GASTRIC ACIDITY AND GASTRIC BIOPSY IN THYROTOXICOSIS

BY

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The occurrence of thyrotoxicosis and pernicious anaemia in the same patient was first described by Neusser in 1899, and there is now good evidence for an association between these two diseases (Tudhope and Wilson, 1960; McNicol, 1961).

It was subsequently noted that many patients with thyrotoxicosis had achlorhydria when examined with the Ewald one-hour test meal or the gruel fractional test meal (Miesowicz, 1904; Wolpe, 1912; Lockwood, 1925; Lewit, 1925; Moll and Scott, 1927) and that the administration of thyroid extract to healthy persons reduced the volume and acidity of the gastric juice (Badykas, 1924). Later studies with conventional doses of histamine (Table I) confirmed that achlorhydria was more common in thyrotoxicosis than in the general population (Table II). Lerman and Means (1932), for example, noted that 19 (38%) of their 50 patients with thyrotoxicosis had achlorhydria, whereas only 26 (13%) of 200 normal persons had achlorhydria after the administration of the same combined parietal-cell stimulants, 50 ml. of 70% alcohol by mouth and 0.01 mg. of histamine per kilogram body weight by injection. Similar results were obtained by Brown, Pendergrass, and Burdick (1941).

TABLE I.—*Reported Incidence of Achlorhydria in Thyrotoxicosis*

Authors	Stimulant	No. of Patients Studied	With Achlorhydria
Lerman and Means (1932) ..	Histamine	50	38%
Berryhill and Williams (1932)	Alcohol	50	68%
Wilkinson (1933) ..	Histamine	100	36%
Louis and Wills (1937) ..	Alcohol	18	44%
McElroy <i>et al.</i> (1938) ..	Histamine	50	12%
Thiele (1939) ..	Alcohol	70	30%
Brown <i>et al.</i> (1941) ..	Histamine	24	58%

TABLE II.—*Reported Incidence of Achlorhydria in Normal Persons*

Authors	Stimulant	No. of Patients Studied	With Achlorhydria
Lerman <i>et al.</i> (1932) ..	Alcohol	200	13.0%
Vanzant <i>et al.</i> (1932) ..	Histamine	3,381	9.3%
Polland (1933)	Gruel	988	9.3%
Lander and MacLagan (1934)	Histamine	108	0.9%
Ruffin and Dick (1939) ..	Alcohol	1,917	11.0%
Winkelstein (1942) ..	Histamine	5,585	1.2%
Doig <i>et al.</i> (1950) ..	Gruel	134	0.7%

Moll and Scott (1927) noted that achlorhydria was more common in patients with a long history of thyrotoxicosis, and Wolpe (1912) and Lerman and Means (1932) thought that achlorhydria could be correlated directly with the severity of the disease. On the other hand, Berryhill and Williams (1932) found that the incidence of achlorhydria was not related to the age of the patients, the duration of the symptoms, or the degree of elevation of the metabolic rate, though it appeared to be a manifestation of active thyrotoxicosis, because acid was detected in 19 of the 34 patients with achlorhydria when they were re-examined

six months after operation. Louis and Wills (1937) made similar observations.

In contrast to the large number of reports on gastric secretion in thyrotoxicosis published before 1941, few observations appear to have been made since. The study of Maldonado Allende (1946), who used gruel as the stimulant, is poorly documented. No reports have as yet been published on the results of the augmented histamine test in patients with thyrotoxicosis, although Card and Sircus (1958), at the end of a discussion on anacidity, stated that "in all of many cases of thyrotoxicosis examined by this test, gastric secretion has been within normal limits."

Siurala and Lamberg (1959) compared the gastric biopsy findings in 41 patients with thyrotoxicosis and 65 other patients not suffering from thyrotoxicosis. Gastritis was present in 78% of the patients with thyrotoxicosis and 52% of the controls ($P < 0.001$). Only nine of the 41 thyrotoxic patients had normal biopsies whereas 31 of the 65 control patients were normal.

We have been interested in the association between thyrotoxicosis and pernicious anaemia, and report here observations on the augmented histamine test, serum-vitamin-B₁₂ levels, and gastric biopsy appearances in patients with thyrotoxicosis.

Material

Forty-seven patients with active thyrotoxicosis were studied. The diagnosis of thyrotoxicosis was suspected on clinical grounds and confirmed by laboratory tests (basal metabolic rate, protein-bound iodine, and uptake of radioactive iodine). All the patients were later treated for the disease.

Observations on 46 patients who had been treated for thyrotoxicosis between one and nine years previously are also included in this report. These patients were seen in the course of an attempt to study the prevalence of overt and latent pernicious anaemia in patients who had been treated for thyrotoxicosis in the United Oxford Hospitals in the decade 1950-9. The formal prevalence study was abandoned because only a third of the first 150 patients written to were prepared to undergo investigation.

Methods

Augmented Histamine Test (A.H.T.).—The test was performed as originally described by Kay (1953) with minor modifications (Bock, Richards, and Wits, 1963). The results were expressed as the total milliequivalents of HCl (total mEq HCl) secreted in one hour after augmented histamine stimulation. Achlorhydria was considered to be present when zero total mEq HCl was secreted (Bock, 1962).

Azuresin ("Diagnex") Test.—After an overnight fast the patients were given either 50 mg. of betazole hydrochloride ("histalog") or 500 mg. of caffeine benzoate with a glass of water. One hour later they emptied the bladder and swallowed 2 g. of the granules containing azuresin ("diagnex blue"). After another two hours the bladder was emptied again and the test specimens were obtained. Negative tests were usually repeated. We have found that

false-positive results are rare when the test is accurately performed (Bock and Witts, 1961).

Serum Vitamin B₁₂.—The level of vitamin B₁₂ in the serum was measured microbiologically using *Lactobacillus leichmannii* as test organism. The normal range in this laboratory is 150 to 1,000 µg./ml. (mean 450 µg./ml.), while in nearly all patients with pernicious anaemia the level is less than 100 µg./ml. (mean 64 µg./ml.).

Gastric Biopsies.—These were performed with a modified Wood's tube. The sections were stained with haematoxylin and eosin and classified as normal, superficial gastritis, atrophic gastritis, or gastric atrophy. **Superficial gastritis:**—There was inflammatory cell infiltration of the mucosa, often with distortion of the superficial epithelium, but there was no atrophy of the specific cells. **Atrophic gastritis:**—There was inflammatory cell infiltration of the mucosa with variable but not complete atrophy of the specific cells. Islands of intestinal metaplasia were sometimes present. **Gastric atrophy:**—Atrophy of the specific cells was severe or complete, intestinal metaplasia was often conspicuous, and there was little or no inflammatory cell infiltration of the mucosa. A more detailed account of the histological features for each diagnosis has been given elsewhere (Bock, Arapakis, Witts, and Richards, 1963).

Results in Patients with Untreated Thyrotoxicosis

The literature led us to believe that achlorhydria and gastritis were common in patients with untreated thyrotoxicosis. It was therefore decided to screen the patients for achlorhydria by means of the azuresin test and to carry out augmented histamine tests in those in whom the azuresin test revealed no acid. It was also decided to perform gastric biopsies on those patients who would tolerate the procedure. However, there was no instance of achlorhydria amongst the first 18 patients studied, and six of the ten gastric biopsies showed no abnormality; the other four patients had superficial gastritis.

A more critical study was therefore planned, using the A.H.T. as the initial test of gastric function. Augmented histamine tests were performed on 29 patients. Barium-meal examinations were carried out on 25 of these patients and no peptic ulcers were found. This excluded the possibility that the responses to the A.H.T. had been modified by unexpected coexistent gastric or duodenal ulceration. Gastric biopsies were carried out in 26 of the patients and the serum vitamin B₁₂ was estimated in the same number. The results are shown in Table III.

Haemoglobin Concentration.—Anaemia was not present in any of the patients.

Serum-vitamin-B₁₂ Concentration.—The mean value in the 26 patients was 497 µg./ml., which is a little higher than the mean value for the laboratory (450 µg./ml.). This observation does not confirm the finding of Ziffer, Gutman, Pasher, Sobotka, and Baker (1957), who noted that the whole blood vitamin-B₁₂ levels of 10 patients with thyrotoxicosis were lower than the mean value of six normal persons.

Gastric Biopsy

In all, 36 gastric biopsies were performed on patients with untreated thyrotoxicosis. Of these, 25 (70%) showed no abnormality, 8 (22%) had superficial gastritis, and 3 (8%) had atrophic gastritis. No biopsies were classified as gastric atrophy. The mean age of the patients with normal gastric biopsies was 33 years, which was two years less than the mean age of the patients with gastritis, but on the average the patients with normal gastric biopsies had suffered from thyrotoxicosis for one month longer.

Acid Secretion

The mean acid secretion of the 24 women was 16.1 total mEq HCl in one hour (standard deviation ±8.40 total mEq HCl), with a range of 0 to 46.8 total mEq HCl. The mean volume of the juice secreted in the hour was 144 ml. (standard deviation ±77 ml.). One woman (Case 27) had achlorhydria in the A.H.T., which was confirmed when the

TABLE III.—Augmented Histamine Test (A.H.T.) and Other Data in 29 Patients with Untreated Hyperthyroidism, Including A.H.T. after Treatment in 15 Patients

Case No.	Sex	Age	Duration of Symptoms (Months)	Hb (g./100 ml.)	Serum Vit. B ₁₂ (µg./ml.)	Gastric Biopsy	Barium Meal	A.H.T.		Method of Treatment	Interval between Tests (Months)	A.H.T. after Treatment	
								Vol. (ml.)	Total mEq HCl			Vol. (ml.)	Total (mEq HCl)
1	F	30	6	13.2	340	Normal	Normal	146	16.9				
2	F	32	12	14.0	450	"	"	208	30.8				
3	F	25	36	13.8	320	"	"	100	10.3				
4	F	38	10	14.0	—	"	"	362	46.8				
5	F	26	18	15.1	505	"	"	183	21.1				
6	F	49	6	15.1	480	"	"	143	14.3				
7	F	16	6	14.8	680	"	"	145	15.6				
8	F	22	12	14.2	825	Superficial gastritis	Normal	163	14.4				
9	F	36	9	13.7	425	"	—	217	22.2				
10	F	37	48	14.8	510	"	Normal	195	25.0				
11	M	24	2	13.6	265	Normal	"	98	10.7				
12	M	34	3	17.2	675	"	"	305	43.6				
13	M	38	4	13.6	675	"	"	246	29.6				
14	M	48	7	13.5	300	Atrophic gastritis	"	88	5.0				
15	F	52	4	13.9	490	Normal	"	165	21.6	I	14	189	23.2
16	F	28	6	13.9	210	"	"	164	25.4	S	12	184	23.9
17	F	41	6	13.6	410	"	"	200	25.6	M	9	238	29.6
18	F	37	12	14.8	—	"	"	98	11.8	M	11	88	10.3
19	F	38	3	14.3	425	"	"	123	14.2	M	5	109	13.3
20	F	14	3	13.7	725	Superficial gastritis	"	153	12.1	M	9	178	14.2
21	F	48	6	13.4	650	Atrophic gastritis	"	42	0.6	I	12	50	1.7
22	F	44	8	14.0	—	"	"	174	22.0	M	9	185	24.1
23	F	17	2	13.9	320	Normal	"	128	15.4	S	10	176	20.5
24	M	33	7	17.2	535	Superficial gastritis	"	193	21.6	M	10	150	16.8
25		25	12	13.7	500	Normal	"	105	8.0	S	3	150	13.7
26	F	27	6	14.8	300	"	"	121	7.6	S	12	160	16.1
27	F	47	8	14.4	825	Atrophic gastritis	"	15	0	I	10	164	19.1
28	F	52	10	12.1	650	Normal	"	38	2.6	I	11	212	19.3
29	F	40	3	13.6	420	—	"	66	3.0	S	12	152	16.1

M = Medical treatment. S = Surgical treatment. I = Radioactive iodine.

test was performed again three days later. Her gastric biopsy showed moderate atrophic gastritis. The mean response of these 24 women with thyrotoxicosis was closely similar to that of 28 normal women who were studied by Card and Sircus (1960) and who secreted 17.2 ± 7.21 total mEq HCl.

The five men with thyrotoxicosis secreted 10.7, 43.6, 29.6, 21.6, and 5.0 total mEq HCl respectively in one hour in response to augmented histamine stimulation. The mean value of 20.1 total mEq HCl (standard deviation ± 13.7 total mEq HCl) was statistically no different ($P > 0.10$) from the mean response (22.65 ± 8.37 total mEq HCl) of 29 normal men tested by Card and Sircus (1960).

Because a number of the earlier investigators had noted that acid secretion often returned after treatment in patients who had had achlorhydria beforehand, we thought it would be interesting to study the patients again, and 15 of them volunteered to have further A.H.T.s at intervals varying from 3 to 14 months after treatment (Table III, Chart). Case 25 was studied after three months' medical treatment and again nine months after partial thyroidectomy. All the patients were clinically euthyroid at the time of the second test.

Secretion of acid in the A.H.T. in 15 patients before and 3 to 14 months after treatment of thyrotoxicosis.

There were no appreciable differences in the results of the two tests performed on 10 patients. In the remaining five, however, there was a considerable increase in the secretion of acid. These include one patient (Case 27) who secreted 2.29 total mEq HCl a year after two augmented histamine tests had failed to stimulate acid secretion. This patient had atrophic gastritis. The gastric biopsies in three of the five patients had been normal at the time when treatment of the thyrotoxicosis had been started so that the depression of gastric secretion in them was not attributable to gastritis. The fifth patient did not undergo biopsy.

Kay (1953) and Marks and Shay (1958) showed that the A.H.T. gave consistent results in the same individual, so that our results cannot be explained by lack of repeatability of the test. Nor are they likely to be due to errors in technique. All the stomach-tubes were screened and positioned accurately. Continuous hand-suction was used throughout and all the patients were given 0.04 mg. of histamine acid phosphate per kilogram body weight. In every case, however, the patients got a bigger total dose the second time because of the increase in their weights.

Results in Patients who had Previously been Treated for Thyrotoxicosis

The 46 volunteers who had been treated for thyrotoxicosis between one and nine years previously were examined for evidence of thyrotoxicosis, myxoedema, and anaemia. Venous blood was taken for haemoglobin estimation and serum-vitamin-B₁₂ assay; a smear of the peripheral blood was made and the patients were instructed in the performance of caffeine-azuresin tests which they could do at home.

These screening tests were normal in 37 of the patients, all but two of whom were women. The youngest patient was aged 21 and the oldest 76 at the time of the survey, and the mean age of the 37 was 49 years. Two of the patients were thought to have active thyrotoxicosis and one patient had undoubted myxoedema.

The screening tests were abnormal in nine patients. Two patients had very low serum-vitamin-B₁₂ levels, and they and seven other patients had negative azuresin tests: none of the patients had anaemia. These nine patients were investigated more fully (Table IV).

Cases 38 and 39 had severe reactions 10 to 15 minutes after the injection of 100 mg. of mepyramine maleate ("anthisan") (we have since reduced the dose to 50 mg.), but the pH of the fasting gastric juice of Case 39 was 1.9 and her gastric biopsy showed no abnormality.

Cases 40 and 41 had serum-vitamin-B₁₂ levels of 75 $\mu\mu\text{g.}/\text{ml.}$ Occasional macrocytes were seen in the peripheral blood smear. Augmented histamine stimulation failed to excite acid secretion in these patients, and their barium meals showed gastric atrophy. Gastric biopsy in Case 40 revealed severe atrophic gastritis; no biopsy was obtained from Case 41. The absorption of vitamin B₁₂ was severely impaired in Case 40, whose bone-marrow biopsy showed megaloblastosis. The absorption of vitamin B₁₂ was not determined in Case 41, but her bone-marrow was normal. It is noteworthy that Case 41 had a sister who developed pernicious anaemia five years after a partial thyroidectomy for thyrotoxicosis. Cases 40 and 41 are now receiving regular injections of vitamin B₁₂.

TABLE IV.—A.H.T. and Other Data in Nine Patients who had been Treated for Thyrotoxicosis from One to Nine Years Previously, and in Whom the Caffeine-Azuresin Test had Shown Apparent Achlorhydria

No.	Sex	Age		Duration of Symptoms (Months)	Method of Treatment	Hb (g./100 ml.)	Serum Vit. B ₁₂ Level ($\mu\mu\text{g.}/\text{ml.}$)	A.H.T.		Gastric Biopsy	Barium Meal	Faecal Excretion of 0.5 $\mu\text{g.}$ ⁵⁹ Co-vit. B ₁₂
		At Treatment	Survey					Vol. (ml.)	Total mEq HCl			
38	F	41	45	1	M	13.4	260	Severe anthisan reaction		Atrophic gastritis	Gastric atrophy	—
39	F	43	50	12	I	14.5	615	Severe anthisan reaction. pH 1.9		Normal	Normal	—
40	M	49	58	120	S	14.8	75	25	0	Atrophic gastritis	Gastric atrophy	83%
41	F	66	70	12	I	16.4	75	3	0	Normal	Normal	—
42	F	53	57	8	S	16.7	335	177	17.06	Superficial gastritis	Normal	21%
43	M	40	50	3	S	16.6	440	127	10.57	Atrophic gastritis	Normal	18%
44	F	61	63	72	S	14.3	275	29	1.06	Atrophic gastritis	Gastric atrophy	40%
45	F	53	59	12	M	16.1	470	25	0.2	Normal	Normal	—
46	M	21	43	6	S	14.0	1,300	54	0	Gastric atrophy	Gastric atrophy	—

M = Medical treatment. S = Surgical treatment. I = Radioactive iodine.

Case 44 had a normal blood picture but a very low acid output and atrophic gastritis: her intrinsic-factor secretion was suspect because the radioactive-vitamin-B₁₂ absorption was at the lower limit of normal. Cases 42 and 43 had false-negative azuresin tests and the other investigations were normal.

Case 46 is of some interest. Thyrotoxicosis first appeared at the age of 21 and was treated by partial thyroidectomy. At the age of 35 the disease recurred and was treated with thiouracil for six months. When the patient was seen in the survey he was very thyrotoxic, and this time the disease proved resistant to antithyroid drugs despite the fact that full doses were continued for nearly a year. The disease was finally brought under control with radioactive iodine.

The results on the 46 patients who had been treated for thyrotoxicosis were thus more striking than those in the 47 patients with active thyrotoxicosis. Four of the 46 had complete or practically complete achlorhydria and two of these four had latent pernicious anaemia. The concept of latent pernicious anaemia is beautifully illustrated by Case 40. His gastric mucosa was severely damaged, and he had a low serum-vitamin-B₁₂ level and obvious megaloblastosis of the bone-marrow, yet his blood film was almost normal and anaemia was not present.

Discussion

Achlorhydria is found much more commonly than normal in thyrotoxicosis when conventional tests of gastric secretion such as the fractional test meal and/or a single body-dose of histamine, are used. On the other hand, using the augmented histamine test we have found that achlorhydria is infrequent in thyrotoxicosis and the mean values for acid secretion are the same as in normal people. There thus appears to be a resistance to the usual stimuli to gastric secretion in thyrotoxicosis which can be overcome by maximal stimulation with histamine. We have shown that in some cases active thyrotoxicosis can depress the secretion of acid by the stomach temporarily, even in the A.H.T.

Berryhill and Williams (1932) suggested that an imbalance between the sympathetic and parasympathetic nervous systems was responsible for this phenomenon. In man vagotomy reduces the secretion of acid in response to augmented histamine stimulation (Gillespie and Kay, 1961), and in conscious dogs with gastric fistulae stimulation of the vagus conspicuously increases the maximal histamine acid output (Marks, Komarov, and Shay, 1960). Inhibition of the vagus might account for the lower acid secretion of some patients with thyrotoxicosis, and it would be interesting to examine the effects of cholinergic drugs, and of medical vagotomy induced by injecting hexamethonium and atropine, on the acid output of thyrotoxic patients with depressed acid secretion. Little seems to be known about the effects of the sympathetic nerves on the secretion of acid by the stomach, and the subject is not discussed in a recent monograph on secretory mechanisms of the gastrointestinal tract (Gregory, 1962).

Our other important finding is that complete or nearly complete achlorhydria and latent pernicious anaemia are probably more common than normal in patients who have recovered from thyrotoxicosis, though the number of cases we have examined is smaller than we would have wished. This would suggest that the temporary depression of gastric secretion which occurs in the active phase of thyrotoxicosis can sometimes set in train a process which leads to permanent achlorhydria. However, the relation between thyrotoxicosis and pernicious anaemia is not a simple one

of cause and effect, for frequently the pernicious anaemia precedes the development of the thyrotoxicosis.

The gastric mucosa and the thyroid gland are both derived from the primitive foregut. Each has the property of concentrating iodine (Brown-Grant, 1961) and there are other affinities between them. Taylor (1959) and Schwartz (1960) have demonstrated that the sera of some patients with pernicious anaemia contain an inhibitor of intrinsic factor, and Taylor, Roitt, Doniach, Couchman, and Shapland (1962) have detected antibodies against gastric cytoplasm in 123 out of 143 patients with pernicious anaemia.

It is now generally agreed that disease of the thyroid gland—thyrotoxicosis as well as spontaneous hypothyroidism—is associated with a high incidence of circulating antibodies against one or more of the thyroid antigens (Roitt and Doniach, 1958). Of great interest in relation to the association between the two diseases is the fact that antibodies to thyroid are abnormally common in pernicious anaemia and vice versa. Irvine, Davies, Delamore, and Williams (1962) noted complement-fixing antibodies to thyroid in 37% of cases of pernicious anaemia compared with 4% of hospital control patients, and similarly they found that approximately 25% of patients with spontaneous hypothyroidism or Hashimoto's thyroiditis had positive complement-fixation tests with gastric mucosa as compared with 4% of the hospital controls. Doniach, Roitt, and Taylor (1963) likewise found that the incidence of thyroid antibodies was significantly higher in pernicious-anaemia patients without overt thyroid disease than in normal controls and that there was an increased incidence of gastric cytoplasmic antibodies in thyrotoxicosis and Hashimoto's disease.

There is thus good evidence that autoimmune reactions can be demonstrated in the majority of cases of thyroid disease and pernicious anaemia and that in a smaller proportion of cases cross-reactions occur; but it remains to be shown whether the disturbances in the immune responses are causative or the result of the underlying disease processes. Taylor *et al.* (1962) have shown that there is a lack of correlation between the thyroid antibodies and the gastric antibodies—that is, the antibodies are not similar. However, Meulengracht (1929) made the observation that his patients with pernicious anaemia who had also suffered from thyrotoxicosis were the youngest members of his clinic; this suggests that the pathological mechanisms of thyrotoxicosis can encourage the early development of atrophic gastritis and gastric atrophy. Cases of latent pernicious anaemia and treated thyrotoxicosis should be of special interest for the study of the sequence of events.

Summary

Analysis of the literature reveals that achlorhydria has been found more commonly than normal in patients with thyrotoxicosis when conventional methods of gastric analysis have been used.

Using the augmented histamine test, we have found achlorhydria only once in 47 patients with active thyrotoxicosis.

The mean total mEq HCl secreted in 29 patients with active thyrotoxicosis in the augmented histamine test was normal. Nevertheless, in some of these patients the secretion of acid increased after treatment. It would thus appear that active thyrotoxicosis tends to inhibit the response of the stomach to stimulation of acid secretion.

The majority of the gastric biopsies obtained from 36 patients with active thyrotoxicosis showed no abnormality.

The serum-vitamin-B₁₂ concentrations of 26 patients with untreated thyrotoxicosis were normal.

Among 46 patients who had been treated for thyrotoxicosis between one and nine years previously there were four with complete or nearly complete achlorhydria, of whom two had latent pernicious anaemia.

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ADRENAL CORTICAL AND PITUITARY FUNCTION AFTER INTRARECTAL STEROID THERAPY

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Intrarectal steroids are being used more and more frequently in the treatment of ulcerative colitis. The two methods most commonly used are the slow-infusion method of Truelove (1956), using hydrocortisone hemisuccinate, and the single-dose bag method of Matts, using prednisolone phosphate (Matts, 1960a, 1960b, 1961a, 1962a) or betamethasone phosphate (Matts, 1962b). It is clearly desirable to know whether significant absorption occurs, because of the possibility of adrenal cortical suppression. There have been a few reports which show that hydrocortisone and methylprednisolone are absorbed (Liddle, 1956; Nabarro, Moxham, Walker, and Slater, 1957; Spencer, Kirsner, and Palmer, 1960), but we could find no information on the absorption of prednisolone phosphate or betamethasone phosphate, which are the two steroids used in this hospital. This paper reports our observations on the effect of rectal administration of these two steroids on adrenal cortical and anterior pituitary function.

Materials and Methods

Eighteen patients with ulcerative colitis were studied, the criteria for diagnosis being those laid down elsewhere (Matts, 1961b, 1962a).

Six patients were given enemata containing 5 mg. of betamethasone phosphate and 12 were given enemata containing 20 mg. of prednisolone-21-phosphate; both steroids were given in buffered aqueous solution. The

therapeutic procedure was the same in all cases, the steroids being administered rectally by the single-dose bag method of Matts. During the first week one enema was given night and morning, and for a further three weeks enemata were given at night only.

Adrenal Cortical Function.—This was assessed immediately before and immediately after treatment in 14 patients by determining the response to A.C.T.H. In 12 this was done as follows: three consecutive 24-hour urines were collected, after which 80 units of corticotrophin zinc (Jenkins, 1958) was given daily for three days by intramuscular injection. The urinary 17-hydroxycorticosteroids (17-O.H.C.S.) were estimated by the method of Norymberski (1961). In the other two cases A.C.T.H. was given intravenously (Eik-Nes, Sandberg, Nelson, Tyler, and Samuels, 1954); 25 units were infused in 500 ml. of 0.9% saline over a six-hour period, and the plasma 17-O.H.C.S. was determined by the method of Silber and Porter (1954), as modified by Rudd, Cowper, and Crawford (1961).

Anterior Pituitary Function.—The capacity of the anterior pituitary to secrete A.C.T.H. was tested before and after treatment in four patients treated with prednisolone. After treatment the test was begun 24 hours after the last enema had been given. After two control 24-hour urines the 11-beta-hydroxylase inhibitor metyrapone ("metopirone") was given for 48 hours in a dosage of 750 mg. four-hourly. The pituitary response to the fall