

Complications of long-term steroid therapy for asthma

Phillip Lieberman,* Roy Patterson, and Richard Kunske
Chicago, Ill.

Fifty asthmatic patients on long-term prednisone therapy were evaluated for complications associated with steroid administration. The incidence of these complications was compared with the incidence of similar complaints in an age- and sex-matched group of asthmatic patients not taking corticosteroids. Results indicate that there is an increase in weight gain, fluid retention, appetite, easy bruisability, hypertension, diabetes mellitus, epigastric complaints, and electrolyte disturbances in the steroid group. However, most of these complications were of a benign nature and were easily managed. There was no significant increase in documented peptic ulcer, tuberculosis, cataracts, or psychosis. Frequency of complications increased with the age of the patient and the dose of steroids but was not correlated with the duration of therapy.

The present study evaluates the incidence and severity of complications of long-term steroid therapy in asthmatic patients. The study differs from most previous reports in that a control group is utilized, and factors such as dose, duration of therapy, and patient age are examined with respect to their effects on these complications. The frequency and severity of weight gain, fluid retention, increased appetite, easy bruisability, hypertension, tuberculosis, cataracts, epigastric distress, peptic ulcer, hypokalemia, diabetes mellitus, and mental disturbance in a steroid-treated group were evaluated. The results have been compared with those of other authors.¹⁻¹⁸ No attempt was made to study adrenal-suppressive effects, since this has been adequately reviewed elsewhere.¹⁹⁻²⁰

MATERIALS AND METHODS

All patients evaluated in this study were attending the Northwestern University Medical School Outpatient Allergy Service. A treatment group consisting of 50 asthmatic patients taking prednisone continuously for at least 2 years was compared with an age- and sex-matched control group of asthmatic subjects not taking prednisone. Both groups were followed for a period of approximately 3 months. All socioeconomic classes were represented in each group. Both groups were managed by the same set of physicians and were on standard asthma therapy including regular bronchodilators, immunotherapy for inhalant antigens, and intermittent antibiotic therapy as indicated by the nature of the asthma and the periodic presence of bacterial infection, respectively.

From the Section of Allergy-Immunology, Department of Medicine, Northwestern University Medical Center.

Supported in part by United States Public Health Service Training Grant 5TO1 A1-00057, and by the Ernest S. Bazley Asthma Research Fund to Chicago Wesley Memorial Hospital and the Northwestern University, Chicago, Ill.

Received for publication Sept. 22, 1971.

*Reprint address and present address: Section of Allergy, Department of Medicine, University of Tennessee Medical School, Memphis, Tenn.

TABLE I. Comparison of steroid-treated and control groups

Group	No. of patients	Men	Women	Mean age	Mode age	Age range	Age distribution (yr.)		
							Group I	Group II	Group III
Steroid	50	14	36	44.8	45	15-77	<25 7	25-50 24	>50 19
Control	50	13	37	45.6	45	16-76	7	26	17

TABLE II. Dose of prednisone and duration of therapy employed in steroid-treated patients

Variables	Range	Mean	Median
Daily dose (mg.)	2.5-25	9.4	10
Duration of therapy (mo.)	24-216	57	49
mg.-mo. Therapy*	120-3,240	662	480

*mg.-mo. = Average daily dose times months of therapy.

TABLE III. Division of steroid-treated asthmatic patients into groups based upon age, dose of prednisone, duration of therapy, and milligram-months of therapy

Group	Age (yr.)	Dose (mg.)	Treatment duration (mo.)	Therapy mg.-mo.*
I	<25 (7)	<7.5 (9)	24-47 (17)	120-349 (17)
II	25-50 (24)	7.5-12.4 (23)	48-60 (16)	350-650 (17)
III	>50 (19)	>12.4 (18)	>60 (17)	>650 (16)

Number of patients in each group is shown in parentheses.

*mg.-mo. = Average daily dose times months of therapy.

Steroid treatment group

The steroid-treated group consisted of 50 patients with asthma who required regular steroid therapy to control symptoms. The majority of these patients were referred to the Allergy Service subsequent to the initiation of chronic corticosteroid therapy. In each case periodic attempts were made to reduce the dose or discontinue the steroids entirely, and each patient was maintained at the smallest dose which would prevent disabling symptoms. Prednisone was the only corticosteroid preparation used.

Each patient was questioned about the presence of the adverse effects of steroids. Blood pressures were obtained, and each patient was examined for the presence of edema, cataracts, and striae. Serum sodium, potassium, and 2 hour postprandial glucose determinations were made. Upper gastro-intestinal roentgenograms were ordered when indicated by the presence of epigastric complaints.

Control group

The control group consisted of 50 age- and sex-matched asthmatic patients not taking prednisone. The control group was evaluated in exactly the same fashion except that serum sodium, potassium, and glucose determinations were not routinely performed. To obtain control comparisons for sodium and potassium levels, the treatment group values were compared to results obtained from a random sampling of 500 determinations performed in the laboratory of the Northwestern University Clinics. Normal standards for serum glucose were also supplied by this clinical laboratory. The control incidence of glucose intolerance was based upon data published by the United States Department of Health, Education, and Welfare.²¹ It should be noted that the incidence of diabetes mellitus cited in the control group represents an approximation of the over-all incidence in the population as a whole and does not indicate a distinction with regard to the age of the patient studied. Any blood pressure reading greater than 160 systolic or 90 diastolic was considered abnormal.

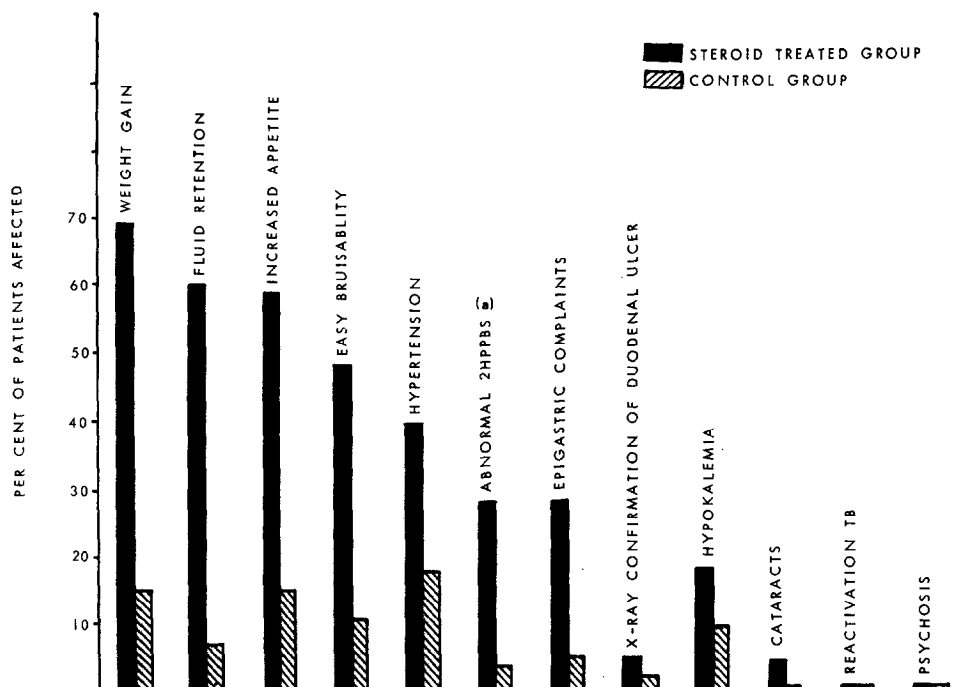


FIG. 1. Comparison of incidence of adverse effects in steroid-treated and control groups. 2HPPBS = 2 hour postprandial blood sugar. (a), See text for interpretation.

The effect of four variables on the incidence and severity of side effects was evaluated. These variables were patient age, dose of prednisone, duration of therapy, and a dose-duration index obtained by multiplying the dose in milligrams by the duration of therapy in months. This index was called milligram-months.

RESULTS

Table I illustrates a comparison of the characteristics of the steroid-treated and control groups. The two groups were well matched according to age and sex.

There was an obvious increase in frequency of side effects in the steroid-treated group (Fig. 1). The most common adverse effects were weight gain, fluid retention, increased appetite, and easy bruisability. There were no cases of reactivated tuberculosis or psychosis.

The mean daily dosage, duration of therapy, and milligram-months of therapy values are seen in Table II. The mean daily dose ranged from 2.5 to 25 mg. The mean for the entire group was 9.4 mg. of prednisone. The duration of therapy ranged from 24 months to 216 months (18 years), with a mean of 57 months for the entire group.

In order to evaluate the effect of age and dose and duration of therapy on the incidence of adverse effects, the steroid-treated patients were divided into three groups based on the age of the patients, the dose of prednisone, and the duration of therapy. The criteria for these divisions and the number of patients in each group are shown in Table III.

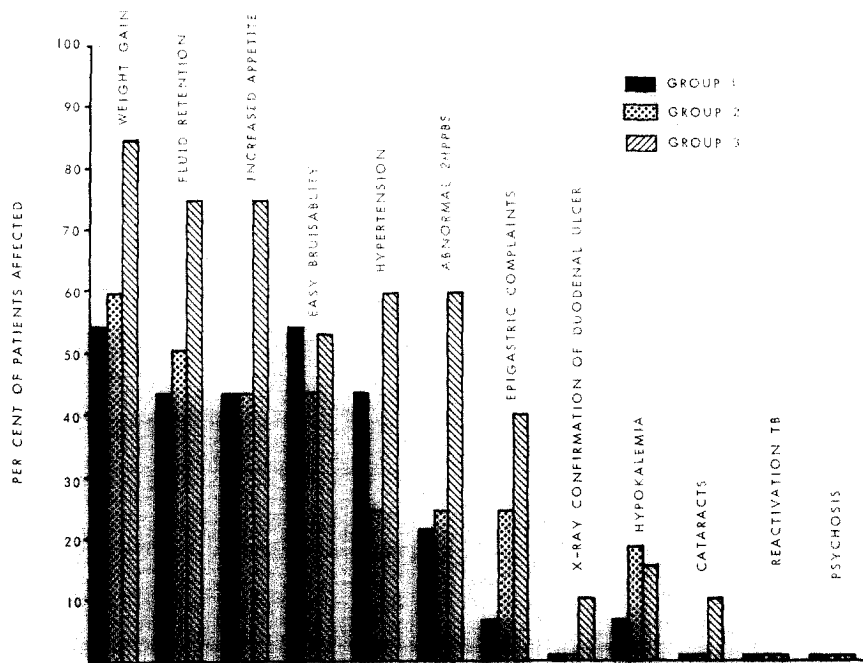


FIG. 2. Effect of age on incidence of adverse effects. Group I, less than 25 years; Group II, 25 to 50 years; Group III, greater than 50 years.

The incidence of side effects was calculated for each group shown in Table III. There was an increased incidence of most side effects with increasing age (Fig. 2). A similar correlation was found as the dose of prednisone increased (Fig. 3). The duration of treatment (Fig. 4) and the milligram-months of therapy (Fig. 5) seemed to have less effect on the frequency of complications of steroid therapy.

DISCUSSION

These data reveal that there was an increased incidence of complications in the steroid-treated group. The most prominent increase was in the symptomatic complaints of increased appetite, fluid retention, easy bruisability, and weight gain. These complaints were difficult to assess because of their subjective nature. Objective confirmation, such as ankle edema, was often lacking. Documentation of weight gain obtained by serial weights could not be accomplished because all of the patients had been on steroids prior to the initiation of the study. The frequency of these complaints increased with age and increasing dosage.

The difference in the incidence of more serious complications between the steroid and the control groups was less marked. The incidence of hypertension in the steroid group was 40 per cent, compared with 18 per cent in the control group. The blood pressure elevations in the steroid group ranged from 160/90 to 220/112. There were no instances of renal insufficiency or myocardial failure. However, 8 of the 20 hypertensive patients in the steroid group were taking or had taken antihypertensives. As expected, the frequency of hypertension

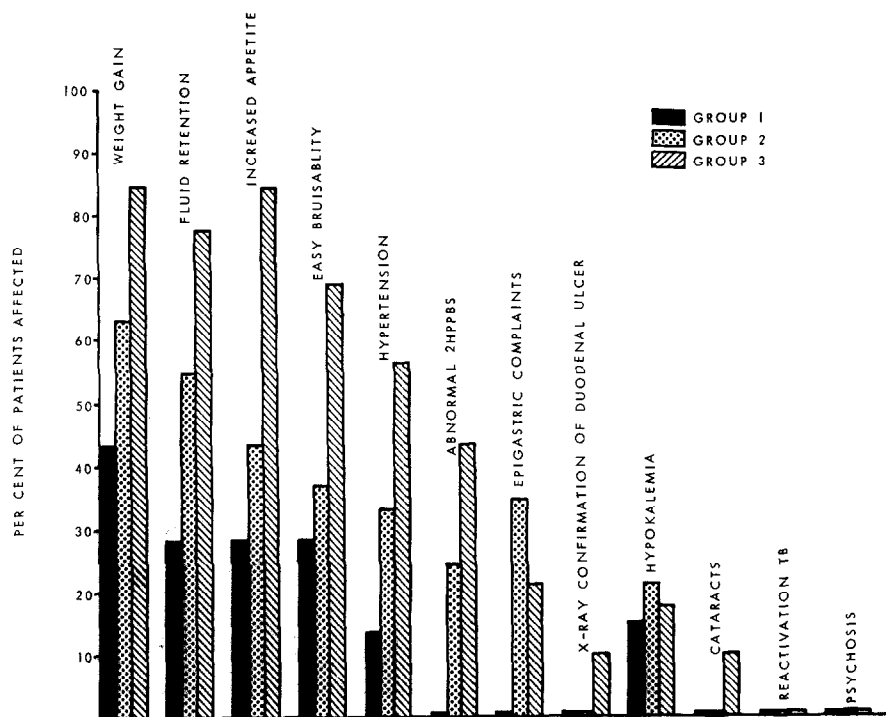


FIG. 3. Effect of dose of prednisone on incidence of adverse effects. Group I, less than 7.5 mg. daily; Group II, 7.5 mg. to 12.4 mg. daily; Group III, greater than 12.4 mg. daily.

increased with increasing age and dose. There was no definite correlation with duration or milligram-months of therapy.

The pattern of glucose intolerance in the steroid group was similar to that of hypertension. There was a 28 per cent incidence in the steroid group. This is higher than that recorded for the population as a whole.²¹ However, it should be noted that the treatment group consisted, for the most part, of patients 25 years of age and older, whereas the figure cited for the incidence of glucose intolerance in the control group was based on that in the population taken as a whole, without regard to age. Since the incidence of glucose intolerance is known to increase with age, the higher incidence in the treated group may be somewhat overstated and represent an artifact produced by the age of the treated group. As with hypertension, there was a positive correlation with age and increasing dose but no definite relation to duration or milligram-months of therapy. The abnormal levels ranged from 130 to 330 mg. per cent. There were no episodes of acidosis, and all patients were managed satisfactorily with oral agents or diet alone.

Complaints of epigastric discomfort were much more frequent in the steroid-treated group. Nevertheless, documentation of peptic ulcer by roentgenographic examination was demonstrated in only 2 patients. However, this lack of radiologic confirmation of peptic ulceration does not entirely rule out the presence of such lesions.

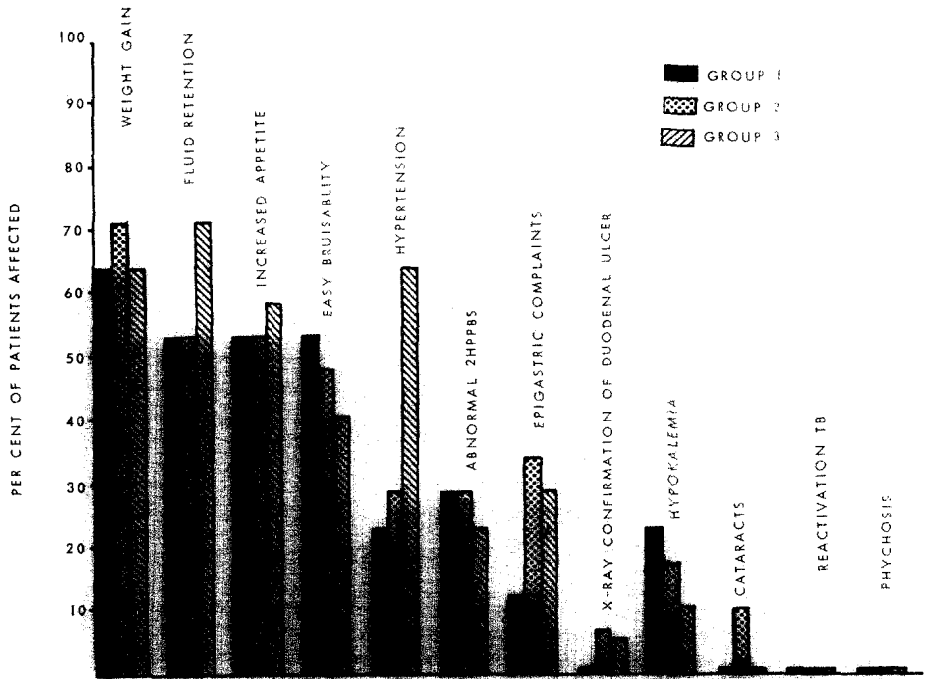


FIG. 4. Effect of duration of therapy on incidence of adverse effects. Group I, 24 to 47 months; Group II, 48 to 60 months; Group III, greater than 60 months.

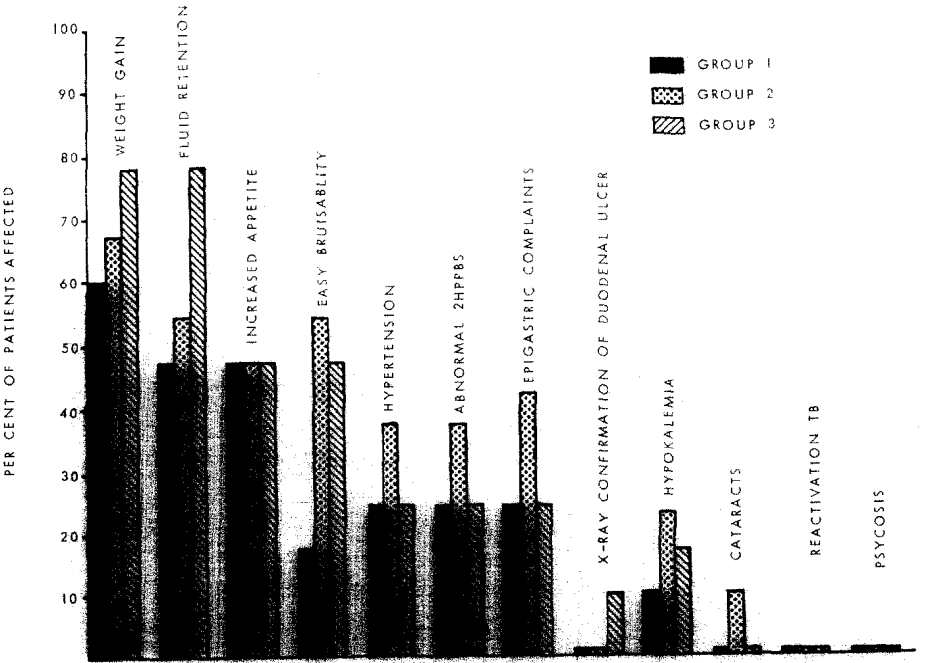


FIG. 5. Effect of milligram-months (average daily dose times months) of therapy on incidence of adverse effects. Group I, 120 to 349 milligram-months; Group II, 350 to 650 milligram-months; Group III, greater than 650 milligram-months.

Hypokalemia occurred in 18 per cent of the patients taking steroids. The lowest potassium value found was 2.8 mEq. per liter. Symptoms consistent with hypokalemia occurred in 2 patients and consisted of mild weakness and fatigue. The high incidence of hypokalemia (8 per cent) in our control group probably reflects the fact that potassium determinations were performed in our clinic population only when abnormalities were considered probable. No abnormalities in serum sodium were noted.

Of note is the absence of reactivation of tuberculosis and steroid psychosis. In addition, there were only two cases of cataracts, and these occurred in older-aged patients. Therefore, no definite conclusions may be drawn concerning the relation of the occurrence of cataracts to steroid administration.

For several reasons it is difficult to compare the data from this study with those from previous reports. Different standards for determination of abnormalities have been used in each study. For example, some examiners consider only a diastolic blood pressure greater than 110 mm. Hg abnormal, whereas others judge any diastolic pressure greater than 90 mm. Hg abnormal. In addition, some series include patients with other diseases. Finally, investigative techniques vary in each study. Nevertheless, gross comparisons do offer useful information to physicians caring for these patients.

If all the papers listed in the bibliography are compiled, a total of 2,830 patients has been studied for complications of steroid therapy. From this total there were only 3 cases of tuberculosis^{5, 7, 11} and no cases of frank steroid psychosis. The incidence of peptic ulcer varied from 0^{10, 16, 18} to 14 per cent.¹³ In the study citing a 14 per cent incidence of peptic ulcer, two or three upper gastrointestinal series were performed annually in each patient to detect the presence of ulcers.

The incidence of diabetes varied from less than one per cent^{7, 16, 18} to 28 per cent in the present study. The incidence of cataracts varied from 0⁸ to 4 per cent in the present study. Hypertension was found in less than one per cent of patients in two series^{6, 15} and in 40 per cent in the present study. Subjective complaints such as fluid retention, epigastric discomfort, easy bruisability, and increased appetite were found with greater frequency in all the studies.

In the present study, an attempt was made to assess the incidence of osteoporosis. Initially lumbosacral roentgenograms were obtained in all patients. It was found that osteoporosis was present uniformly in postmenopausal women and absent in other patients. Because of the difficulty in drawing causal relationships from these results, lumbosacral roentgenograms were discontinued. Vertebral compression fractures were found in one postmenopausal woman. Other examiners attempting to evaluate the problem have recorded an incidence of from one per cent⁶ to 8 per cent¹¹ collapsed vertebrae caused by osteoporosis.

The present study is in agreement with the consensus of previous reports in that the most frequent complications of steroid therapy in asthmatic patients are the less serious effects, such as easy bruisability, weight gain, and increased appetite. When more debilitating complications do occur, they appear to be of a relatively benign nature and are usually easily managed. It should also be noted that patients on alternate-day therapy were not included in the present study.

The latter form of treatment might be expected to further lower the incidence and severity of side effects.

The age of the patient and the mean daily dose of steroids seem to play a more important role in determining the incidence of complications than does the duration of treatment.

REFERENCES

- 1 Rose, B., McGarry, E., and Knight, A.: The management of allergic disorders with anti-inflammatory steroids, *Ann. N. Y. Acad. Sci.* **82**: 913, 1959.
- 2 Drug Committee of the Research Council of The American Academy of Allergy: Side effects of prolonged corticosteroid treatment in patients with asthma, *J. ALLERGY* **40**: 88, 1967.
- 3 McAllen, M.: Long-term side effects of corticosteroids, *Respiration* **27**: (Suppl.) 250, 1970.
- 4 Smyllie, H. C., and Connolly, C. K.: Incidence of serious complications of corticosteroid therapy in respiratory disease, *Thorax* **23**: 571, 1968.
- 5 Maunsell, K., Pearson, R. S. B., and Livingstone, J. L.: Long-term corticosteroid treatment of asthma, *Br. Med. J.* **1**: 661, 1968.
- 6 Rees, H. A., and Williams, D. A.: Long-term steroid therapy in chronic intractable asthma, *Br. Med. J.* **1**: 575, 1962.
- 7 Walsh, S. P., and Grant, I. W. B.: Corticosteroids in the treatment of chronic asthma, *Br. Med. J.* **2**: 796, 1966.
- 8 Livingstone, J. L., and Davies, J. P.: Steroids in the long-term treatment of asthma, *Lancet* **1**: 1310, 1961.
- 9 Pearson, R. S. B., Baylis, J. H., and Smellie, H. C.: Treatment of chronic asthma with prednisolone and the newer steroids, *Br. Med. J.* **1**: 315, 1961.
- 10 Serafini, U.: Long-term therapy of asthma with hormones, *Acta Allergol. (Kbh.)* **15**: (Suppl. 7) 263, 1960.
- 11 Somner, A. R., Rogan, M. C., and Grant, I. W. B.: Prolonged corticosteroid treatment in chronic asthma, *Br. Med. J.* **1**: 1092, 1960.
- 12 Anderson, E., and Bruin, E.: Long-term treatment of bronchial asthma with steroid hormones, *Acta Allergol. (Kbh.)* (Suppl. 7) **15**: 275, 1960.
- 13 Arnoldson, H.: Peptic ulcer as a complication to long-term treatment of asthma with steroids or ACTH, *Acta Allergol.* **15**: (Suppl. 7) 303, 1960.
- 14 Irwin, J. W., and Burrage, W. S.: The role of adrenocortical steroids in the treatment of intractable bronchial asthma, *J. ALLERGY* **29**: 233, 1958.
- 15 Schwartz, E.: Prolonged therapy with adrenocorticosteroids in allergic diseases, *N. Y. State J. Med.* **60**: 3973, 1960.
- 16 Baldwin, H. S., Dworetzky, M., and Isaacs, N. J.: Evaluation of the steroid treatment of asthma since 1950, *J. ALLERGY* **32**: 109, 1961.
- 17 Tuft, L.: Long-term corticosteroid (corticoid) therapy in the chronic asthmatic patient, *Am. J. Med. Sci.* **244**: 686, 1962.
- 18 Keeney, E. L.: The condition of asthmatic patients after daily long-term corticosteroid treatment, *Ariz. Med.* **21**: 463, 1964.
- 19 Harter, J. G., Reddy, W. L., and Thorn, G. W.: Studies on intermittent corticosteroid dosage regimen, *N. Engl. J. Med.* **269**: 591, 1963.
- 20 Thorn, G. W.: Clinical considerations in the use of corticosteroids, *N. Engl. J. Med.* **274**: 775, 1966.
- 21 Glucose tolerance of adults, United States—1960 to 1962: National Center for Health Statistics, Series 11 Number 2, from Vital and Health Statistics, United States Department of Health, Education, and Welfare, United States Public Health Service, May, 1964.