THE ACTION OF MONO-AMMONIUM GLYCYRRHIZINATE ON ADRENALECTOMIZED SUBJECTS AND ITS SYNERGISM WITH HYDROCORTISONE*

FRED ELMADJIAN, PH.D., JUSTIN M. HOPE, M.D. AND GREGORY PINCUS, SC.D.

The Worcester Foundation for Experimental Biology, Shrewsbury, Massachusetts, and Worcester State Hospital, Worcester, Massachusetts

MOLHUYSEN *et al.* (1) demonstrated that licorice extract taken orally by human subjects acted on the electrolyte balance in a manner similar to that of desoxycorticosterone acetate, namely, with the retention of sodium and the excretion of potassium. Groen and his associates (2, 3, 4) extended these findings to demonstrate that glycyrrhizinic acid[1] and its hydrolysis product, glycyrrhetic acid obtained from licorice, were the active ingredients of the extract. Though Groen *et al.* had some success in the maintenance of patients with Addison's disease on licorice preparations, Borst and his associates (5) noted that these preparations in a case of Addison's were ineffective when used alone. However, they did note that small doses of cortisone used in conjunction with licorice were quite effective in maintaining the electrolyte balance in adrenal deficiency states, and suggested that those cases of Addison's disease which did respond to licorice still had remnants of functional adrenocortical tissue (5). Recently Hudson *et al.* reported some studies on the use of small doses of cortisone with licorice preparations in adrenalectomized patients (6, 7).

This study[2] comprises data on the effectiveness of mono-ammonium glycyrrhizinate (MAG) in the maintenance of 2 adrenalectomized patients. Clinical and metabolic observations were made during a period in which varying doses of MAG and hydrocortisone were administered. Laboratory observations included determinations of serum potassium, serum sodium and plasma cholesterol levels, blood eosinophil counts, and urinary sodium, potassium and 17-ketosteroid excretion.

Received May 5, 1955.

* This investigation has been aided by grants from MacAndrews Forbes Company, Camden, New Jersey, and the U. S. Public Health Service, No. M657.

[1] Glycyrrhizinic acid consists of a disaccharide moiety and one molecule of the triterpine, glycyrrhetinic acid.

[2] The authors are deeply indebted to Dr. Lincoln Lebeaux for his invaluable assistance in the execution of this study.

Mono-ammonium glycyrrhizinate was kindly supplied by Dr. C. K. Swift of MacAndrews Forbes Company.

The Endocrine Society. Downloaded from press.endocrine.org by [${individualUser.displayName}] on 08 September 2015. at 02:21 For personal use only. No other uses without permission. . All rights reserved.

ADRENALECTOMIZED SUBJECTS

The subjects selected for this study were 2 chronic schizophrenic female patients (C. P. and P.M.), in each of whom the psychosis was of fifteen years' duration. Both patients had had carcinoma of the breast for which radical mastectomy had been performed prior to their admission to Worcester State Hospital. Bilateral adrenalectomy was performed on June 16, 1952. Although both patients were said to have metastasis, evidence of metastasis was observed only in Patient C.P., who prior to adrenalectomy had an indurated immobile mass the size of a lemon in the postoperative mastectomy scar on the left. Following the adrenalectomy, the mass gradually decreased in size, and by the time of this study was no longer palpable.

In preparation for the mono-ammonium glycyrrhizinate (MAG) experiment, the daily oral dose of 80 mg. of hydrocortisone which the patients were receiving while other studies were in progress, was gradually reduced over a period of sixteen days to 40 mg. per day, at which time the MAG was started in a dosage of 4.0 Gm. by mouth daily with 2.0 Gm. of sodium chloride. *The sodium chloride (2.0 Gm. per day) was given throughout the entire study.* Prior to the beginning of the experiment, both patients were alert, active and voiced no somatic complaints. Both patients had voracious appetities and slept well. During the sixteen-day period immediately prior to the administration of MAG, the blood pressure of Patient C.P. ranged from 144/70 to 130/80, and that of Patient P.M. varied between 104/56 and 102/70.

CASE HISTORIES

Subject C.P.

On May 4, 1953, MAG was started in a dosage of 4.0 Gm. a day orally, in conjunction with oral hydrocortisone, 40 mg. daily. The patient was kept on this regimen for seven days. The medication schedule may be seen in Figure 1. During this period no changes were observed, except a tendency to sleep more. On May 11, the hydrocortisone was reduced to 20 mg. a day. During this period the patient's appetite, though adequate, was not voracious as it had been and she was less active. On May 13, pitting peripheral edema was noted for the first time and this persisted for three days before subsiding. During one period when MAG was reduced from 4.0 to 2.0 Gm. daily (May 18–22), the patient's appetite became poor, she was lethargic and exertional dyspnea was noted for the first time. When MAG was increased to 4.0 Gm. a day, the patient showed marked clinical improvement and despite the fact that on May 25 the hydrocortisone was reduced to 10 mg. per day, her condition remained satisfactory for the next eleven days. The lethargy disappeared and her food intake returned to its previous ravenous level. The only abnormality on physical examination during this period was an occasional extra cardiac systole.

On June 8, hydrocortisone was discontinued and the patient was maintained on MAG, 4.0 Gm. per day. For the first twenty-four hours, no untoward symptoms were

The Endocrine Society. Downloaded from press.endocrine.org by [${individualUser.displayName}] on 08 September 2015. at 02:21 For personal use only. No other uses without permission. . All rights reserved.

noted. However, by the second day she lost all spontaneous volubility, answered questions with a paucity of words and spoke only in monosyllables. The tendency to sleep became prominent and the patient remained in bed all day. Peripheral edema returned and the blood pressure dropped to 122/72, from the 140/90 observed on June 8. On June 11, the patient was lethargic, weak, anorexic and took small amounts of liquid only after strong urging. There was a marked oliguria and she passed three watery stools during the day. The blood pressure dropped to 114/89, the temperature rose to 100.6° F rectally and the pulse was rapid at an average rate of 104 per minute. Since the patient's condition was becoming worse and circulatory embarrassment was evident, hydrocortisone was resumed in a dosage of 10 mg. per day orally. On June 12, a clysis of 1,000 cc. of 5 per cent glucose was given. No improvement was evident for the next thirty-six hours. However, by the evening of the second day after resumption of hydrocortisone, definite improvement was discernible and by the third day the patient was eating well, spoke spontaneously and got out of bed. By June 17, the peripheral edema had disappeared and no signs of circulatory embarrassment were evident.

On June 29, hydrocortisone was again discontinued and the patient was maintained on MAG, 4.0 Gm. per day. The clinical status was characterized by increasing irritability, restlessness, lethargy, lack of appetite, weakness and somnolence—a clinical picture which was similar to that which occurred during the previous period when the hydrocortisone was discontinued. On July 4, oral hydrocortisone in a dosage of 20 mg. per day was begun. The patient's condition was again markedly improved. Gradually the hydrocortisone was increased to 40 mg. a day and on July 15 the MAG was discontinued. The clinical status of the patient was satisfactory during the remainder of the study.

Subject P.M.

In Patient P.M. the medication schedule was similar to that in Patient C.P. On May 4, 1953, MAG was started in a dosage of 4.0 Gm. daily, the oral dose of hydrocortisone having been gradually decreased over the preceding sixteen days from 80 mg. per day to 40 mg. per day. The following day the patient became restless, paced the floor and although she frequently returned to bed, did not sleep soundly. The next day her face was swollen and an erythematous flush of butterfly configuration covered the nose and the malar prominences. This condition was diagnosed as erysipelas. Although the patient's temperature was not elevated, she was given penicillin, 300,000 units a day, for three days. By May 8, the swelling and discoloration of the face had subsided. She recovered from this facial infection with no signs of adrenal deficiency; there was no increase in the daily dose of hydrocortisone. When the dosage of hydrocortisone was reduced to 20 mg. a day on May 11, pitting peripheral edema developed; she complained of fatigue and was quite lethargic. These untoward manifestations persisted for two days and then spontaneously disappeared without change in the medication schedule. On May 18, the hydrocortisone was decreased to 10 mg. and the MAG to 2.0 Gm. daily. Despite the development of a florid perineal cellulitis which required 600,000 units of penicillin for relief, the patient's general physical condition remained satisfactory and there were no signs of adrenal embarrassment. On May 22 MAG was increased to 4.0 Gm. daily.

On June 8, the hydrocortisone was discontinued, but the MAG was kept at 4.0 Gm. per day. At 6:00 A.M. the following day the patient complained of nausea and vomited a small amount of greenish liquid. The temperature was 100.4° F and the pulse was weak and rapid at 114 per minute. The blood pressure was stable at 120/80. The following day

The Endocrine Society. Downloaded from press.endocrine.org by [${individualUser.displayName}] on 08 September 2015. at 02:21 For personal use only. No other uses without permission. . All rights reserved.

the temperature rose to 102° F. Because of the hyperpyrexia, persistent nausea and vomiting, tenderness to palpation in the right upper quadrant and the history of a previous attack of empyema of the gallbladder, a diagnosis of acute cholecystitis was made. On June 10, penicillin was started in a dosage of 600,000 units twice a day, and parenteral fluids were given.

On June 12, the patient had a brief period of unconsciousness during which she slumped in the nurse's arms while attempting to use the bed pan. The blood pressure dropped to 100/80, and the possibility of impending adrenal crisis prompted the resumption of hydrocortisone, 10 mg. per day. The patient responded well to hydrocortisone at this dosage level and a satisfactory clinical status was restored on June 14. Throughout the next two weeks her condition was good, with the maintenance of normal eating and sleeping habits.

On June 29, hydrocortisone was again discontinued. On July 1, the patient was observed to be drowsy. Drowsiness continued during the following day, but physical examination revealed no other abnormality. On July 3, she was lethargic, complained of nausea, and refused to eat dinner or supper. During the night she retained only small amounts of fluid. However, no circulatory embarrassment was evident and the blood pressure was 112/80. On July 4, hydrocortisone was resumed in a dosage of 20 mg. a day orally. The patient remained listless and nauseated, but did not vomit. On July 7, she had pain in her left shoulder and vomited periodically throughout the day. She complained of feeling cold and her skin was cold to touch, although her temperature was 99.8° F rectally. Her blood pressure dropped to 90/52, the pulse was feeble and rapid, and circulatory embarrassment was evident. The inability of the patient to retain oral medication necessitated the intravenous administration of hydrocortisone, 100 mg. in 500 cc. of saline. Though a favorable clinical response to this measure was promptly discernible, it was of short duration. The following day she again lapsed into a state of crisis. She was given hydrocortisone, 100 mg. in 500 cc. of saline intravenously, and cortisone acetate, 25 mg. three times a day intramuscularly. She responded favorably to these measures and by the following evening her clinical status had significantly improved. This improvement was maintained. On July 12, the cortisone acetate was reduced to 25 mg. per day intramuscularly and on July 16 it was discontinued. On July 17 the MAG was discontinued and the patient remained in good clinical condition for the remainder of the study on an oral maintenance dosage of 40 mg. of hydrocortisone daily.

Both of these patients had had schizophrenia for many years, for which they had been institutionalized. At the time this study was instituted both patients showed the cardinal signs of this illness, *i.e.*, a flat, inappropriate affective response, disorganization of thought processes, tangential and irrelevant associations, restriction of the scope of awareness and a complete loss of insight. The psychiatric status of both patients remained unchanged throughout the entire period of study, except on those occasions when they lapsed into an adrenal crisis. On such occasions both patients showed none of the cardinal signs of schizophrenia on examination. However, as soon as adrenal balance was restored by appropriate treatment the unmistakable signs of an active schizophrenic process again became evident in both subjects.

The Endocrine Society. Downloaded from press.endocrine.org by [${individualUser.displayName}] on 08 September 2015. at 02:21 For personal use only. No other uses without permission. . All rights reserved.

METABOLIC STUDIES

Blood

Figures 1 and 2 show the blood pressure, eosinophil counts, serum Na/K ratio, plasma cholesterol level, and the medication schedule of MAG and adrenal steroids for C.P. and P.M., respectively.

In general the eosinophil pattern was similar in both patients. During the first period of hydrocortisone discontinuance an abrupt increase in the count was noted. With return to a dosage of 10 mg. of hydrocortisone a day, the count became stabilized at the higher levels. Again, with the second

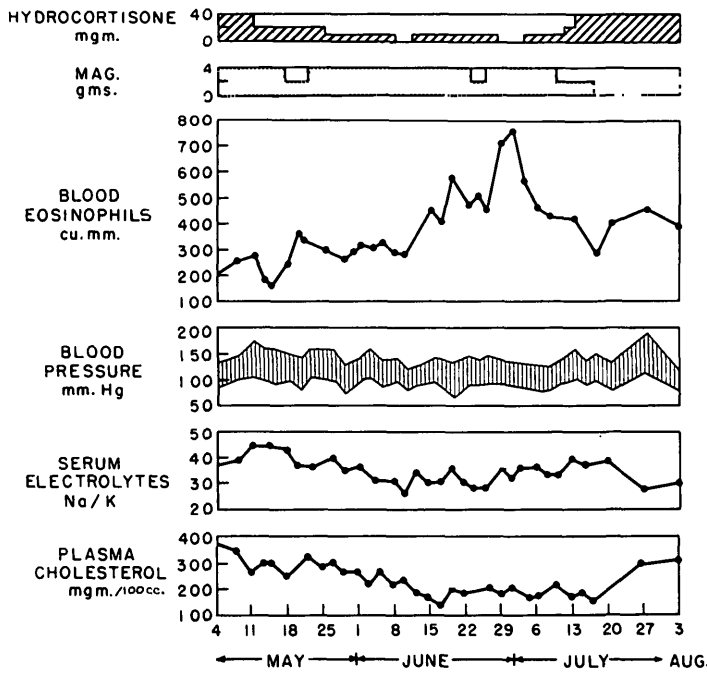

FIG. 1. Medication schedule and blood data on adrenalectomized Patient C.P.

period of steroid abstinence the eosinophil count rose promptly. It may be observed that Patient P.M. showed a pronounced rise in the eosinophil count during the adrenal crisis; following the intravenous administration of 100 mg. of hydrocortisone there was a marked drop. By the end of the study period the eosinophil counts had decreased steadily. However, both patients at this time showed higher eosinophil counts than at the initiation of the observations.

There is evidence to suggest that the serum Na/K (molar ratio) and blood pressure are positively related. Increases and decreases of the Na/K ratio followed very closely the corresponding changes in blood pressure. In the course of the study it became evident that these fluctuations were also

The Endocrine Society. Downloaded from press.endocrine.org by [${individualUser.displayName}] on 08 September 2015. at 02:21 For personal use only. No other uses without permission. . All rights reserved.

related to the clinical condition of the patients (*see* case histories). The blood pressure and electrolyte ratio at the end of the study, when a dose of only 40 mg. of hydrocortisone was being administered, were lower than when 40 mg. of hydrocortisone was supplemented by 4.0 Gm. of MAG at the beginning of the observation period.

A feature of the blood chemistry data which was not related to the clinical condition of the patients but rather to the dose of hydrocortisone, was the plasma cholesterol level. In both patients a steady decline in the

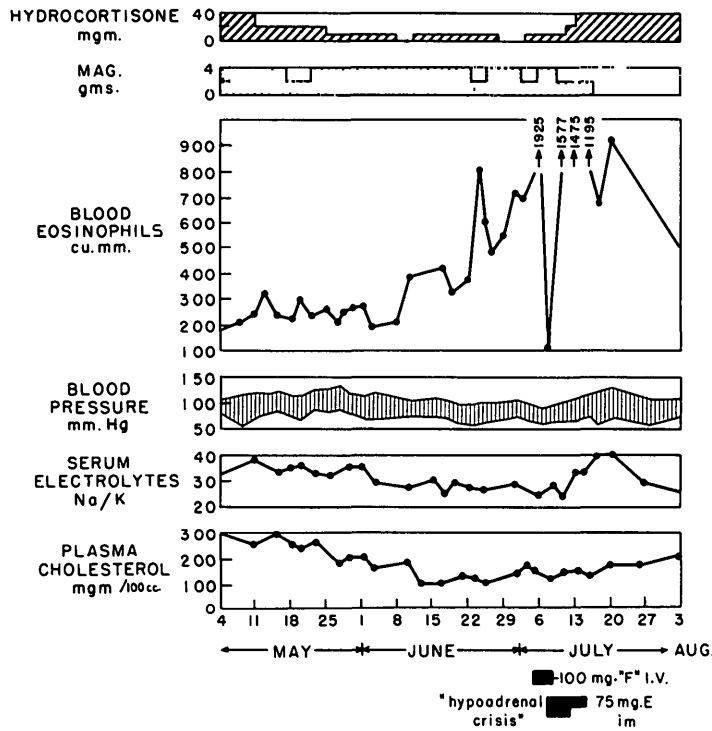

FIG. 2. Medication schedule and blood data on adrenalectomized Patient P.M.

cholesterol values was associated with a reduction in the dose of hydrocortisone. The lowest cholesterol values were observed during the periods when the patients received no hydrocortisone or when the dosage was reduced to 10 mg. a day. With the return to higher dosage levels of hydrocortisone there occurred a steady rise in the cholesterol values to those observed at the initiation of the study.

Urine

Urine collections were made on both patients during the study. Patient P.M. was more cooperative, and therefore her data are more complete.

The Endocrine Society. Downloaded from press.endocrine.org by [${individualUser.displayName}] on 08 September 2015. at 02:21 For personal use only. No other uses without permission. . All rights reserved.

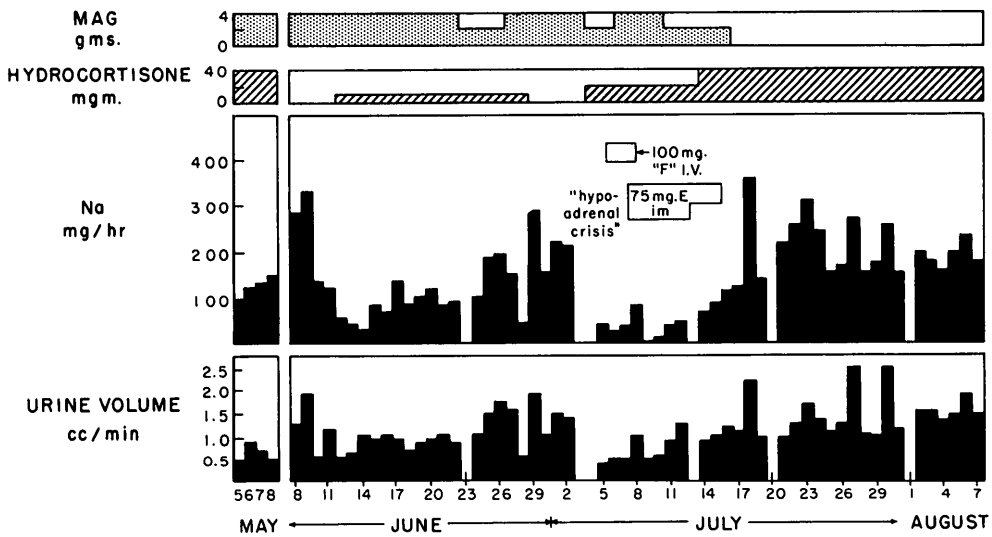

FIG. 3. Rate of urinary sodium and urine excretion in adrenalectomized Patient P.M.

Figure 3 shows the urinary sodium excretion of Patient P.M. recorded in mg. per hour and urinary volume in cc. per minute; and Figure 4 depicts the K/Na ratio (by weight) and the 17-ketosteroid excretion in mg. per twenty-four hours. The corresponding data on Patient C.P. are listed in Table 1.

In Figures 3 and 4 it should be noted that there is a period from May 8

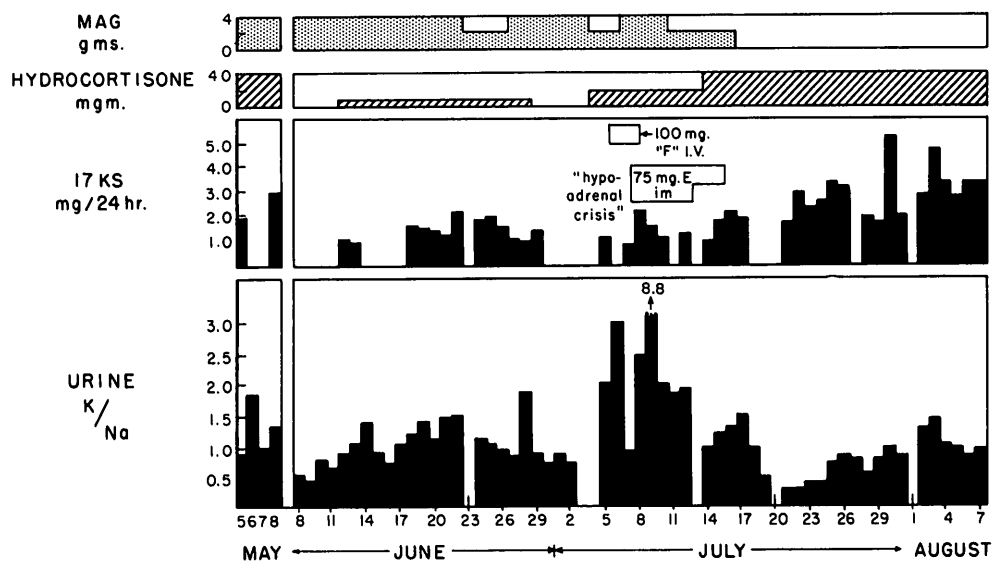

FIG. 4. 17-Ketosteroid excretion and K/Na ratio of urine in adrenalectomized Patient P.M.

The Endocrine Society. Downloaded from press.endocrine.org by [${individualUser.displayName}] on 08 September 2015. at 02:21 For personal use only. No other uses without permission. . All rights reserved.

TABLE 1. URINARY ELECTROLYTE AND 17-KETOSTEROID EXCRETION OF PATIENT C.P.*

Date (1953)	Urine vol. (cc./min.)	Na (mg./hr.)	K (mg./hr.)	17-KS (24 hrs.)
May 5	.49	120	101	4.32
6	.85	142	153	—
7	.60	115	94	—
8	.69	131	118	2.40
June 8	.49	103	131	—
9	.48	63	35	—
14	.67	18	14	.60
15	.47	33	17	—
16	.52	69	47	—
19	.34	36	48	.62
24	.79	74	41	.70
26	.61	91	36	.53
27	.40	62	37	.72
28	.53	43	26	.72
29	.31	31	44	.76
30	.35	34	26	—
July 7	.43	23	160?	1.82
8	.38	46	53	.87
9	.86	86	103	.98
10	.53	35	30	.65
11	.67	75	99	.86
12	.80	95	110	1.18
14	.81	78	92	1.10
15	.74	90	61	1.20
17	.80	112	72	1.68
18	.50	68	49	1.61
21	.36	74	34	1.20
22	.55	85	45	1.08
24	.80	136	61	1.56
25	.72	212	143	2.38
29	.58	·85	102	1.99
30	.74	—	—	2.40
Aug. 4	.76	142	107	2.88
5	1.10	169	111	3.12
6	.94	150	113	2.40
7	.93	164	124	1.80

* *See* Figure 1 for medication schedule, and text for case history.

The Endocrine Society. Downloaded from press.endocrine.org by [${individualUser.displayName}] on 08 September 2015. at 02:21 For personal use only. No other uses without permission. . All rights reserved.

to June 8 when no collections were obtained.

During the period when Patient P.M. was receiving 40 mg. of hydrocortisone daily supplemented by 4.0 Gm. of MAG, the 17-ketosteroid excretion rate was 2–3 mg. per twenty-four hours. Immediately following the first period, during which hydrocortisone was withheld, the 17-ketosteroid excretion decreased to less than 1 mg. per day. At a dosage level of 10 mg. of hydrocortisone daily the steroid excretion rose slightly, varying between 1 and 2 mg. per day. Again, during the second period of hydrocortisone abstinence beginning on May 29, the steroid excretion dropped to less than 1 mg. per day. With the resumption of larger doses of hydrocortisone an increase in 17-ketosteroid excretion was noted. At the end of the study the excretion values had returned to the levels of 2–3 mg. per day and higher which prevailed at the initiation of the study. It should be noted that during the period of administration of intramuscular cortisone acetate and intravenous hydrocortisone, the increase in 17-ketosteroid excretion was not commensurate with the amount of steroids administered.

The volume of urine excreted appeared to be correlated with the amount of sodium excreted. This was strikingly evident in Patient P.M. (Fig. 3). During the first period in which hydrocortisone was withheld there was a pronounced loss of water and sodium, which was followed by a reduced urinary volume and sodium excretion. During the period of marked clinical deterioration (June 10 through June 11) this relationship was also reflected by a decline in the urinary K/Na ratio (*cf.* Fig. 4). With the resumption of hydrocortisone in a dosage of 10 mg. per day, the sodium excretion slowly increased and continued at the levels which existed a month earlier during the period when the patient was receiving hydrocortisone, 40 mg. daily supplemented by 4 Gm. of MAG. On May 23, when the MAG was reduced to 2 Gm. per day, an increase in sodium excretion was again noted, but this was not as large as during the omission of hydrocortisone. Upon the resumption of MAG (4.0 Gm. a day) on May 27, marked sodium retention was evident by the second day. These changes in electrolyte balance were reflected by decreases and increases in the urinary K/Na ratio. When the patient was maintained on 4.0 Gm. of MAG per day in the absence of hydrocortisone, inability of the patient to retain sodium was again observed. Upon resumption of hydrocortisone (20 mg. per day), the electrolyte pattern returned to normal, showing sodium retention and an increase in the K/Na ratio. However, when the patient was unable to retain oral medication, adrenal crisis occurred. The measures taken to control the adrenal crisis, namely, the administration of hydrocortisone intravenously and cortisone acetate intramuscularly, caused further reten-

The Endocrine Society. Downloaded from press.endocrine.org by [${individualUser.displayName}] on 08 September 2015. at 02:21 For personal use only. No other uses without permission. . All rights reserved.

tion of sodium and excretion of potassium as indicated by the high urinary K/Na ratio. When the MAG was discontinued on July 17, there was a marked increase in the excretion of sodium, which remained high for the remainder of the study except for a slight decrease observed by the end of the period of observation.

Figure 5 contains data regarding the sodium excretion and urinary K/Na ratio of Patient P.M. during the period in which hydrocortisone (40 mg. per day) was being administered. Placebos of lactose were given during the control period and during the experimental period when the

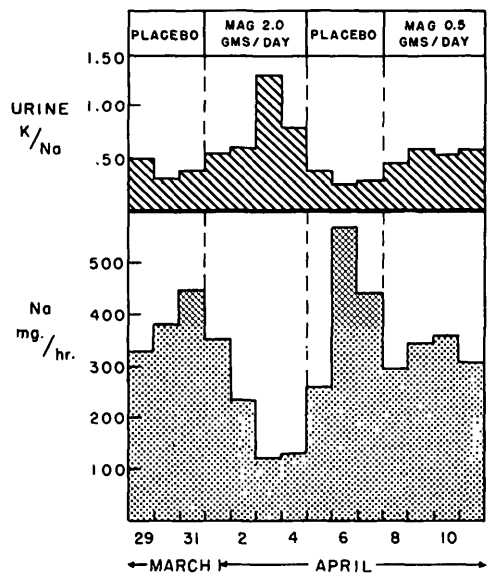

FIG. 5. The effect of varying doses of MAG on the electrolyte excretion of Patient P.M. maintained on 40 mg. of hydrocortisone and 2.0 Gm. of sodium chloride orally per day.

patient was receiving MAG, 2.0 and 0.5 Gm. per day respectively. It may be seen that a daily oral dose of 2 Gm. of MAG has a potent sodium-retaining effect when supplemented by 40 mg. of hydrocortisone, but not when employed in conjunction with a daily dose of only 10 mg. of hydrocortisone (*cf.* Fig. 3). The smaller dose of 0.5 Gm. of MAG has little if any sodium-retaining effect.

DISCUSSION

MAG alone, given in the dosage employed in these studies, was ineffective in the maintenance of 2 adrenalectomized patients. On two occasions an attempt was made to maintain the patients on 4.0 Gm. of MAG per day alone (2.0 Gm. of salt per day was given throughout the study).

The Endocrine Society. Downloaded from press.endocrine.org by [${individualUser.displayName}] on 08 September 2015. at 02:21 For personal use only. No other uses without permission. . All rights reserved.

Within the first twenty-four hours there was a loss of sodium and fluid, followed promptly by a decline in the clinical status of both patients which was evident by the second day. However, as little as 10 mg. of hydrocortisone orally in conjunction with the 4.0 Gm. of MAG per day was effective in maintaining a satisfactory clinical state, as well as fluid and electrolyte balance. On the occasions when the dose of MAG was reduced from 4.0 to 2.0 Gm. daily while hydrocortisone was maintained at a level of 10 mg. daily, there was a perceptible decline in the clinical status associated with sodium and fluid depletion. When Patient P.M. was given 2.0 Gm. of MAG while receiving 40 mg. of hydrocortisone per day, there was a sharp reduction in urinary sodium excretion, which was promptly reflected by a corresponding rise in K/Na ratio (Fig. 5).

The results of this study do not supply conclusive answers to the question of whether MAG, when employed alone, is in fact sufficient to maintain life in adrenalectomized patients. Hudson and his associates (6, 7) apparently were able to maintain life in 1 of 3 adrenalectomized patients for several weeks, employing glycyrrhizin alone. However, all 3 patients were in a grave clinical condition throughout the period of treatment. The occurrence of drowsiness and lethargy during the abstinence from hydrocortisone is not, in all probability, due to a specific MAG effect, but rather to the state of extreme hypoadrenalism. These studies confirm the observation of Borst *et al.* (5) to the effect that MAG alone is ineffective in the maintenance of certain patients with Addison's disease in whom there are no remnants of adrenal tissue.

The metabolic data indicate that MAG is not effective in the maintenance of electrolyte balance when given alone to adrenalectomized patients. The electrolyte data on both serum (Figs. 1 and 2) and urine (Figs. 3 and 4) also show this to be the case. However, in conjunction with small doses of hydrocortisone, MAG in a daily dosage of 4.0 Gm. is quite potent. Furthermore, MAG had no effect on the eosinophil count or the plasma cholesterol level. The steady decline in the cholesterol values was closely related to the hydrocortisone dosage. The possibility of diet playing a role in determining the plasma cholesterol level must be considered. However, it is apparent in both patients that, though a period of loss of appetite occurred, this was only short lived and on the occasions when the patients were receiving 10 mg. of hydrocortisone in conjunction with 4.0 Gm. of MAG per day, their appetites were as voracious as at any time throughout the entire period of study. It is probable that these observations on cholesterol values are similar to those of Di Luzio *et al.* (8), who showed that plasma lipid levels were increased when adrenalectomized dogs were given large doses of cortisone in addition to desoxycorticosterone acetate.

The Endocrine Society. Downloaded from press.endocrine.org by [${individualUser.displayName}] on 08 September 2015. at 02:21 For personal use only. No other uses without permission. . All rights reserved.

SUMMARY

Two adrenalectomized patients who were given mono-ammonium glycyrrhizinate (MAG) in an oral dosage of 4 Gm. daily were not maintained in a satisfactory clinical state.

The desoxycorticosterone acetate-like action of MAG, observed in subjects with intact adrenals, was absent.

When as little as 10 mg. of hydrocortisone per day was given orally with 4.0 Gm. of MAG, both adrenalectomized patients were maintained in excellent clinical condition. Reduction of the dosage of MAG from 4.0 Gm. to 2.0 Gm. per day was followed by a deterioration in the clinical condition of the patients as well as an increase in sodium excretion. When the dosage of hydrocortisone was raised to 40 mg. daily, the administration of 2.0 Gm. of MAG daily resulted in marked sodium retention. Thus, hydrocortisone and mono-ammonium glycyrrhizinate have synergistic effects in the adrenalectomized patient.

Eosinophil counts and plasma cholesterol values were unaffected by mono-ammonium glycyrrhizinate. Plasma cholesterol values were positively related to the dosage of hydrocortisone.

REFERENCES

1. Molhuysen, J. A.; Gerbrandy, J.; de Vries, L. A.; de Jong, J. C.; Lenstra, J. B.; Turner, K. P., and Borst, J. G.: A liquorice extract with desoxycorticosterone-like action, *Lancet* **2**: 381–386, 1950.
2. Groen, J.; Pelser, H.; Willebrands, A. F., and Kamminga, C. E.: Extract of licorice for treatment of Addison's disease, *New England J. Med.* **244**: 471–475, 1951.
3. Groen, J.; Pelser, H.; Frenkel, M.; Kamminga, C. E., and Willebrands, A. F.: Effect of glycyrrhizinic acid on electrolyte metabolism in Addison's disease, *J. Clin. Invest.* **31**: 87–91, 1952.
4. Pelser, H. E.; Willebrands, A. F.; Frenkel, R. M.; Van Der Heide, R. M., and Groen, J. : Investigation of electrolyte metabolism during treatment of Addison's disease with glycyrrhizinic acid and glycyrrhetinic acid, *Nederl. tijdschr. v. geneesk.* **97**: 348–359, 1953.
5. Borst, J. G.; ten Holt, S. P.; de Vries, L. A., and Molhuysen, J. A.: Synergistic action of liquorice and cortisone in Addison's and Simmonds's disease, *Lancet* **1**: 657–663. 1953.
6. Hudson, P. B.; Mittleman, A., and Mann, P.: Urinary steroid excretion after total adrenalectomy. I. Level of 17-ketosteroids in cancer patients maintained on varying amounts of cortisone acetate and glycyrrhizin, *J. Clin. Endocrinol. & Metab.* **13**: 1064–1069, 1953.
7. Hudson, P. B.; Mittleman, A., and Podberezec, M.: Use of glycyrrhizin after bilateral adrenalectomy, *New England J. Med.*, **251**: 641–646, 1954.
8. Di Luzio, N. R.; Shore, M. L., and Zilversmit, D. B.: Effect of cortisone and desoxycorticosterone acetate on plasma lipids of adrenalectomized dogs, *Metabolism* **3**: 424–430, 1954.

The Endocrine Society. Downloaded from press.endocrine.org by [${individualUser.displayName}] on 08 September 2015. at 02:21 For personal use only. No other uses without permission. . All rights reserved.