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PROLONGED UNINTERRUPTED CORTISONE THERAPY IN RHEUMATOID ARTHRITIS

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A little more than two years have elapsed since Hench, Kendall, Slocumb, and Polley (1949) first reported that the adrenocortical hormone, cortisone, and pituitary adrenocorticotrophic hormone (A.C.T.H.) exerted powerful antirheumatic effects when administered to patients with rheumatoid arthritis. This epochal discovery opened new avenues of approach to the many unanswered basic problems of the disease, and engendered hope that these endocrine substances might be directly applied for the practical benefit of patients. Unprecedented amounts of clinical and laboratory research have already been accomplished, and, as knowledge has accumulated, the usefulness and limitations of cortisone and A.C.T.H. as therapeutic agents have become clearer.

The application of cortisone as a practical treatment for rheumatoid arthritis is beset with problems. When the hormone is administered to patients with active disease the reversible manifestations improve with remarkable promptness and consistency, but unfortunately the benefits are not lasting and symptoms reappear with impressive regularity when it is withdrawn. The favourable action of cortisone is suppressive only, not curative, and its administration probably does not alter the eventual course of the disease. As rheumatoid arthritis is a chronic and often progressive malady, it follows, from the facts now available, that if improvement is to be sustained cortisone must be given more or less continuously for an indefinite period of time.

Patients with rheumatoid arthritis present no clinical signs of adrenocortical deficiency (Hench *et al.*, 1950a; Sprague *et al.*, 1950b), and by gross and histological examinations their adrenal glands are not anatomically changed (Sokoloff *et al.*, 1951). Recent laboratory studies suggest, however, that the urinary excretion of steroids may be quantitatively altered and that either the production or metabolism of adrenal cortical hormones may be abnormal (Dobriner, 1951). Nevertheless, the amounts of cortisone required for desirable antirheumatic response appear to be substantially greater than the quantities of corticosteroids which are produced by the patient's own adrenal glands under normal circumstances. It is therefore logical to assume that the suppression of rheumatoid arthritis which results from cortisone administration is due to an exogenously induced state of hormone excess rather than to the correction of a glandular deficiency with substitution therapy (Sprague *et al.*, 1950a). But

cortisone is a potent agent which is capable of exciting diverse physiological activities in many organs and tissues. When a state of hypercortisonism is continued, a variety of metabolic and hormonal manifestations may develop, many of which are objectionable from the standpoint of treatment.

Morphological changes of a regressive nature have been repeatedly observed in ductless glands following the administration of large amounts of hormone secreted by the gland. More relevantly, atrophy of the adrenal cortices has been demonstrated in experimental animals (Ingle, 1938; Ingle and Mason, 1938; Antopol, 1950; Winter *et al.*, 1950) and in humans (Sprague *et al.*, 1950a) following the use of large amounts of cortisone. During treatment with the hormone certain laboratory tests, such as the eosinopenic response to A.C.T.H. and the urinary excretion of 17-ketosteroids, indicate that adrenocortical function is depressed (Forsham *et al.*, 1950b; Sprague *et al.*, 1950a; Dobriner, 1951). With short-term or relatively short-term administration, such functional arrest is temporary and the tests revert to normal after cortisone is withdrawn. Studies relating to functional recovery after long-term therapy have not yet been reported, however, and fear has been voiced that the prolonged use of cortisone might induce irreversible atrophy and permanent adrenal cortical insufficiency.

These considerations prompt three pertinent questions bearing on the practicability of employing cortisone continuously for long periods: (1) Can satisfactory suppression of rheumatoid arthritis be maintained indefinitely or will refractoriness to the drug and deterioration of improvement eventually occur? (2) Will continued administration be accompanied by unfavourable hormonal effects of such numbers and intensity as to necessitate discontinuation of treatment? (3) Will prolonged administration, especially if continuous, cause irreparable damage to vital organs such as the adrenal cortices?

With these questions in mind, a study of the effects of prolonged uninterrupted cortisone acetate therapy in patients with rheumatoid arthritis was undertaken.* The results of this investigation constitute the basis for the present report.

*The cortisone acetate used, and hereinafter referred to as cortisone, was supplied in part through the courtesy of the Medical Department of Merck & Co., Inc., Rahway, N.J.

Selection of Patients and Plan of Investigation

A total of 76 patients with chronic rheumatoid arthritis were started on treatment between January 1 and August 31, 1950. It was planned to continue cortisone administration for prolonged periods in each instance, but treatment was discontinued in 16 patients within six months for various clinical reasons. The 60 remaining patients received the hormone without interruption for periods ranging from 6 to 15 months; the average duration of treatment for these was 10.2 months, and 27 patients were treated for more than one year.

Each of the 76 patients had active rheumatoid arthritis with reversible changes, but various degrees of disease severity, functional impairment, and structural change were embraced by the group. The arthritis was graded as severe in 36 patients, moderately severe in 27, moderate in 12, and mild in 1. Articular involvement was restricted to peripheral joints in 56 patients, to the spine in 3, and 17 had combined peripheral and spinal arthritis. Forty-five of the patients were women and 31 were men, and their ages ranged from 19 to 80 years.

During cortisone administration no other medications designed to influence the course of the disease or to provide symptomatic relief were permitted. Salicylates or other analgesics, physiotherapeutic measures, and other supportive adjuncts were stopped at the beginning of the treatment.

Route of Administration

Intramuscular administration was used exclusively during the early months of the investigation. Since June, 1950, when it was learned that cortisone was effective by mouth (Freyberg *et al.*, 1950), the majority of patients have received oral preparations; most of those initially treated by the intramuscular route were transferred to oral medication, and all patients started on treatment since June have received the drug by mouth. Of the 60 long-term cases, 54 were given oral preparations, either in the form of tablets or as a liquid prepared by mixing the suspension, as supplied for parenteral use, with a flavoured syrup.

Parenteral injections were administered once daily at the beginning of treatment—later, when maintenance dosage was established, they were given either daily or every other day, or, in some cases, three times a week. Because intramuscular absorption is relatively slow, a double dose every other day was found to be just as effective as single doses given each day (Boland, 1950a, 1950b; Freyberg, 1950; Freyberg *et al.*, 1951).

Oral administration has distinct advantages in the practical management of patients; it eliminates the discomfort from injections and allows patients to be independent of others for their medication. In most instances the antirheumatic response is comparable to that resulting from intramuscular injection, but a very few patients, presumably because of faulty alimentary absorption, fail to react satisfactorily to oral administration. Usually the hormone works with greater speed (often within four to six hours) when given by mouth—and the effects wear off sooner. Because the anti-rheumatic action is rapidly dissipated, more uniform symptomatic control is afforded when the total daily oral amount is taken in divided doses, at fairly equally spaced intervals of six to eight hours.

For convenience' sake, however, most patients took their medication four times each day, at meal-times and before retiring; if the daily maintenance dose was 75 mg., for example, a whole tablet (25 mg.) was taken at breakfast, one-half tablet at noon, a whole tablet at the evening meal, and one-half tablet at or near bedtime. Symptomatic response was not influenced by whether the drug was given before, with, after, or between meals, but tendencies toward insomnia were lessened when a smaller dose was taken at bedtime. In a previous study no constant dosage ratio between the oral and intramuscular routes could be established, but the amounts needed for equivalent relief were surprisingly similar; sometimes the effective doses were the same, but more often oral doses were slightly greater, ranging from one-fifth to one-third more (Boland and Headley, 1951).

Dosage Schedule

The plan of dosage used was prompted by three preliminary observations (Boland and Headley, 1950): (1) The amounts of cortisone needed for effective control varied in individual cases, but, in general, depended more on the severity of the rheumatoid arthritis than on any other single factor—with more severe disease, more cortisone was required. (2) If the rheumatic manifestations were first suppressed by large doses, adequate control could be supported, in most cases, with smaller maintenance doses. (3) The incidence and severity of adverse hormonal reactions were decidedly less when smaller doses of the hormone were used. Regardless of the route of administration, a fairly uniform plan of dosage was followed. This consisted of three stages: (1) period of initial large suppressive doses; (2) period of gradual dose reduction; and (3) period of smaller maintenance dose administration.

Initial Suppressive Doses.—For severe and moderately severe cases 200 or 300 mg. of the hormone was given for one or two days, followed thereafter by 100 mg. daily. For moderate and mild cases 100 mg. was given on the first and subsequent days. These suppressive amounts were continued until the clinical manifestations were brought under control. The period required ranged from 7 to 36 days and in general the time lengthened with the severity of the disease. In a few severe cases amounts of 100 mg. a day were employed throughout because lesser quantities failed to maintain the desired degree of comfort.

Reduction in Dosage.—When rheumatic activity was satisfactorily suppressed with large doses, the daily amounts of cortisone were gradually decreased in a step-like manner. The necessity for gradual reductions was made apparent in some of the early cases which escaped control after the dose was abruptly lowered. The step-down in dosage was made more slowly in severe than in less severe cases. Reductions were usually accomplished at intervals of every four to seven days—by 10 mg. a dose with intramuscular administration, and by 12.5 mg. (one-half tablet) with oral medication.

Maintenance Doses.—Because it was proposed to continue treatment for long periods and because the incidence of unwanted side-effects was greater when large amounts of the hormone were employed, the smallest daily amount which would adequately control the clinical manifestations was considered as the patient's maintenance dose. Attempts were not made to restrain the disease completely, unless this could be accomplished

with relatively small doses, as in some less severe cases. In terms of long-range results it seemed more expedient, as well as more prudent, to be content with satisfactory improvement short of serious hormonal reactions than to strive for total inactivation with large and less safe amounts. Once established, the maintenance dose was continued without interruption. In most cases the amount was not fixed, however, as adjustments in dosage were required from time to time to meet fluctuations in disease activity.

Results of Prolonged Cortisone Administration

Improvement was graded into five categories, as follows: very marked, marked, moderate, slight, and unimproved. The response to treatment was measured by objective and subjective changes in the rheumatic manifestations, increases in functional capacity, improvements in the general constitutional reaction, and corrections of abnormal laboratory findings. The degree of overall improvement was considered satisfactory or adequate if the patient was able to perform his normal business or duties comfortably without analgesics, but perhaps with some restriction in physical activity; this was usually equivalent to improvement graded as very marked or marked.

Overall Results

In 60 of the original 76 patients cortisone administration was carried on continuously for more than six months. Treatment was stopped within the first six months in 16 patients for the following reasons:

(1) In eight patients the response to initial suppressive amounts or large maintenance doses was not sufficient to warrant continuing treatment; improvement was never more than moderate in four, and no antirheumatic effect at all was noted in two (both with spondylitis only). Two patients experienced excellent early results, but after two and four months respectively relapse occurred in spite of increased dosage. Five of the eight patients had very severe disease, and, whereas more benefit might have been realized if massive doses, such as 200 mg. a day, had been given, such amounts would not have been practical for extended use.

(2) In seven patients cortisone was discontinued because unduly troublesome hormonal reactions intervened and doses small enough to avoid them were not sufficient to provide adequate therapeutic results; the disease was graded as severe in five of these.

(3) In one patient complete clinical remission developed after four months' treatment, and administration was stopped. Relapse occurred after five months, and recently cortisone therapy was resumed.

Satisfactory degrees of improvement (very marked or marked) were maintained for periods exceeding six months in 48 of the remaining 60 patients. If the entire group of 76 patients is considered (including those whose treatment was stopped within six months because of poor

results or complications and excluding the one patient who developed a temporary remission), it was possible to maintain satisfactory suppression of the disease for long periods (6 to 15 months) in slightly less than two-thirds (48 of 75) of the patients (Table I).

TABLE I.—*Prolonged Cortisone Therapy in Rheumatoid Arthritis: Overall Results in Entire Series of 76 Patients*

Severity of Disease	No. of Cases	Adequate Antirheumatic Control (Very Marked or Marked Improvement) for 6 mths. or Longer	Inadequate Antirheumatic Control but Therapy Continued for 6 mths. or Longer	Reason Cortisone Discontinued before 6 mths.				
				Inadequate Initial Response	Early Deterioration of Improvement	Adverse Hormonal Reactions	Clinical Remission	
Severe ..	36	17 (47.2%)	8 (22.2%)	5	1	5	0	
Mod. sev.	27	19 (70.4%)	4 (14.8%)	1	1	1	1	
Moderate	12	11 (91.7%)	0	0	0	0	0	
Mild ..	1	1 (100%)	0	0	0	0	0	
Total	76	48 (63.2%)	12 (15.8%)	6	2	7	1	

General Results in Long-treated Cases

Among the 60 patients treated for periods ranging from 6 to 15 months improvement was graded as follows: very marked in 18 (30%), marked in 30 (50%), moderate in 11 (18.3%), and slight in one (1.7%) (Table II). Thus adequate control was upheld in 48 (80%) of the long-term cases.

In 12 patients (20%) minor and, by our standards, inadequate degrees of improvement were retained. Adverse hormonal effects developed in five of these which subsequently prevented the use of doses large enough to regulate the disease properly. Five others (three with severe and two with moderately severe arthritis) failed to improve more than moderately with continued 100-mg. doses. Two patients were kept under excellent control for 10 and 13 months with quantities of cortisone ranging from 37.5 to 62.5 mg. a day, and then, for unknown reasons, improvement deteriorated; relapse persisted despite increasing daily amounts of cortisone up to 125 mg. a day and intermittent booster doses of 200 mg.

Results in Relation to Severity of Disease

In general, the likelihood of promoting and sustaining major clinical improvement depended more on the severity of the rheumatoid arthritis than on any other single factor. Results were poorer in severe cases because these required continued large, or relatively large, amounts of cortisone which often incited adverse reactions—large but efficient doses often had to be reduced with detriment to clinical results.

Of the 25 severe cases treated for more than six months marked improvement was preserved in 16 and very marked improvement in only one (Table II). Among

TABLE II.—*Prolonged Cortisone Therapy in Rheumatoid Arthritis: Results in Patients Treated Continuously for 6 to 15 Months*

Severity of Disease	No. of Cases	Maintenance Dose Required (mg.)		Degree of Improvement Maintained				Degree of Improvement Considered Adequate		Adverse Hormonal Effects
		Average for Group	Range	Very Marked	Marked	Moderate	Slight	Adequate	Inadequate	
Severe ..	25	80.5	37.5-125	1 (4%)	16 (64%)	7 (28%)	1 (4%)	17 (68%)	8 (32%)	14 (56%)
Moderately severe	23	64.1	37.5-100	8 (34.8%)	11 (47.8%)	4 (17.4%)	0	19 (82.6%)	4 (17.4%)	8 (34.8%)
Moderate	11	55.4	37.5-75	8 (72.7%)	3 (27.3%)	0	0	11 (100%)	0	2 (18.2%)
Mild ..	1	37.5	37.5	1 (100%)	0	0	0	1 (100%)	0	0
Total	60	68.8	37.5-125	18 (30%)	30 (50%)	11 (18.3%)	1 (1.7%)	48 (80%)	12 (20%)	24 (40%)

the original 76 patients the rheumatoid arthritis was graded as severe in 36, and in 11 of these treatment was stopped within six months because of unsatisfactory response or adverse reactions. Thus only 17 of the original 36 severe cases, or less than 50%, were controlled adequately for prolonged periods.

Better results were obtained in patients with less severe rheumatoid arthritis. Very marked or marked improvement was held in 19 of 23 (82.6%) long-term cases, and in 19 of the 27 (70.4%) original cases graded as moderately severe. Satisfactory improvement was maintained in all of the long-term cases with moderate or mild disease, and in 11 of the 12 (91.7%) original cases graded as moderate (Tables I and II).

Size of Maintenance Doses in Long-term Cases

The maintenance requirements for cortisone varied in individual cases and were contingent on several factors. The dose needed for effective control was governed largely by the severity of the arthritis and the amount of physical and/or emotional stress to which the patient was subjected. The average daily maintenance doses in milligrams for the various groups were as follows: severe, 80.5; moderately severe, 64.1; moderate, 55.4; mild, 37.5 (Table II). It should be kept in mind that these figures are for oral administration in the majority of cases (54 of 60) and are probably slightly higher than would be found for a comparable group of patients treated wholly by the intramuscular route. Further, the development of adverse reactions prevented the use of optimal therapeutic doses in some cases; if this had not been so the average amount for severe cases would have been greater.

Stability of Maintenance Doses

The maintenance dose was by no means fixed throughout the course of treatment; in most instances it had to be manipulated from time to time. The natural course of rheumatoid arthritis is subject to fluctuations in activity, and it is reasonable to expect that the dosage requirements of a suppressive drug would vary with oscillations of the disease. Such changes in activity were encountered during treatment; sometimes they occurred spontaneously, while at other times exacerbations were related to some added stress, such as physical overactivity, emotional upset, intercurrent infection, fatigue, etc.

The maintenance dose remained fairly stable, with only minor adjustments being needed periodically, in 36 of the 60 patients (60%).

In nine patients (15%) the dosage remained fairly constant, except that temporary increases in rheumatic activity occurred on one or more occasions which required "booster doses" for the resumption of satisfactory control. Booster doses usually consisted of 100 or 125 mg. of the hormone daily for four or five days, followed by a gradual step-down in dosage to the previous level.

In four patients (7%) the maintenance requirements fluctuated widely from time to time. One patient with moderately severe rheumatoid arthritis, for example, remained very markedly improved for eight months on doses averaging 50 mg. a day. The cortisone requirement then gradually increased and for four months daily doses of 100 to 125 mg. were used. Then, for no apparent reason, the amount called for gradually decreased again, and for the next three months very marked improvement was held on doses of 37.5 to 50 mg. a day.

In five patients (8%) the maintenance dosage gradually increased over the months. The response to initial suppressive therapy was excellent in each instance and adequate control was sustained by smaller amounts for long periods. Improvement then gradually deteriorated and increasing quantities of the hormone became necessary to provide relief. Two patients finally became refractory to even large doses, and eventually cortisone was stopped, after 10 and 13 months of continuous therapy; after a three-months abstinence cortisone was resumed and was again effective in both patients. No reason was evident for the declension of results in three of the five patients, but two ignored advice and assumed additional business responsibilities.

The requirement for cortisone gradually decreased in six patients (10%). In three of them doses as low as 25 mg. a day finally became sufficient, and, with the hope that lasting remissions might have been produced, treatment was stopped after seven, nine, and ten months. Relapse occurred in one patient after seven weeks and in another after two months, while the third is still in remission after three months.

Adverse Effects from Long-continued Cortisone Therapy

Incidence

Twenty-four of the 60 patients (40%) developed undesirable hormonal side-effects at some time during the course of cortisone administration. A single abnormality was presented by 12 patients, whereas the other 12 demonstrated multiple reactions; a total of 45 adverse signs were witnessed in the group (Table III).

In most instances the signs of hormone excess were minor or transient and of little consequence. Of the 45 reactions the severity was graded as mild in 31, moderate in 13, and severe in one (spontaneous fracture). They were sufficiently troublesome to warrant cessation of therapy in only two of the long-term cases (after seven months of administration in one and after 11 months in the other), but their appearance often influenced management of the disease, making temporary or permanent restriction in dosage necessary.

Unfavourable effects were fewer and usually less pronounced when smaller doses of cortisone were used; at the time of their appearance the average daily dose was 75 mg. or more in 17 patients, 62.5 mg. in six patients, and 50 mg. in one patient. Because, in general, the incidence varied directly with the size of the dose, reactions developed most frequently in severe cases and during early suppressive treatment. The number of unwanted effects did not increase greatly with prolongation of treatment; the presently reported incidence of 40% is surprisingly close to that of 35.7% reported in a preliminary study of continuous therapy for periods ranging from two to six months (Boland and Headley, 1950).

Our experience parallels that of others (Freyberg, 1950; Hench *et al.*, 1950a, 1950b; Sprague *et al.*, 1950b; Bunim, 1951), who have noted that undesirable signs are more likely to develop in women than in men. Of the 24 patients exhibiting reactions, 17 were women and seven were men; these represented 44.2% of the 36 women and 29.2% of the 24 men in the long-treated group. Signs of fluid retention, increased androgenic activity, and psychic alterations were more prone to occur in females.

TABLE III.—*Individual Adverse Hormonal Side-reactions in Patients Treated Uninterruptedly with Cortisone for 6 to 15 Months*

Case No.	Sex	Average Daily Dose at Onset (mg.)	Onset of Reaction in Relation to Length of Treatment			Severity of Reaction	Adverse Hormonal Reaction											
			Before 3 mths.	Between 3 and 6 mths.	After 6 mths.		Fracture	Purpura	Pigmentation	Mooning of Face	Skin Tags	Thyroid Enlargement	Nervousness	Oedema	Menstrual Changes	Acne	Hypertrichosis	Dec. Glu. Tolerance
1	M	75.0	*			Mild												*
2	F	75.0	*	*		Mod.											*	
3	F	75.0	(1,2,3,4)			Mod. (1,2,3,4)												
4	M	100.0		*		Mod. (1,2)			*	*		*				*		
5	F	87.5		(1,2,3,4)		Mild (3,4)			(4)	(1)						(3)		
6	M	75.0	*	*		Mild (1,2)				*			(2)			*		
7	M	100.0	(1,2)		*	Mild				(1)						(2)		
8	F	100.0 (1,2)	*		*	Mod. (1,2)		*		*				*			*	
9	F	62.5 (3,4)	(1,2)		(3,4)	Mild (3,4)		(2)		(4)				(1)			(3)	
10	F	75.0	*		*	Mild				*								
11	M	100.0	(1,2)			Mod. (1)				(2)				(1)				
12	F	75.0	(4)	(1,2)	(3)	Mild (1,3)	*			(1)	*							(4)
13	F	75.0	(1)	(2)		Mod. (1)				(2)				*				
14	F	100.0 (1)	(1)	(2)		Mild (2)				(2)				(1)				
15	F	50.0 (2)		(1,2,3)		Mild (1,2)				(1)				(2)	*	(3)		
16	F	75.0	*		*	Mild (3)								*				
17	F	62.5		*	*	Mild								*				
18	F	62.5		(1)	(2)	Mild (1,2)									*	(2)	(1)	*
19	M	75.0	*		*	Mild								*				
20	F	62.5			(1,2)	Mod. (1)				*				(1)		*		
21	F	62.5		*		Mild (2)				(2)					*	(1)		
22	F	62.5	*	(1,2)		Mild (1,2)											*	
23	F	50.0			*	Mild				*							*	
24	M	100.0		*		"											*	

Individual Hormonal Side-effects (Table III)**Changes in Fat Metabolism**

Although little is known about the physiological processes involved there is ample laboratory evidence that cortisone may induce alterations in the metabolism of fat. Clinically it has been shown that the hormone may in some cases cause increases in total and esterified serum cholesterol values (Adlersberg *et al.*, 1950) and transient ketonuria (Perera *et al.*, 1949). Apparently the hormone enhances both the absorption and storage of fat, and the distribution of adipose tissue may be so influenced that changes in body configuration similar to those observed in spontaneous Cushing's syndrome may develop.

During the early part of this study diets were unrestricted, and moderate to marked gains in body weight occurred routinely. Generalized obesity became excessive in a few patients and, because of increased appetite and tendency towards fat storage, this was difficult to correct. More recently the caloric intake has been curtailed as soon as the optimal body weight is reached, and excessive gains have been avoided.

Increased deposit of fat in the cheeks, giving rise to rounding of the facial contour, or "mooning," was the most frequent endocrine abnormality noted. It was manifested by 12 patients, nine of whom were receiving relatively large daily amounts (75 mg. or more) of the hormone. The "mooning" usually improved or was corrected by decreasing the dose of cortisone and, if associated with general obesity, by lowering the caloric intake. Two instances of so-called "buffalo hump" due to fat deposit in the back of the neck were noted.

Changes in Carbohydrate Metabolism

Early investigations indicated that cortisone exerts a definite influence on carbohydrate metabolism. When

the hormone is administered in large doses to small laboratory animals that are force-fed, hyperglycaemia and glycosuria may be induced (Ingle, 1941), and when given to partially depancreatized animals glycosuria is greatly augmented (Long *et al.*, 1940). Yet, clinically, significant alterations in carbohydrate tolerance are uncommon in non-diabetic patients treated with the hormone. Based on body weight, the amounts of cortisone used therapeutically are relatively small when compared to quantities used to induce a diabetic state in small laboratory animals, and apparently non-diabetic patients have a large functional reserve of islet tissue with which to offset the anti-insulin properties of cortisone (Forsham *et al.*, 1950a). In patients with pre-existing diabetes, however, the diabetes may be intensified, sometimes considerably, during cortisone administration (Boland and Headley, 1949; Brown *et al.*, 1950).

Decreases in carbohydrate tolerance developed in three patients in the present study—one with a normal pre-treatment curve and two with latent diabetes mellitus beforehand. Glycosuria was well controlled in each instance with moderate dietary restriction of carbohydrates (and without insulin) and there was no tendency toward progressive impairment of carbohydrate metabolism in spite of the fact that cortisone was continued for months.

Although the presence of frank diabetes mellitus requiring sizable quantities of insulin for metabolic control appears to be a contraindication to the use of cortisone, clinically mild diabetes need not necessarily prohibit its use. Several patients with rheumatoid arthritis and coexisting mild diabetes, not included in this series, have been cautiously treated with cortisone by us, and sugar metabolism was controlled by the usual diabetic management, employing insulin when necessary.

Changes in Protein Metabolism

Very large doses of cortisone may give rise to increases in urinary nitrogen and the development of a negative nitrogen balance (Sprague *et al.*, 1950b). Diets high in protein, the simultaneous administration of testosterone propionate, and the complementary use of potassium salts have been suggested as measures to circumvent this tendency. Such precautionary steps were not resorted to in the present study, as it seemed improbable that the therapeutic amounts of cortisone used were large enough to cause significant acceleration of protein catabolism.

Changes in Electrolyte Metabolism

Cortisone has a relatively weak sodium-retaining effect, estimated to be about one-thirtieth as great as desoxycorticosterone acetate (desoxycortone acetate *B.P.*) (Thorn *et al.*, 1949). In our experience clinical signs of sodium chloride and water retention usually have not appeared unless relatively large doses of the drug are taken.

Oedema developed in nine patients of this study, all of whom were women, and seven of whom were receiving 75 mg. or more of the hormone each day. Invariably the oedema responded readily to reduction in dosage and dietary restriction of sodium, and diuresis could be hastened by giving saline or mercurial diuretics. During the latter months of the investigation perceptible oedema and sudden weight gains were largely avoided by placing patients on salt-poor diets at the beginning of treatment while initial suppressive doses were given, and by continuing this restriction if maintenance doses greater than 50 mg. a day were employed.

Cortisone is also capable of causing increased urinary excretion of potassium. Instances of potassium depletion from large doses of the hormone, with resultant symptoms of muscular weakness, arterial hypotension, and electrocardiographic changes characteristic of hypopotassaemia, have been reported. Obviously such changes, especially if combined with salt and water retention, could be hazardous in patients with impaired cardiac function. This complication has not been observed in any of our patients, possibly because we have adhered to smaller dosage schedules.

Cutaneous Changes

Alterations of the skin and subcutaneous tissues, like those which occur in Cushing's syndrome and some credited to increased androgen activity, have been observed during cortisone administration. Hypertrichosis was noted in seven women of this series; it was most pronounced on the face, and usually mild, but in two patients it was disturbing and the excessive hair was removed by electrolysis. Two men and one woman developed an acneiform eruption; this cleared spontaneously in one and remained in mild form in the other two. Small papillary skin tags appeared on the necks of two patients and these were removed surgically for cosmetic reasons. Mild purpura, unaccompanied by increased capillary fragility or demonstrable abnormalities in coagulation factors, developed on the lower legs of one patient but disappeared soon after the dose of cortisone was reduced. Slight, but definite, skin pigmentation involving the posterior cheeks and anterior neck occurred in one male patient; this developed early and persisted, but did not intensify despite the fact that he received 100 mg. of cortisone daily for 15 months.

Menstrual Disturbances

Oligomenorrhoea was encountered in three patients, two of whom presented other signs of increased androgen activity (hypertrichosis in one and acneiform eruption in the other).

Skeletal Changes

Cushing's syndrome may be complicated by osteoporosis, excessive calcium excretion, and the development of pathological fractures, especially of the vertebrae and ribs. This suggests that skeletal decalcification and fractures might be provoked by induced hyperadrenocorticalism, particularly when cortisone is given to elderly individuals with pre-treatment osteoporosis.

Spontaneous fractures developed in two of our patients. A 65-year-old man with severe rheumatoid arthritis and spinal osteoporosis beforehand experienced a compression fracture of the twelfth thoracic vertebra after 53 days of treatment. The fracture responded well to orthopaedic management, and cortisone therapy was not discontinued. The second patient, a 66-year-old woman, developed a fracture of the right femoral neck after 34 days of cortisone therapy; no history of injury could be elicited. Open surgical reduction revealed extreme osteoporosis of the femoral head and neck. The possibility of this complication makes one cautious in recommending cortisone therapy for elderly patients, and it would be wise to obtain radiographs of the spine and pelvis for senile osteoporosis routinely in prospective patients over the age of 60.

Psychic Changes

Mental reactions are altered, usually for the better, in most patients who receive cortisone; feelings of well-being are promoted, thought processes are accelerated, attitudes become cheerful, and reprieve from suffering brings hope that crippling may be prevented. In general, the mood is one of elation, and sometimes frank euphoria is encountered which is disproportionately greater than would be expected from the relief of pain alone. Although certain individuals seem to be more susceptible than others, the degree of mental stimulation seems to depend mainly on the size of the dose administered. During the early part of treatment, when large doses of the hormone are being employed, heightened psychomotor activity may be manifest by insomnia, agitation, nervous tension, and increased physical and mental drive. These symptoms usually taper off gradually as treatment is continued and especially after smaller maintenance amounts of the drug are instituted; insomnia and restlessness, for example, are rarely troublesome with daily doses of 75 mg. or less.

Pronounced degrees of mental stimulation occurred transiently in two patients of this series. Both were women in their climacteric who had been emotionally unstable for several years prior to treatment, and in both the symptoms appeared early when large suppressive amounts of cortisone were being given. Other investigators have reported overt psychotic changes coincident with cortisone therapy, but usually there has been evidence of psychopathic disposition beforehand. No instances of real mental depression or maniacal behaviour were encountered in this study; this may be due, in part at least, to the fact that cortisone has been

avoided in patients with psychotic histories or evident emotional instability, and because smaller maintenance amounts of the hormone have been used.

Effects of Prolonged Cortisone Administration on Adrenal Cortical Function

Ingle, Higgins, and Kendall (1938) demonstrated that large doses of cortisone produced regressive changes in the adrenal cortices of rats; cytoplasmic bodies were diminished in size and the cells were depleted of lipid; the extent of the atrophy resembled that which resulted from anterior pituitary insufficiency in hypophysectomized animals. Subsequently several investigators described in more detail the atrophy produced by large amounts of the hormone. The inner zones of the gland—the zonae fasciculata and reticularis—are principally affected, while the zona glomerulosa is only slightly altered (Stebbins, 1950; Winter *et al.*, 1950). Cholesterol and ascorbic acid concentrations of the glands are reduced. The anatomical alterations so induced are apparently reversible and the cortices are restored to normal size and appearance within 10 to 17 days after cortisone administration is stopped (Winter *et al.*, 1950). Recently Sprague *et al.* (1950a), as well as others (Sokoloff *et al.*, 1951), have demonstrated atrophy of the adrenal cortices, at necropsy, in human subjects treated with large amounts of the hormone for a variety of clinical conditions.

Immediately after cessation of cortisone therapy some patients present symptoms of fatigability and weakness, lasting for varying periods, which have been interpreted as due to inhibited cortical function. During administration the urinary excretion of 17-ketosteroids and the eosinopenic response to a single intramuscular injection of A.C.T.H. are reduced (Forsham *et al.*, 1950b). These changes reflect a depressed functional state of the adrenal cortex. With short-term or relatively short-term therapy the abnormalities have been temporary, however, and after treatment is discontinued the tests revert to normal (Sprague *et al.*, 1950b).

To determine the rate of recovery of adrenocortical function following long-term cortisone administration, the drug was withdrawn in 11 patients included in the present study; they received uninterrupted treatment for periods ranging from 8 to 14 months, and the average maintenance doses of cortisone varied from 37.5 to 100 mg. a day. Withdrawal was accomplished slowly, the daily amounts of hormone being gradually tapered off over periods of 10 to 16 days; this was done in an effort to minimize post-cortisone asthenia and the tendency towards acute articular exacerbations which not infrequently follow sudden cessation of the drug. The response of circulating eosinophils to A.C.T.H. was noted and urinary steroid excretion studies were performed while the usual treatment was being continued, at the end of the period of gradual withdrawal, and at intervals of every one to three weeks thereafter until the determinations returned to accepted normal values.

Details of this study will be reported separately (Boland *et al.*, 1951). In general, the tests indicated that adrenal cortical function was depressed during cortisone administration but that the suppression was not permanent and function returned to normal after withdrawal, even though the hormone was given without interruption for periods up to 14 months. For example, the response of the circulating eosinophils to A.C.T.H. (test of Thorn, Forsham, Prunty, and Hills, 1948) was

abnormal in each case during the administration of cortisone—a decrease in eosinophils four hours after a single intramuscular 25-mg. injection of A.C.T.H. either failed to occur or was definitely less than the accepted normal fall of 50%. In 10 of the 11 patients this test gradually improved after cessation of the hormone and reached normal values within periods of 10 to 90 days. In one patient the total eosinophil count before A.C.T.H. was very low, and, although a fall of 50% was recorded on the forty-eighth day, the possibility of experimental error was too great to permit a definite conclusion. It would appear, therefore, that, with the doses given and for the length of administration covered, uninterrupted treatment with cortisone does not produce irreversible functional impairment of the adrenal cortex.

Comment

As clinical experience with cortisone widens doubtless present methods of administration and dosage will be improved upon. Of the various schemes devised and tried so far, however, the uninterrupted method of administration has proved to be the most successful. Our attempts to employ the so-called "course method," which consists of relatively short periods of cortisone administration alternating with intervening rest periods, have not been satisfactory. While improvement has occurred each time the hormone was given, relapse has invariably occurred with interruption of treatment, lasting remissions have not been promoted, and the degree of relapse on withdrawal has not lessened with successive courses. From the standpoint of rehabilitating the arthritic patient for gainful occupation the repetition of alternating relief and relapse has not been practical.

Uninterrupted cortisone administration was effective in controlling the rheumatic manifestations for extended periods in many, but not all, patients with chronic rheumatoid arthritis. Actually it was possible to preserve satisfactory improvement in approximately two-thirds of the cases initially started on treatment. Fluctuations of rheumatic activity commonly occurred during the course of treatment, which required periodic adjustments in dosage, but long-continued administration rarely resulted in refractoriness to the drug. The chief deterrent to successful management was the intervention of objectionable hormonal reactions. Many of the failures were among patients with severe disease whose dosage requirements were large; the quantities needed for proper regulation often provoked unwanted signs of hormone excess, which in turn necessitated a lowering of dosage, often to the sacrifice of clinical improvement.

Unless more effective methods of administration are discovered it is apparent that other measures capable of favourably influencing the activity of the disease will be needed in combination with cortisone if major improvement is to be attained in many patients with severe rheumatoid arthritis. The fact that continued large doses of cortisone almost invariably lead to the development of endocrine complications has prompted a general policy of being content with the best results which can be obtained with smaller maintenance amounts of the hormone, even though only partial rehabilitation is achieved, rather than striving for total symptomatic remission with large and unsafe doses.

With the dosage schedules employed in the present investigations, unwanted side-effects from cortisone

occurred in 40% of cases. This high figure does not give a true picture, however, as most of the reactions were minor and/or transient and of little consequence. The chief disadvantage in their appearance was the fact that they forced a reduction in dosage, often to the detriment of clinical response. The number and intensity of the reactions were greatly reduced when smaller maintenance amounts of cortisone were used. A hormone with less tendency to produce adverse endocrine reactions or one with equal liabilities but greater effectiveness, milligram for milligram, would have advantages in the practical management of patients.

Serious complications during continuous therapy were few and were restricted to patients of the older age group. Vascular thromboses have occurred and have terminated fatally in two patients not included in the reported series; acute coronary thrombosis developed in a 72-year-old man, and cerebral thrombosis occurred in a 74-year-old woman. It seems probable that these complications may have been coincidental with, rather than provoked by, cortisone therapy. More disturbing has been the development of spontaneous fractures in three elderly patients, two of whom are included in the present study. Two of them suffered compression fractures in the lower dorsal spine, and one developed a fracture of the neck of the femur. In each instance the rheumatoid arthritis was severe and of long standing; these factors, in addition to senility, are conducive to osteoporosis, but it is likely that skeletal demineralization was accelerated by the induced state of cortisone excess. Each of the three patients was being maintained on large daily doses (100 mg.) of the hormone when the fractures occurred. More experience will be necessary to determine whether this complication might eventually develop in some younger persons or in those treated with smaller maintenance doses for longer periods than 15 months.

It is now apparent that the depression of adrenal cortical function which occurs during cortisone administration is temporary and the adrenal cortex recovers when the hormone is withdrawn. As judged by steroid excretion studies and the eosinophil response to A.C.T.H., adrenal cortical function returns to normal even after replacement therapy has been given without interruption for periods of up to 14 months. It may be argued that irreversible changes might ensue after cortisone has been administered continuously for longer periods, but this is unlikely. An analogous situation exists in patients with Cushing's disease, when a state of prolonged hormone excess is produced by a unilateral tumour of the adrenal cortex. The contralateral cortex undergoes pronounced atrophy, but after surgical removal of the hyperfunctioning tumour the atrophic cortex recovers functionally and anatomically (Kepler *et al.*, 1948).

Cortisone may be applied successfully as a therapeutic agent in many patients with rheumatoid arthritis, but there are definite limitations to its use. The hormone may be used as a potent antirheumatic weapon, but it probably should be reserved for cases that are resistant to more usual forms of treatment, and, in the light of present knowledge, it should not be considered as the drug of choice for all cases of rheumatoid arthritis. It must be remembered that good results are often attained from more conservative measures and from chrysotherapy. This attitude will be appreciated when it is realized that cortisone does not cure the under-

lying disease process, that its beneficial influence is only suppressive and is not lasting, and that in instituting it for a chronic disease, such as rheumatoid arthritis, the patient is committed to long and expensive treatment which is not without hazard.

Summary

The administration of cortisone to patients with rheumatoid arthritis usually produces prompt and often dramatic suppression of the disease manifestations. The effects of the hormone do not endure, however, and after withdrawal relapse ensues. For sustained improvement in a chronic disease such as rheumatoid arthritis it appears that cortisone must be given more or less continuously, but its uninterrupted use raises the question of whether administration may be continued effectively and safely for long periods.

Seventy-six patients with rheumatoid arthritis were given cortisone in the hope that treatment could be continued uninterruptedly for extended periods. For various clinical reasons it was necessary to discontinue treatment in 16 of these before six months, but the remaining 60 patients received the hormone uninterruptedly for 6 to 15 months. By using initial large suppressive amounts, then gradually reducing the dosage, and finally employing smaller maintenance doses, adequate degrees of rheumatic control were maintained in approximately two-thirds of the original 76 patients. The ability to maintain satisfactory improvement varied indirectly, in general, with the severity of the rheumatoid arthritis; very marked or marked antirheumatic response was upheld for long periods in 47% of severe cases, 70% of moderately severe cases, and 92% of moderate and mild cases. The chief obstacle to better results in the severer cases was the intervention of adverse hormonal side-effects which developed frequently when large or relatively large maintenance doses were required to support satisfactory improvement.

Unwanted signs of hormonal excess developed in 40% of cases at some time during the course of treatment. Most of them were mild or transient and disappeared or lessened when the dose of cortisone was reduced. The principal objection to their development was that they necessitated a lowering of dosage, which in turn often resulted in clinical deterioration.

During prolonged cortisone therapy evidence of functional suppression of the adrenal cortices, as indicated by a decreased response of circulating eosinophils to exogenous A.C.T.H., was present. The depression of cortical function was temporary, however, and in patients from whom cortisone was withdrawn after 6 to 14 months of continuous therapy tests of adrenocortical function returned to normal within periods ranging from 10 to 90 days.

As experience with cortisone broadens it becomes increasingly evident that there are distinct limitations, difficulties, and dangers in its use in the treatment of chronic diseases. At the present state of our knowledge it appears that cortisone may be employed as a powerful weapon in the management of many cases of rheumatoid arthritis, but it should not be considered as the treatment of choice for most cases, and not as a cure for any case.

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ANTIDIURETIC EFFECT OF NICOTINE AND ITS IMPLICATIONS*

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Antidiuretic Effect of Acetylcholine

Anyone who is prepared to investigate the effects of tobacco smoking lays himself open to the suspicion that he may be a crank and is probably a killjoy. Nevertheless, it must be admitted that the habit of smoking tobacco is widespread, and that the pharmacologist ought to pay some attention to the effects of a drug which is used in greater amount than any other.

Our interest in nicotine began as a consequence of observations made in Edinburgh by Dr. Mary Pickford (1939). She observed that acetylcholine possessed an antidiuretic action in dogs. We know acetylcholine to be the substance which transmits the nervous impulses passing along the vagus to the organs it innervates, and we also know acetylcholine to be a substance liberated in autonomic ganglia, where it transmits the impulse from the pre-ganglionic to the post-ganglionic fibre. The actions which acetylcholine exerts at vagal nerve endings were described by Dale as resembling the actions of muscarine, while those exerted at autonomic ganglia were said to resemble the actions of nicotine. The two kinds of action can be distinguished, as the muscarine actions are abolished by atropine, and in animals under atropine only nicotine-like effects are seen.

Dr. Pickford observed the antidiuretic action by giving dogs water by mouth, and, having also given

atropine, she injected acetylcholine intravenously when diuresis was at its height. The antidiuretic action was seen at once and lasted for nearly an hour. She proved that it was due to liberation of the hormone of the posterior lobe of the pituitary, by removing almost the whole of this lobe in some of her animals; in these, only a small fraction of the antidiuretic response to acetylcholine remained. Thus she showed that one of the nicotine-like properties of acetylcholine was to liberate the antidiuretic hormone of the posterior lobe.

Later Dr. Pickford (1947) was able to demonstrate that the site of action of the acetylcholine was the supraoptic nucleus from which nerve fibres pass to the posterior lobe. She accomplished this by making injections of small amounts of acetylcholine (2–40 µg.) directly into the supraoptic nucleus; these caused the antidiuretic action.

The Action of Nicotine

To test nicotine to see if it exerted a similar action was then an obvious step, which we took in the Oxford laboratory (Burn, Truelove, and Burn, 1945). We made observations in groups of rats and showed that nicotine exerted an antidiuretic effect, but failed to do so if rats were used from which the pituitary body was first removed. The amount of nicotine needed to produce the antidiuretic action was large, being 0.16 mg. per 100 g. rat. We had therefore established a point of some slight academic interest.

In view of the dose of nicotine required in the rat it seemed scarcely worth while to test the effect of nicotine in man, and we were greatly surprised to discover that the smoking of one or more cigarettes, according to the sensitivity of the subject, caused an inhibition of the diuresis which followed the drinking of 1 litre of water, and that the antidiuretic action lasted for one, two, or even three hours.

The observations were made on subjects each of whom emptied his bladder at 15-minute intervals. When it was observed that the excretion was regular and less than 25 ml., the subject drank 1 litre. By 45 minutes later the excretion of water had reached perhaps 70 ml. per 15 minutes, and at that point he began to smoke, and was asked to inhale as much as he felt inclined. The inhibition occurred within 10–15 minutes, and in those subjects in whom it was prolonged it was accompanied by toxic symptoms such as pallor, sweating, dizziness, nausea, and sometimes vomiting. These were, however, of short duration, and the period of inhibition outlasted them by two to three hours. When the period of inhibition was shorter, as after smoking one cigarette, it was rare to observe any toxic effects other than transient dizziness and pallor.

Intravenous Injection of Nicotine

To establish that the effect of smoking was due to the nicotine inhaled, we carried out experiments in which the subject did not smoke, but received an intravenous injection of nicotine acid tartrate. We observed that amounts corresponding to 0.33 to 1 mg. of nicotine (as free base) caused an antidiuretic action resembling in duration that due to the smoking of one to three cigarettes. Ling and Wynn Parry (1949) have estimated as a result of a careful study that the amount of nicotine entering the mouth of a smoker from one cigarette is about 1 mg. If it is assumed that about one-third of this is absorbed into the blood stream when the subject

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