. Unfortunately, drugs that further reduce arterial oxygen are frequently used in these seriously ill patients. On the whole, most clinicians prefer to use a single agent for inhalers. Usually isoproterenol is chosen. It is obvious from the author's results that further studies are needed.—Ed.]

(1) Brit. M. J. 4:579-582, Dec. 5, 1970.

Some Central and Peripheral Effects of Meclastine, a New Antihistaminic Drug, in Man. Meclastine is a benzhydryl ether (Fig. 1) reported to have marked antihistaminic activity but minimal anticholinergic and central nervous depressant effects. Annmarie Hedges, M. Hills, William P. Maclay, A. J. Newman-Taylor and Paul Turner[2] (London) made a double-blind study of its effects in 9 normal volunteers aged 19-43.

Meclastine (1 mg.), chlorpheniramine maleate (4 mg.) or placebo was administered orally 28, 16 and 4 hours before intradermal injection of 0.1 ml. histamine acid phosphate (0.5 mg./ml.) and, 10 cm. away, 0.1 ml. normal saline. The diameter of the wheals produced was measured 5, 10



(+)-2-[2-(p-chloro-α-methyl-α-phenylbenzyl)oxy]ethyl]-1-methylpyrrolidine

Fig. 1.—Formula for meclastine. (Courtesy of Hedges, A., *et al.*: J. Clin. Pharmacol. 11:112-119, Mar.-Apr., 1971.)

and 20 minutes after the injections. Both drugs significantly inhibited formation of wheals, but meclastine was significantly more potent than chlorpheniramine.

Tests of central nervous system function (critical flicker frequency, disk dotting and serial subtraction) were made 4 hours after a single dose of 25 mg. promethazine hydrochloride, 1 mg. meclastine hydrogen fumarate or placebo. In multiple dose studies, 1 mg. meclastine hydrogen fumarate or placebo was given 28, 16 and 4 hours before the central nervous system tests. Promethazine produced a significant fall in critical flicker frequency, whereas meclastine had little, if any, central depressant effect. The disk dotting and serial subtraction tests were not as sensitive as critical flicker frequency in demonstrating differences between the drugs.

► [This new antihistamine has a structure similar to other antihistamines, and resembles diphenhydramine in several aspects and triprolidine in others. Both of these antihistamines produce drowsiness. Although meclastine is potent, it remains to be seen whether it is a real advance. Its chemistry would not suggest any unusual properties.—Ed.]

Recurrent Hepatitis Due to Methoxyflurane Anesthesia. Sensitization to halothane rarely may cause severe hepatitis. Alan I. Brenner and Marshall M. Kaplan[3] (Tufts-New England Med. Center) describe a patient in whom methoxyflurane, a halogenated ether structurally related to halothane, produced a similar type of hepatitis.

Woman, 49, with a history of asthma, hay fever and dermatitis secondary to ampicillin, had had an uncomplicated hysterectomy and laminectomy, both with

(2) J. Clin. Pharmacol. 11:112-119, Mar.-Apr., 1971.
(3) New England J. Med. 284:961-962, Apr. 29, 1971.