THE YEAR BOOK
of
DRUG THERAPY

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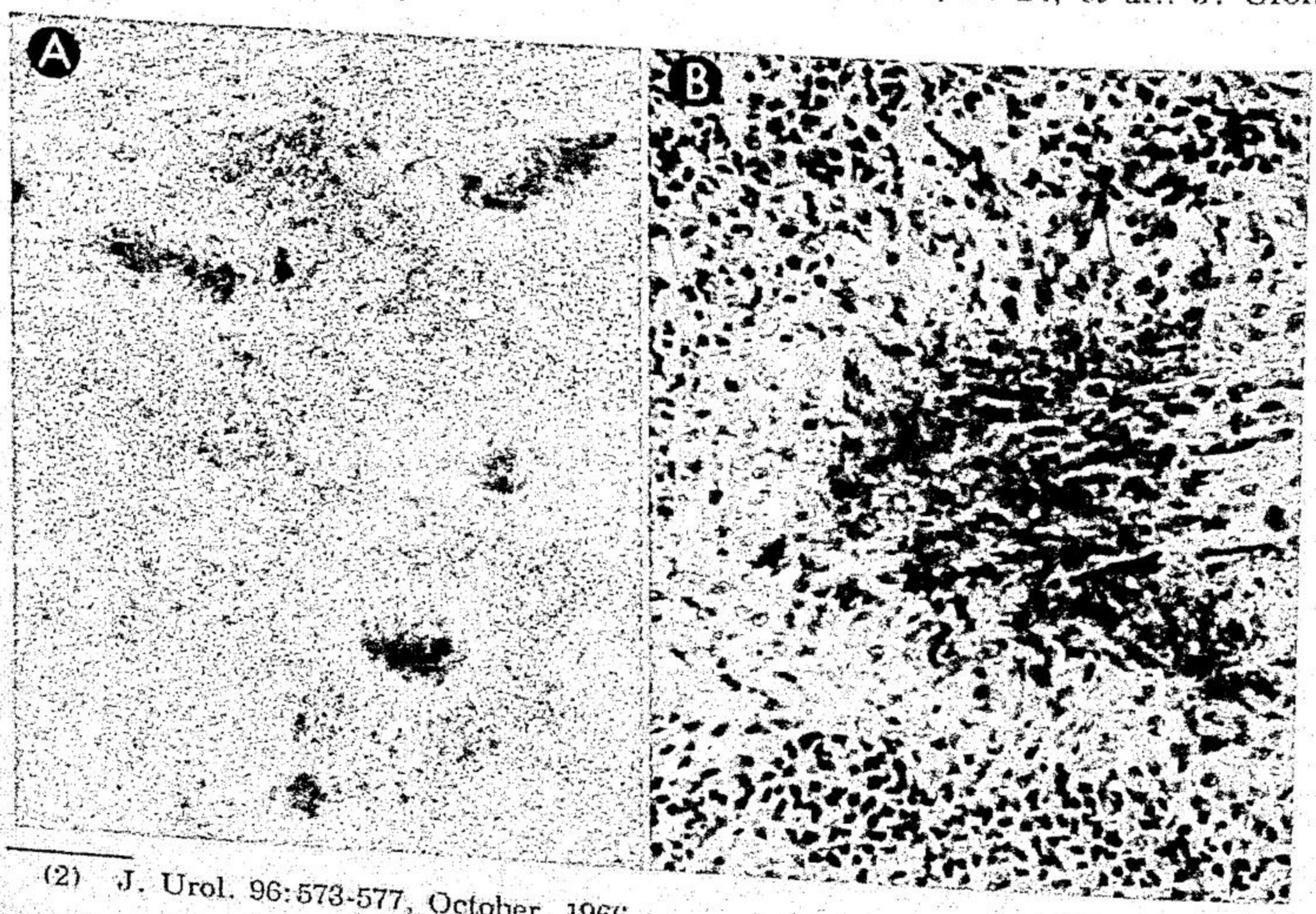
Prednisone is the steroid of choice because it is cheap and effective. It was rarely found necessary to exceed a daily starting dose of 20 mg.

► [It is notable in this article that, although the authors have used ACTH and corticosteroids twice as frequently in the most recent 8 years as in the preceding 8 years, the increase was principally due to short courses given to abort exacerbations that were not responding to conventional therapy, or in some cases to avert hospitalization. If the drugs *must* be used over a relatively long period, switching from one compound to another is sometimes helpful in avoiding the cushingoid state.—Ed.]

Allergic Granulomas of the Prostate: Treatment with Steroids is described by Panayotis P. Kelalis, Edgar G. Harrison, Jr., and David C. Utz[2] (Mayo Clinic and Found.). Allergic granuloma of the prostate gland is a rare but dangerous condition, which until now has occurred exclusively in patients with bronchial asthma. It is marked by distinct features in both the history and pathology. The lesion, a necrotizing granuloma, is thought to result from a prostatic hypersensitivity reaction initiated by an exacerbation of asthma. Microscopically, scattered stellate areas of fibrinoid necrosis are surrounded by palisading histiocytes and associated with an intense eosinophilic cell infiltration (Fig. 1).

Fig. 1.—Allergic granuloma of prostate. *A*, scattered areas of fibrinoid necrosis with intense infiltration of eosinophils; hematoxylin-eosin, reduced from ×50. *B*, area of fibrinoid necrosis surrounded by palisading histiocytes and abundant eosinophils; hematoxylin-eosin, reduced from ×200. (Courtesy of Kelalis, P. P., *et al.*: J. Urol. 96:573-577, October, 1966.)



(2) J. Urol. 96:573-577, October, 1966.

Man, at age 24 had burning on urination followed by marked symptoms of prostatic obstruction associated with hardness and fixity of the prostate, which had been found on digital rectal examination to be the size of a tennis ball. Transurethral prostatic resection had relieved symptoms greatly. A year later the symptoms recurred. Prednisone therapy, given for several days, brought much clinical improvement. During the next 3 years he continued to take the drug intermittently in varying doses.

In November, 1964, at age 28 he again experienced frequency, dysuria and perineal pain, with fever and later left testicular swelling. History disclosed that asthma had affected his own son and his father, brother and mother's brother. A sister had allergic rhinitis. The patient himself, however, had no seasonal allergy or clinical manifestations of asthma. At age 12 he had had what appeared to be eczema.

A large hard, prostatic mass, locally invasive through the prostatic capsule and involving the seminal vesicles, was noted on digital rectal examination. Multiple nodular lesions not exceeding 1 cm. in diameter were present around the penile base. Excretory urography demonstrated severe right hydronephrosis and hydroureter; the left kidney was functionless. Retrograde pyelography showed a large hydronephrotic mass secondary to obstruction in the left pelvic ureter. Transurethral biopsy of the prostate revealed allergic granuloma, as did biopsy of a nodule from the base of the penis.

Prednisone therapy was instituted with doses of 10 mg. given 4 times daily. Symptoms were almost immediately relieved. On the 3d day of treatment, rectal digital examination verified that the prostate was distinctly softer and much reduced in size. On the 5th day of treatment, excretory urography showed marked reduction of the right hydronephrosis. The patient was dismissed with a program for gradual reduction of prednisone dosage to 5 mg. twice daily. By June, 1965, he was taking 15 mg. prednisone daily and was entirely asymptomatic. However, if he discontinued the medication, burning on urination immediately returned and the penile nodule became tender, painful and enlarged.

This is the first reported case of allergic granuloma of the prostate in which treatment with steroids was used. Such treatment should be instituted promptly on discovery of the disease, with care that the steroid dosage be high enough until regression has occurred and a state of relative normalcy has been achieved.

► [This diagnosis has not been made on either the surgical or the necropsy services at our hospital since 1951 when the entity was described.—Ed.]

Evidence for Local Action of Intranasal Dexamethasone Aerosols in Suppression of Hay Fever Symptoms. This study by Philip S. Norman, Walter L. Winkenwerder, George W. Murgatroyd, Jr., and John W. Parsons[3] (Johns Hopkins Univ.) was to determine whether the therapeutic effect of the aerosol

(3) J. Allergy 38:93-99, August, 1966.

is due to direct local action of the steroid or due first to systemic absorption followed by its characteristic peripheral anti-inflammatory action.

Each spray delivers, at the nozzle, the equivalent of 0.08 mg. dexamethasone as the alcohol; thus, 12 inhalations deliver 1 mg. at the nozzle. Capsules contained 0.1 mg. dexamethasone; the total daily dose of 0.3 mg. is estimated to give the same metabolic effect as the aerosol. Some patients received dexamethasone aerosol and placebo capsules, others received placebo aerosol and dexamethasone capsules and others served as controls, receiving placebo aerosol and placebo capsules. At the beginning of the ragweed season, patients were instructed to use the aerosol unit, 2 whiffs in each nostril 3 times a day, and at the same time to take a capsule. Two weeks later, the 106 patients were switched from one treatment plan to another.

The superiority of nasal dexamethasone aerosol was demonstrated by the number of patients who were better during nasal administration of the drug than during either oral administration or placebos. Of 31 patients who used nasal dexamethasone during one period and placebos during the other, 25 had lower scores during nasal medication and 3 had lower scores during placebo. Three patients had the same score during each period. A similar ratio was obtained among patients who compared nasal dexamethasone with oral steroid. There was essentially no difference when oral dexamethasone was compared with placebos.

► [An unfortunate feature of this study is the fact that a trial of all three combinations in a complete crossover study was impossible because of the shortness of the pollen season. Nevertheless, the findings are extremely interesting, although it is hoped that the authors' admonition to delay routine use of this type of therapy until further information is available will be heeded.—Ed.]

BRONCHOPULMONARY DISORDERS

Serum Theophylline Levels and Control of Asthma Following Rectal Theophylline [Monotheamin]. John W. Yunginger, M. Shigeta, I. Smith, Martin Green and Hans G. Keitel[4] (Jefferson Med. College) report results of giving rectal retention enemas containing variable amounts of theophylline or isotonic saline to 51 children with intractable asthma.

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(4) Ann. Allergy 24:469-483, September, 1966.

When theophylline was given, the serum theophylline concentration increased significantly in all patients within 15 minutes and reached a peak value within 60 minutes in two-thirds. Correlation was significant between the highest serum theophylline concentration attained and the dose of theophylline monoethanolamine expressed in milligrams per kilogram weight. In most of the symptomatic patients some clinical improvement of the asthma was observed. Total vital and the maximum breathing capacities improved.

There was no significant correlation between serum theophylline concentration and degree of clinical improvement or incidence of side actions. In 43% of the patients given theophylline and 40% of those given isotonic saline rectally, untoward reactions, most of them minor and all transitory, were recorded.

The suggested dose of rectal theophylline for treatment of asthma in children is 5 or 6 mg. theophylline monoethanolamine per kg. At this dosage toxicity of appreciable severity is infrequent and might be due simply to rectal administration per se. The minimal toxic dose and the therapeutic dose overlap in a few children.

The significant correlation found between the dose of theophylline administered and the highest serum concentration achieved implies regularity of absorption of theophylline when administered in a retention enema and contrasts with the unpredictability of absorption reported with rectal suppositories.

Of the untoward reactions, nausea and headache were the most common and not infrequently occurred at rather low theophylline concentrations, but all symptoms cannot be ascribed to theophylline toxicity. The finding of similar "toxic" symptoms in the children who received isotonic saline rectally supports this view.

► [The authors note an incidence of untoward reactions in the children given only isotonic saline rectally that was practically as high as in the children who were given theophylline by the same route, and they ascribe this to symptoms "inherent in the acute asthmatic episode itself." But what of the procedure itself as inducive of reaction in these youngsters, whose ages were said to be between 4 and 15 years, without stipulation of how many were in the younger range? The insertion of a rectal unit, followed by bleedings at 15-, 30-, 60- and 120-minute intervals, with simultaneous recording of the vital signs, must surely have been very disturbing affairs in a large proportion of the patients. I find the most rewarding of the observations made in this excellent article to be the regularity of absorption of theophylline when given by the retention enema, in contrast to the unpredictable absorption from a suppository.—Ed.]

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Metaproterenol [Alupent], a New Bronchodilator: Comparison with Isoproterenol [Isuprel]. A new bronchodilator, metaproterenol, has recently become available in both oral and aerosol forms. It is a derivative of isoproterenol, which has been found to have a greater bronchodilating effect and a longer duration of action, presumably because of better absorption. Also, it causes less tachycardia, arrhythmia and hypotension. Herman H. Pelz[5] (Jewish Hosp., Brooklyn) compared isoproterenol and metaproterenol aerosols by spirometric tests in a double-blind study. The 8 males and 14 females studied were aged 12-61; 4 were aged 12-16. Most patients had moderate to severe bronchial asthma, a few had pulmonary emphysema, and several had chronic bronchitis. All had recurrent acute bronchospasm. They received single doses of two whiffs of metaproterenol (0.65 mg. each) or isoproterenol (0.075 mg. each).

Metaproterenol was superior to isoproterenol in every lung function test except the forced expiratory volume (FEV) at 30 minutes. The superiority was significant for the FEV and 1-second FEV at 1 and 2 hours and for the midexpiratory flow rate at 2 hours. Metaproterenol was superior in improving pulmonary function in most patients and the effect lasted longer. At 2 hours, 82% of the patients on metaproterenol showed improvement in the 1-second FEV, compared with only 23% of those on isoproterenol. In 7 of the 8 patients with combined disorders of emphysema or chronic bronchitis with or without asthma, the new drug produced greater and longer improvement than isoproterenol. One patient reported feeling worse after either medication; no other patient reported any side effects with either drug.

Metaproterenol appears to have distinct advantages over isoproterenol, affording prompt and more prolonged relief of acute bronchospasm.

► [We continue to have favorable reports on the use of this new drug as a bronchodilator, but a fact not often brought to the attention of the readers of these accounts is that addiction to the use of sympathomimetic amines in aerosol form is not an unusual occurrence. Patients often spray several times daily, even when assured by their physician that their difficulty is thereby increased. Instances of this sort are exemplified in the immediately following article.—Ed.]

Iatrogenic Asthma Associated with Adrenergic Aerosols. John F. Keighley[6] (State Univ. of New York, Syracuse) re-

(5) Am. J. M. Sc. 253:321-324, March, 1967.
(6) Ann. Int. Med. 65:985-995, November, 1966.

ports 3 cases which demonstrate that, in susceptible patients, administration of a therapeutic dose of isoproterenol as an aerosol may precipitate severe prolonged airway obstruction indistinguishable from a clinical attack of asthma.

Man, 40, was admitted in status asthmaticus. Childhood asthma had remitted spontaneously at puberty. A mild productive cough had been noted in recent years and there was a tendency for mild wheezing to develop with minor respiratory infections. Isoproterenol by nebulizer had provided immediate symptomatic relief, but progressively more frequent inhalations had become necessary. On admission, the chest findings were those of moderately severe asthma. Therapy with subcutaneous epinephrine, intravenous Aminophylline and an isoproterenol aerosol gave no immediate improvement; intravenous hydrocortisone was added and he improved rapidly. However, the symptoms returned 2 days after steroids were discontinued. Aerosolized isoproterenol was given by intermittent positive-pressure breathing along with the steroids, but progressive dyspnea developed. The patient became cyanotic and unrousable and stopped breathing spontaneously. Within 24 hours of the cessation of isoproterenol, he felt much better.

In a placebo study, inhalation of 1:400 isoproterenol in water led to an increase in forced expiratory volume and midexpiratory flow rate and progressive ventilatory impairment. Rapid improvement was seen when steroid therapy was started and all aerosols were stopped. A sustained response was later obtained using 0.25% isoproterenol given from a microaerosol generator. Symptoms and a fall in airway resistance followed the administration of atropine methonitrate and isoproterenol from freon-powered cartridges at a time when the patient was in complete remission.

Airway obstruction was controllable in all 3 patients with conventional therapy including high doses of steroids, but complete remission was not attained until all adrenergic aerosols were withdrawn. The mechanism of this response is not known. The delayed onset of the reaction, its slow and sustained progression, the poor response to parasympatholytic drugs and antihistamines and the reversibility with sympathomimetic agents and corticosteroids are consistent with a smooth muscle response to a slow-acting substance. Possibly, degradation products formed in the course of aerosol generation and deposition could sensitize susceptible individuals after repeated exposure. The possibility of this form of response should be considered in asthmatic patients who are refractory to treatment and who are receiving sympathomimetic aerosol therapy.

► [Dr. David M. Glassner of our staff comments as follows:

"The phenomenon of a decreasing response with increasing use of aerosols has been reported many times since it was first brought to our attention by Benson and Perlman 20 years ago (J. Allergy 19:129, 1948). The pathophysiology underlying the reaction is believed to be bronchial irrita-

tion, increased secretion and loss of ciliary action. With still larger and more frequent doses of aerosols, or larger particles landing on isolated areas of the mucosa, ulceration occurs with actual loss of cilia and with epithelial exfoliation (J. V. Galgiani, F. Proescher, W. Dock and M. L. Tainter, J.A.M.A. 112:1929, 1939). However, the process suggested by Keighley, if it actually occurs, would be expected to be free from such bronchial pathology, as these patients were studied in remission with controlled dosages of aerosols. Certainly, a worthwhile project would be serial spirometric studies at 2-hour intervals for 24-36 hours after a test dose of aerosol therapy on a large series of such patients whose asthma was currently in remission."—Ed.]

Effects of Injections of Chorionic Gonadotropin on Adolescent Asthmatic Boys. Christopher Grimaldi[7] (Bristol, England) treated 37 asthmatic boys, aged 10½-16 years, with chorionic gonadotropin (Pregnyl) in the past 8 years. The patients accepted the injections fairly well. Three injections of Pregnyl (1,500 I.U.) a week were given for 6-8 weeks, followed by 2 injections a week for 2 weeks and then 1 injection a week for 2 weeks.

The results are shown in the table. The average weight gain in 8 weeks was 12.3 lb., the average gain in height was 1.5 in. and the average increase in chest expansion was 1.6 in. In 1 boy, treatment was stopped because of severe headache and hemospermia. All boys were fairly severe asthmatics in whom normal treatment methods had failed to provide much relief. There was a great range of weight at all ages. The degree of airway obstruction was unchanged in most cases. There was no apparent premature epiphysial closure leading to reduced adult height in this series.

The results were encouraging. There was improvement in the patients' self-confidence. However, a fairly large proportion of boys lose their asthma at puberty in any case. It appears that it might be worthwhile to try this treatment in boys who have not responded to other treatment.

RESPONSE OF 37 ASTHMATIC BOYS TO A COURSE OF CHORIONIC GONADOTROPIN

Age (years)	Symptom free	Much improved	Still asthmatic	Total
10½	3			4
11	7		1	9
12	4	1	2	5
13	4	1		6
14	7		1	7
15	5			5
16	1			1

(7) Practitioner 198:559-562, April, 1967.

► [This uncontrolled study is by no means convincing, but I have included it because the trials were made as a logical result of clinical observation Any approach that even promises to be of value in childhood asthma is worth noting so that extensive trials may be made.—Ed.]

Controlled Study of Iodotherapy for Childhood Asthma. Constantine J. Falliers, William P. McCann, Hyman Chai, Elliot F. Ellis and Nasser Yazdi[8] (Jewish Nat'l Home for Asthmatic Children, Denver) conducted a 3-year double-blind study of iodotherapy in 36 boys and 16 girls, aged 8-16 years (median age, 11.5 years). Steroid therapy was required by 32 patients for temporary control of asthma at some time during the study. Each child received 3 courses of treatment, each lasting 12 weeks: (1) 100 mg. potassium iodide 3 times daily; (2) 300 mg. 3 times daily; and (3) placebo 3 times daily. All 6 possible treatment sequences were equally represented (table). Each child served as his own control.

A definite, uniform trend was found toward improvement in all asthma-related variables (history, physical examination, bronchodilator inhalations, steroid therapy and peak expiratory flow rates) when the high-dose potassium iodide regimen was compared with placebo. The trend appeared great enough to suggest true improvement in at least some children. Passage of time alone did not influence weekly scores for any of the variables recorded. Reduction in prednisone dosage was possible during high-dose potassium iodide treatment; the other two regimens had no appreciable effect on steroid dosage.

Sex and age distributions were similar in the improved and unimproved groups, as was incidence of undesirable side effects. The mean serum inorganic iodide levels were consistent with the dose of potassium iodide given. No meaningful correlation between these levels and the therapeutic response could be established. Thyroid enlargement was noted after 3-6 weeks of iodide therapy in 18 patients.

TREATMENT SEQUENCE FOR IODOTHERAPY FOR ASTHMA

	Period (12 weeks each)		
Group	*A*	*B*	*C*
I	KI, 100 mg.	KI, 300 mg.	Placebo
II	KI, 100 mg.	Placebo	KI, 300 mg.
III	KI, 300 mg.	KI, 100 mg.	Placebo
IV	KI, 300 mg.	Placebo	KI, 100 mg.
V	Placebo	KI, 100 mg.	KI, 300 mg.
VI	Placebo	KI, 300 mg.	KI, 100 mg.

(8) J. Allergy 38: 183-192, September, 1966.