HYPOADRENOCORTICISM

JOHN W. TINTERA, M.D. MEMORIAL ISSUE
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"The primary objective in the treatment of Hypoadrenocorticism is to achieve a state of Homeostasis between the endocrine glands, their dependent systems, and the organism as a whole. Homeostasis is the establishment of a balanced relationship between the dietary, hormonal and nervous functions (systems) of the body. The purpose, therefore, in endocrinology is to strive primarily to attain this state of balance and secondarily, to maintain this balance by a state of mutual reciprocity."

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TABLE OF CONTENTS

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The Hypoadrenocortical State and Its Management

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IN A SELECT recorded group of 200 subjects studied over the past fifteen years, the varied symptoms exhibited, suggested some phase of adrenocortical dysfunction: either lack of adequate adrenal cortical hormone production or an imbalance among these hormones. Essentially, all of the symptoms seemed to have some bearing on the integrity of the adrenal cortex and responded, in effect, to the same mode of therapy. This report will use the conveniently designated topic of hypoadrenocorticism, and elaborations around it will be on the practical plane.

Etiology and Pathogenesis

Simply stated: hypoadrenocorticism is Addison's disease. The usually encountered case dealt with herein is actually "subclinical Addison's disease." By thus defining it, a former hypothesis—that the adrenal cortex functioned according to the classic "all or none" law—is repudiated as being contrary to both clinical and experimental experience.

Hypoadrenocorticism may be congenital or acquired, complete or partial. The two former subdivisions frequently fail of recognition. An etiologic classification, therefore, also derives from practical considerations:

1. Constitutional or primary hypoadrenocorticism
2. Congenital hypoadrenocorticism
3. Secondary hypoadrenocorticism
   A. Hypopituitarism
   B. Acquired hypoadrenocorticism
      1. Stress
      2. Steroid therapy (cortisone and hydrocortisone)

CONSTITUTIONAL OR PRIMARY HYPOADRENOCORTICISM. — The constitutional type may be a Mendelian trait. Because it is most common, it typifies subjects discussed in this paper. The cognitive, characteristic asthenic habitus, peculiar idiosyncrasies and sensitivities, longevity, etc., may be traced in the family history, maternal, paternal, or both.

CONGENITAL HYPOADRENOCORTICISM. — This type is encountered in the infant whose mother is deficient in adrenal cortical secretion. During pregnancy the adrenal of the growing fetus and the placenta apparently supplement the mother with the necessary adrenal hormones. It may be presumed that the fetal adrenals can be thus depleted. Infants manifesting such adrenal insufficiency often die neonatally; "pyloric stenosis" has been so ascribed. Others may manifest hypoadrenocorticism only as they grow older with the deficient gland inadequate to ordinary stress.*

* Natelson, *et al.*[1] studied the "immature infant" and observed that "adrenal immaturity" is a common finding in the premature infant. They use the term to denote a condition resulting in the inability of the infant to hold water, sodium ion, and chloride ion with no unequivocal histologic or pathologic evidence to show the adrenal involvement. It has also been found that the thymus gland does not regress in children with immature adrenals. Since hypersecretion from a stimulated adrenal during the alarm reaction does cause thymic involution,[2] it is logical to treat status thymicolymphaticus with adrenal cortical extracts.

SECONDARY HYPOADRENOCORTICISM (HYPOPITUITARISM AND ACQUIRED HYPOADRENOCORTICISM). — Hypofunction of the anterior hypophysis produces a variety of clinical pictures, depending on the amounts of specific tropic hormones produced, and so we may find hypoadrenocorticism as the result of such a condition flowered by symptoms of other glandular malfunctions.

Aside from cases resulting from hypopituitarism and steroid therapy, individuals subjected to great stresses, such as those referred to by Selye[3] in his "general adaptation syndrome" (G.A.S.), may develop hypoadrenocorticism. In these instances the glands work beyond their capacity, passing through the alarm reaction, the stage of resistance, and finally reaching the stage of exhaustion.

Symptomatology and Diagnosis

The chief or presenting complaints, associated symptomatology, related systemic disorders, and physical and laboratory findings are given in Table I. The order of percentage frequency by which they are tabulated is based on convenience for presentation (a few of the percentage assignments are based on a smaller sampling since these, emerging only as the series progressed, were not sought for and elicited except in more recently studied patients). However arbitrary this tabluation, its perusal reveals one significant fact. *The chief complaints listed for patients with hypoadrenocorticism are often similar to those found in persons who are in the hypoglycemic state.* Patients finally adjudged to be hypoadrenocortic invariably report feelings of weakness, fatigue, and faintness, all of which could result from periods of low blood sugar level, usually extant. These periods of hypoglycemia are exacerbated by and follow bouts

of emotional upsets after the initial hyperglycemia. In a series of business executives, Portis[4] has shown that hypoglycemia is definitely related to emotional stress. He suggested that the emotional centers which are exposed excessively to these stresses transmit impulses which cause overactivity of the parasympathetic system. This heightened vagal response stimulates the islet cells of the pancreas. Hyperinsulinism, which produces a low blood sugar level, develops from the stimulation of the islet cells.

TABLE I. — SYMPTOMATOLOGY IN 200 CASES

	Per Cent of 200 Cases
Chief Complaints*	
Fatigue (excessive)	94
Nervousness and irritability	86
Mental depression	79
Apprehensions	71
Weakness (excessive)	65
Lightheadedness	47
Faintness or fainting spells	42
Insomnia	40
Systemic Symptoms	
Head	
Headache	68
Tinnitus	3
Cardiovascular	
Palpitation	57
Tachycardia	15
Bradycardia	6
Gastrointestinal	
Craving for salt	84
Craving for sweets	75
Alcohol intolerance	66
Epigastric distress	51
Food or drug idiosyncrasies	47
Alternate diarhhea and constipation	45
Indigestion	40
Anorexia	34
Chronic colitis	4
Genitourinary	
Infrequency	25
Nocturia	17
Catamenial	
Premenstrual tension	85
Midperiod slowing	33
Neuromuscular	
Pain in sternomastoid and trapezius muscles	65
Backaches	48
Vertigo	20
Cerebral	
Inability to concentrate	77
Fears and apprehensions	65
Confused intervals	61
Poor memory	59
Feelings of frustration	56
Compulsive behavior	38

	Per Cent of 200 Cases
Associated or Possible Resulting Conditions	
Allergies	73
Hay Fever	23
Urticaria	20
Asthma	12
Others	18
Skin dermatitides	39
Heat exhaustion	36
Rheumatoid arthritis	21
Migraine	9
Rheumatic fever	7
Nephrosis	5
Epilepsy	3
Findings on Physical Examination	
Postural hypotension	93
Generalized cervical lymphadenitis	93
Skin thin and dry	91
Perspiration scanty	91
Hair sparse	83
Typical denture formation	80
Asthenic habitus	78
Positive Rogoff sign	71
Redness of thenar and hypothenar eminences	28
Blanching on exposure to cold	21
Laboratory Findings	
Low basal metabolic rate (average — 12)	85
X-ray — J-shaped stomach and visceroptosis	73
Eosinophilia	58
Glucose tolerance test (low flat curve)	51
Relative lymphocytosis	51
17-ketosteroids low	
Male (2.4 to 29; average 10.9 mg. per 24 hours)	
Female (1.2 to 22; average 7.7 mg. per 24 hours)	

* These are hypoglycemic in nature and tend to follow physical, mental, or emotional stress.

Whether the low blood sugar in the patient with hypoadrenocorticism is a result of similar autonomic manifestations remains undetermined. It may well be the case, however, since this type of patient is emotionally labile and responds vigorously to crucial stressful situations. Many of our patients show a glucose tolerance curve which forms practically a straight line at a low level. However, if the adrenals have been subjected to increased stress through indiscretions, e.g., high carbohydrate intake or abuses through alcohol or other toxic agents, changes occur in the liver so that a condition of fatty infiltration or degeneration ensues. With this situation a sudden rise in the blood sugar level as high as 300 or 400 mg. per 100 cc. of blood may occur, followed by a sudden drop to hypoglycemic levels. It is this sudden drop which usually precipitates symptoms.*

* Striker[5] has demonstrated that a patient maintaining a blood sugar of over 400 mg. had definite hypoglycemic reactions, pointing out that it is the suddenness of the fall in blood sugar which produces general reactions and not the level from which or to which it may have fallen.

Diagnosis should be possible from the history and symptomatology, together with the glucose tolerance curve and complete blood count. Inability to concentrate, loss of memory, mental depression, insomnia, periods of irritability, and a tendency to negativism and other personality aberrations are to be regarded as significant. Of pathognomonic significance, these patients are usually of the constitutionally inferior asthenic type, often falling in the allergic diathesis group, usually revealing a positive Rogoff Sign, relative lymphocytosis, and a typical low glucose tolerance curve. However, these findings may be masked, for example, in the patient who has a superimposed gonadal deficiency, with its typical obesity, or an altered glucose tolerance curve in an advanced case with hepatic damage. In addition, a history of great longevity without senility of the forebears is obtained.

Since the *gastrointestinal system* is particularly sensitive to emotional stress, many symptoms involving the digestive tract are reported. Chief among these is a dull ache or dragging or gnawing sensation in the epigastrium. With upset of carbohydrate metabolism pain or distress may occur in the epigastrium referred from the liver. In addition, these patients often have alternate periods of diarrhea and constipation. Their stools are frequently in the form of scybala, and chronic mucuous colitis or chronic ulcerative colitis may develop. Bercovitz,[6] in his treatment of ulcerative cases with adrenal cortical extract, states that, "It is quite obvious from even a casual observation of these patients that they are deficient in their adrenal cortical output."

GENITOURINARY COMPLAINTS. — The menarche has its onset somewhat later than average, and although it occurs regularly, there is an atypical flow lasting about seven days with profuse bleeding. In 33 per cent of the cases the peculiar aspect of this type of flow was that it ceased on about the fourth day almost completely or with just slight staining, started up again profusely on the fifth or sixth day, and then slowed up or stopped on the seventh. Eighty-five per cent of the women had premenstrual tensions with such manifestations as nervousness and emotional instability, headaches, and the accentuation of carbohydrate craving and, particularly in the alcoholic group, an almost uncontrollable desire to start drinking again. Dysmenorrhea is a frequent complaint because of infantile uteri, markedly retroflexed or retroverted. These small uteri may be the cause of the repeated spontanous abortions recorded in this series. It is possible that the abortions result from the fact that although the fetus grows at a normal rate, this rate is disproportionate to the rate of development of the uterus.*

* Pertinent to the assignment of abortion tendency in this category of patient is the fact that most effective treatment has been found to be estrogenic hormones and adrenal cortical extract administered during the first eight months of gestation.

Most of the men were found to have normal sexual development. The secondary sex characteristics, aside from the hair distribution, were normal. In Timme's syndrome, in addition to an adrenal insufficiency, there is a persistence of the thymus together with a gonadal deficiency, accounting for the low blood pressure, hypoplasia of the heart and vessels, and the characteristic scrotal fold surrounding the base of the underdeveloped penis in preadolescent boys. At times in this latter condition there is an abnormal bony structure simulating that seen in Paget's disease. In chronic alcoholism many cases of gonadal atrophy and gynecomastia were observed resulting in sterility or loss of libido.

PERSONALITY MANIFESTATIONS. — Hypoadrenocortical patients are usually very meticulous in all of their work. They are perfectionists who often drive themselves to exhaustion since they do not know the meaning of the word "relaxation." Their greatest periods of activity occur after meals. Sluggishness, lack of concentration, etc., occur just prior to lunch when the blood sugar is at a low ebb. There is a feeling of well-being after eating, but symptoms again become severe at about 3:00 or 3:30 in the afternoon. This depression can be alleviated in approximately twenty minutes by eating a bar of candy, but unfortunately, an even greater period of depression is experienced an hour or two afterward. Of much greater value would be the ingestion of a glass of milk or some fruit at this time. These patients feel best after their principal meal in

the evening, and this feeling of well-being lasts for several hours. More profound personality involvements are seen in some patients with actual schizoid tendencies, particularly in the younger individuals, and gratifying results were obtained with the treatment to be outlined later. These severe personality defects had been previously classified as schizophrenia, manic depression, and postpartum psychosis.

As previously noted, hypoadrenocorticism is often seen in children either or both of whose parents has an adrenal insufficiency. The most outstanding change in such a child is the development of an abnormal craving for carbohydrates. This desire for candy and sweets may be so intense as to be the basis of so-called "behavior problems." In addition, many children complain of suffering from "growing pains." These may conceivably be early manifestations of the rheumatoid type of arthritis which is seen in adults with hypoadrenocorticism.

It is important to emphasize the fact that individuals of all ages suffering from hypoadrenocorticism can undergo severe personality and emotional changes but which, fortunately, in most instances are reversible.

In studying juvenile delinquents it is well to evaluate the glandular setup of the individuals before passing judgment on their antisocial acts. Included in this series were children considered as serious behavior problems but who responded dramatically to proper regulation of diet with a minimal amount of hormonal therapy. Many children were reported to have a high I.Q. but still failed in their scholastic studies, particularly mathematics which requires concentration, and who after therapy became outstanding honor students. Abnormal sexual behaviors, as exhibitionism and homosexuality, respond favorably if accompanied by adequate psychotherapy.

Alcoholism as a Manifestation of Hypoadrenocorticism

Two distinct groups of alcoholic patients have been observed. The first group comprised individuals who were typical of hypoadrenocorticism, e.g., asthenic in habitus, little or no chest hair, hypotensive, and not infrequently gynecomastic. These patients had varying degrees of hypoadrenocorticism manifested by hypoglycemia, low titer of 17-ketosteroids, etc. Such patients were found to have a constitutionally low tolerance to alcohol and were considered as likely to become alcoholics at an early age. The second group had no pre-existing hypoadrenocorticism but, through alcoholic indulgence, caused damage to the adrenal cortex and to the other glands involved in the metabolism of carbohydrates. These alcoholic patients nearly always exhibited hypoglycemia during their dry periods.[7-10]

We believe that when the blood sugar falls to a certain low level, a craving for alcohol results. Actually, this is a craving for sugar, but these patients inherently know they will respond quicker to the intake of alcohol. Continued drinking produces three changes: (1) eventual decrease of the blood sugar, (2) depletion of the liver glycogen stores, and (3) fatty infiltration of the liver.[11] In this state the liver is unable to detoxify the estrogens, and sex changes found in chronic alcoholism result, e.g., gynecomastia, loss of body hair, and gonadal atrophy.

Physical Findings

APPEARANCE. — The appearance of hypoadrenocortical patients is very characteristic. They are usually tall, fair, and asthenic and have a full head of very fine and abundant hair. The hair distribution on the body, however, is rather sparse. In males the hair on the lower lateral two thirds of the legs is usually absent with little or none on the chest, and there is often a delay in the start of shaving. The palms of the hands show a marked reddening of the thenar and hypothenar eminences, and in some patients even the tips of the fingers become a very brilliant red. The nails are brittle, which may be accentuated if the patient has been subjected to prolonged periods of stress. The skin is thin and dry, but there may be increased sweating of the palms and axillae. There is frequently an easy bruisability as a result of increased vascular fragility. Constitutional therapy as described later has been most effective in clearing such conditions as infantile eczema and, in later life, the neurodermatitides, circumscribed or disseminated, as well as other allergic symptoms of these patients who fall into the allergic diathesis group. These include asthma, allergic rhinitis, hay fever, urticaria, psoriasis, and ichthyosis.

BLOOD PRESSURE. — A hypotension is usually found in association with a droplet shaped heart. Postural hypotension is usual in that the blood pressure may be 105/60 on standing and may be elevated to 120 or 130/70 or 80 on reclining. This is considered to be the reason why many patients find it difficult to fall asleep and reading in a semireclining position for fifteen to twenty minutes is very conducive toward sleep.

POSITIVE ROGOFF'S SIGN. — When pressure is applied over the adrenal area (junction of lower rib with erector spinae muscles), a very definite tenderness, with some patients experiencing excruciating pain, may be elicited.

SWELLING OF THE EXTREMITIES. — This symptom is found in alcoholics, arthritics, and many other cases of hypoadrenocorticism. It is probably a result of changes in the sodium-potassium relationship. It responds readily to therapy and occasionally to the simple expedient of

providing additional salt to the diet. In our patients we have observed ankle edema resulting from the poor peripheral circulation, particularly with a sudden change in temperature or atmospheric pressure. Some may have a marked puffiness of the lower lids upon awakening which does not subside for a couple of hours or until the circulation has improved by activity. Several cases of nephrosis in children with marked generalized edema and ascites, included in our series, have responded to the general treatment as outlined for hypoadrenocorticism.

PIGMENTATION. — Generally, hyperpigmentation of the skin or palmar creases is not a consistent finding. In several cases, including two children with the nephrotic syndrome, an almost black discoloration of the entire skin faded within two weeks of therapy. Other cases had vitiligo without demonstrating the severe symptoms of Addison's disease.

Laboratory Findings

LOW BLOOD SUGAR. — Much information can be obtained from the glucose tolerance test. It is helpful in evaluating the condition of the liver (reaching hyperglycemic levels), pancreas (hypoglycemia), adrenal cortex, and pituitary (low flat curve).

LOW BASAL METABOLISM. — Some texts have referred to this condition as being an atypical hypothyroidism because of the regular incidence of a low basal metabolic rate. In almost all these cases a basal metabolic rate of −11 to −15 is found. A low basal metabolic rate is not necessarily an indication for thyroid medication, especially since these patients have been found to be extremely sensitive to thyroid extract, a fact which can be explained by the physiologic relationship between the thyroid and the adrenals.[12]

LOW TITER OF 17-KETOSTEROIDS. — Another indication of adrenal involvement is the low titer of 17-ketosteroids. The normal range is 12 to 15 mg. in men and 8 to 10 mg. in women, whereas in these patients we may find 3 to 12 mg. in men and 2 to 8 mg. per twenty-four hours in women. However, much higher levels are possible if the determination is made at a time of stress or strain.

BLOOD COUNT. — A relative lymphocytosis (35 to 55 per cent), an eosinophilia (1 to 9 per cent), and a moderate neutropenia have been recorded in our series.

OTHER TESTS. — These include the Robinson-Kepler-Power water test and its modifications by Soffer and Gabrilove and, more recently, by Oleesky[13]; the Thorn eosinophil test; the salt deprivation test; the prolonged fast; the intravenous glucose tolerance test; and the insulin sensitivity test. These usually give corroborative information but are not to be considered as diagnostic; and moreover, the latter four may entail

some danger to the patient. Equivocal values have been obtained in determinations of the serum sodium, potassium, and chlorides as well as urinary 17-hydrocorticoids. However, electrocardiographic observations in hypoadrenocorticism and particularly in acute or chronic alcoholism reveal a lowering or inversion of the T waves indicating hyperkalemia which disappears after a few days treatment with adrenal cortical extract.

Grouping of Adrenal Steroids

Every symptom of hypoadrenocorticism may be accounted for by a particular group of hormones produced by the adrenal cortex, of which about 28 have been isolated. These hormones may be divided into three groups:

1. Glucosteroids: These steroids function principally in the control of carbohydrate (and protein) metabolism. Failure to utilize sugar properly is the chief cause of symptoms in this syndrome.

2. Mineralosteroids: The water-salt balance of the body is dependent upon these steroids; the imbalance resulting from the excessive excretion of urinary sodium and cellular retention of potassium accounts for the lack of perspiration, craving for salt, and characteristic electrocardiographic findings.

3. Sexogens or 17-ketosteroids: These include the estrogens, androgens, and progesterone-like compounds, any one or combination of which may alter the sex characteristics of the individual.

Treatment of Hypoadrenocorticism

Because the symptoms of hypoadrenocorticism are often so similar to those found in patients with purely psychosomatic disorders, differentiation between those on a psychic basis and those resulting from an adrenal insufficiency is necessary. A complete history, thorough physical examination, and indicated laboratory tests are usually sufficient. In this category of patients treatment should be started only after a diagnosis has been reached through an evaluation of the facts and results obtained from them. In certain urgent categories the therapeutic test must antecede final diagnostic evaluation.

It has been observed that patients respond more rapidly to treatment if they are given a complete but simple explanation of the nature of their illness. Patients with hypoadrenocorticism are subject to various stresses and must be told how they are harmfully affected by such things as dietary indiscretions, fatigue, worry, etc. They will adjust their activities and keep to the prescribed diet more willingly if they understand how emotions can produce symptoms and how excessive carbohydrate intake produces their feelings of fatigue and weakness following a short period

of well-being. Once the nature of their condition has been discussed, the three aspects of treatment may then be instituted.

ADJUSTMENT OF ACTIVITY. — Many of these patients have worked out routines for themselves which help in controlling their symptoms. They soon realize that they can prevent hypoglycemic reactions by eating between meals, taking snacks before retiring, eating less at mealtime, etc. A number of them have learned to avoid eating candy because the transitory respite is offset by the ensuing aggravation of symptoms. The most difficult part of their readjustment is to learn how to avoid fatigue. They must be taught how to take environmental and emotional stresses in stride. Many learn to reduce their activities; others, through discussions of a psychotherapeutic nature, soon change their attitudes and ideas. This aspect of treatment is most important and probably most difficult to achieve quickly and successfully.

DRUG THERAPY. — The primary aim is to put the adrenal cortex at rest temporarily in order to allow the cells to return to a functioning state so that subsequently they may respond normally to stress. Sufficient amounts of adrenal cortical extract are given so that the target organs depending on these hormones are adequately supplied to return to normal function. Depending upon the severity of the condition 10 cc. of adrenal cortical extract are administered intravenously at varying intervals ranging from every four hours initially to as long as once a week. Eventually the patient may be expected to progress satisfactorily without the injections, provided there is no undue abuse of any one or combination of the factors discussed, i.e., diet, emotional and physical exertion. As the signs of adrenal cortical insufficiency diminish, the dosage of adrenal cortical extract is gradually reduced. Drug therapy application utilizes not only adrenal cortical extract but also autonomic blocking agents as well. Their respective operations are elaborated:

*Adrenal Cortical Extract.** — This tends to adjust carbohydrate metabolism by supplying glucosteroids, to correct walter-salt imbalance through its mineralosteroid activity, and to mediate secondary sex characteristics which are controlled by the precursors of the 17-ketosteroids. Once the symptoms of adrenal insufficiency are alleviated, the adrenal cortical extract is curtailed, being reinstituted if indicated at the time of periodic checkups.

Agents Influencing the Autonomic Nervous System. — The autonomic nervous system undoubtedly plays a major part in converting emotional stimuli into symptoms. In order to minimize the role of emotions in the production of functional symptoms in patients with adrenal insufficiency, it has been found advisable to prescribe a combination of l-hyoscyamine, ergotamine tartrate, and phenobarbital (Bellergal).†

Large doses of this preparation are not required because of a probable synergistic action with adrenal cortical extract. Patients are generally started on three tablets a day, one on arising, one at about two o'clock in the afternoon before the expected fall in blood sugar, and then one between dinner and retiring. After approximately one to two months the Bellergal is reduced to two tablets a day and then to one tablet daily. This dosage has been continued for as long as six years. This autonomic preparation helps reduce the intensity of the emotional stimuli, thus acting to prevent the development of functional disturbances.

* Eschatin, Parke, Davis Co., Detroit, Michigan.
† Bellergal, Sandoz Pharmaceuticals, Hanover, New Jersey.

DIET. — We cannot overemphasize the importance of a proper diet. These patients will usually adhere to the prescribed diet, once they realize from our discussion that dietary indiscretions will cause an exacerbation of their symptoms. The diet essentially consists of the strict elimination of rapidly absorbed carbohydrates in order to obviate the sudden rise in blood sugar with its subsequent fall. Between meals, feedings of milk or fruit are advised to prevent any slackening off of blood sugar levels, which are prone to occur two to three hours after eating. Salt is allowed in unrestricted amounts because of the tendency to sodium depletion. During hot weather we advise supplementary salt in the form of tablets to replace the loss caused by perspiration. The following is a list of foods permitted and to be avoided:

ANTIHYPOGLYCEMIA DIET

Foods Allowed

All meats, fish, and shell fish
Dairy products (eggs, milk, butter, and cheese. Also recommended—1 pint to 1 quart of acidophilus milk daily)
Milk between meals; milk, cheese, and/or butter and saltines before retiring
All vegetables and fruits not listed below
Salted nuts (excellent between meals)
Peanut butter
Protein bread
Sanka, weak tea, and sugar-free sodas
Soybeans and soybean products
Sucaryl as a substitute for sugar

Foods to Avoid

Potatoes, corn, macaroni, spaghetti, rice
Pie, cake, pastries, sugar, candies
Dates and raisins
Cola and other sweet soft drinks
Coffee and strong tea
All hot and cold cereals (except occasionally oatmeal)

Comment

The thesis that hypoadrenocorticism is a syndrome entity has been made. Its symptoms typify those found in adrenal cortical disease. The usual case presents those of a subclinical degree. While many of the latter point to emotional instability, they are primarily functional in nature and actually can be considered as being directly attributable to a hypofunction of the adrenal cortex. Adrenal cortical hormones have been shown to play vital roles in maintaining homeostasis in many abnormal conditions involving stress, and, therefore, the adrenal cortex appears to control this homeostatic mechanism of the body.

The use of the whole adrenal cortical extract in the treatment of adrenal disease, neglected since the devlopment of adrenocorticotropic hormone and cortisone, is herein re-emphasized. It must be pointed out that these latter agents produce dramatic and permanent results only in such acute conditions as, for example, delirium tremens, certain ophthalmologic diseases, and other emergency crises, but the results are only temporary in chronic conditions, specifically the collagen diseases.

Unfortunately, adrenal cortical extract therapy has been employed empirically regardless of clinical observations and with apparent lack of rationale. However, with adequate dosage many conditions under the heading of "hypoadrenocorticism" have responded favorably. But, it has been argued, the amount of beneficial glucocorticoids (cortisone) in 10 cc. of adrenal cortical extract is minimal and of about the order of 1 mg. of cortisone-like activity. Why then should such good therapeutic results be obtained with it?

As yet, no reliable laboratory tests have been devised to determine adrenal cortical activity, particularly when the gland has not been damaged by infectious or toxic agents. Clinically we have shown that the activity of adrenal cortical extract is far above that which is expected from its ascribed cortisone content. From our own clinical observations we feel that there is something physiologic about adrenal cortical extract since there is probably a balanced mixture of adrenal cortical hormones, whereas the current literature is increasingly warning us that there is something very unphysiologic about cortisone.

No one has yet distinguished between the effects of adrenal cortical insufficiency and adrenal cortical imbalance. It would be perfectly possible to have sufficient amounts of "S" and "N" hormones, as Albright[14] classifies them, yet if one were present in excess of the other, the mutually antagonistic forces would be upset and would give rise to clinical signs. Cortisone, hydrocortisone, or glucocorticoid substances apparently alleviate certain disease processes, probably via biocatalytic modification of enzyme systems. That is to say, it is not cortisone specifically but gluco-

corticoid activity that gives beneficial results in relieving most of the symptoms of Addison's disease. Who knows whether or not other, still unisolated corticoids will not prove to have still greater activity along these lines and that they may be suppressed or minimized by creating an artificial imbalance by the injudicious use of synthetic steroids.

Aside from the possibility of artificially creating an imbalance, we must also consider the effects of indiscriminate exclusive steroid medication on tropic influences. ACTH is now almost universally viewed as the tropic hormone for cortisone. Is it also to be considered the tropic influence for the other 27 steroids, or do these compounds appear solely as a physiologic response to the needs of the body? The evidence is more and more pointing to the fact that specific steroids may require specific tropic hormones. Selye[15] feels that somatotropic hormone (STH) may be a tropic hormone for the adrenal cortex, stimulating the production of desoxycorticosterone acetate.

Is there then more than one ACTH, or does this compound serve to stimulate compound E and compound F as well as all the other compounds with similar activity? The possibility of the presence of more than one ACTH has already been proposed.[15] With this in mind, if we view the adrenal in hypoadrenocorticism as a "tired out" gland, unable to produce the correct or adequate supply of hormones, being constantly bombarded by stimulatory influences from above, we are in a better position to evaluate adrenal cortical extract versus cortisone or ACTH therapy. If we give ACTH, we are, so to speak, whipping a tired horse, getting a little extra cortisone to be sure, but at what expense? If we give cortisone, we stop the bombarding of the gland by tropic influences from above with respect to the cortisone only. What about the tropic influences for the other steroids? Now, if we give adrenal cortical extract, presumably we are supplying the adrenal steroids in the same ratio to each other that they normally bear. Increased amounts of these in the bloodstream would tend to shut off all tropic influences by the general rule of endocrinologic action. If 10 cc. of adrenal cortical extract are given intravenously, that is certainly not replacement therapy (since the daily adrenal output is many times that amount), but at the time of injection, blood circulating in the region of the pituitary contains increased amounts of the whole circulating hormones. This shuts off all pituitary tropic influences, not just ACTH for cortisone. The adrenal is not under constant bombardment until the adrenal cortical extract is metabolized in the liver or tissues. The inhibition is off the pituitary, and tropic hormones are again released if the need arises. In the meantime the tired adrenal has had a chance to rest and to build up its tone. At this time another injection of adrenal cortical extract will suffice again

to allow it to regain more tone but will not entirely cause a cessation of activity, as would large doses of cortisone, for the glucocorticoid portion.

Usually desoxycorticosterone acetate is not indicated in these cases. There is most frequently a craving for salt, which is not harmful in itself if given with adrenal cortical extract but this must be regulated when the patient has received this mineralosteroid. Although desoxycorticosterone acetate may improve the absorption of carbohydrates from the intestine, it does not enhance gluconeogenesis during stress, and clinical results have not warranted its general usage in hypoadrenocorticism.

Summary

An attempt has been made to condense and describe a vast syndrome which has been recognized in a group of over 200 patients. *Diagnosis is possible by means of a careful endocrine history and physical examination, rather than by elaborate laboratory tests.* We have observed that hypoadrenocorticism may result in fatigue, mental confusion, various arthritic pains, gastrointestinal disorders, inability to concentrate, signs of disturbed carbohydrate metabolism, etc. These patients respond to therapy which includes an autonomic stabilizer, adrenal cortical extract injections, and an antihypoglycemia diet. The rationale for adrenal cortical extract therapy has been discussed.

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References

1. Natelson, S., Crawford, W. L., and Munsey, F. A.: Correlation of Clinical and Chemical Observations in the Immature Infant, Rockford, Illinois, Munson Printing Co., 1952, p. 11.
2. Hartman, F. A., and Brownell, K. A.: The Adrenal Gland, Philadelphia, Lea & Febiger, 1949, p. 421.
3. Selye, H.: J. Clin. Endocrinol. 6: 153 (Feb.) 1946.
4. Portis, S. A., Zitman, I. H., and Lawrence, C. H.: J.A.M.A. 144: 1162 (Dec. 2) 1950.
5. Striker, C.: Illinois M. J. 102: 235 (Oct.) 1952.
6. Bercovitz, Z. T.: New York State J. Med. 53:2200 (Oct. 1) 1953.
7. Tintera, J W.: Unpublished data.
8. Tintera, J. W., and Lovell, H. W.: Geriatrics 4: 274 (Sept.-Oct.) 1949.
9. Lovell, H. W., and Tintera, J. W.: *ibid.* 6: 1 (Jan-Feb.) 1951.
10. *Idem:* M. Times 80: 191 (Apr.) 1952.
11. Webster, J. J.: Ann. Int. Med. 38: 854 (Oct.) 1950.
12. McGavack, T. H.: The Thyroid. St. Louis, C. V. Mosby, 1951.
13. Oleesky, S.: Lancet 1: 769 (Apr.) 1953.
14. Albright, F.: Harvey Lect. 38: 152 (1943).
15. Selye, H.: Annual Report on Stress, Montreal, Canada, Acta, 1951, p. 217.

Endocrine Aspects of Ophthalmologic and Otolaryngologic Allergy

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SIDNEY SMITH (1771-1845): I am suffering from my old complaint, the hay fever (as it is called). My fear is, perishing by deliquescence: I melt away in nasal and lachrymal profluvia. My remedies are warm pediluvium, cathartics, topical application of watery solution of opium to eyes, ears and the interior of the nostrils. The membrane is so irritable, that light, dust, contradiction, an absurd remark, the sight of a dissenter, — anything, sets me sneezing: and if I begin sneezing at twelve, I don't leave off till two o'clock, and am heard distinctly in Taunton, when the wind sets that way — a distance of six miles. Turn your mind to this little curse. If consumption is too powerful for physicians, at least they should not suffer themselves to be outwitted by such little upstart disorders as the hay fever.
Letter to Dr. Holland, June 1835.

Dr. Goldman, your President, asked me as an introductory speaker to pique your curiosity concerning many of the ophthalmological and rhino-otolaryngological conditions which relate to the whole man and his general chemistry. I feel that galucoma, conjunctivitis, rhinitis, asthma, hay fever, Meniere's Disease, and chronic bronchitis are manifestations of a disturbance of the whole man rather than specific entities in themselves. They are signs of a basic chemical derangement which must be taken into consideration if treatment is to be effective. In my experience these manifestations occur in individuals who evidence adrenal cortical dysfunction. For the sake of this discussion, we will speak of these patients as being hypoadrenocortic. The primary objective in the treatment of hypoadrenocorticism is to achieve a state of homeostasis involving the endocrine glands, their dependent systems, and the organism as a whole. Homeostasis implies a balanced harmonious inter-relationship of the nutritional, endocrine and nervous aspects of the organism. The therapeutic purpose, therefore, in endocrinology is to set up this state of balance and then maintain it.

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This is a new era of diagnosis in which we are able to detect inborn errors of metabolism even at birth. Every chemical action in the body involves an inherited enzyme system which, in turn, is modulated by hormones. Tests are rapidly being developed which detect abnormal amounts of amino acids or other substances including incomplete steroids. Deficiency of an essential enzyme can also be exposed.

In the infant, eczema of the external auditory canal is not specific in itself. Bronchitis has a systemic basis. In a normal individual glaucoma does not occur as a separate disease. The pain of advanced, irreversible glaucoma is relieved by pilocarpine but it is more rational to relieve it by helping to restore homeostasis in the victim. Bronchitis has a systemic basis and may lead to asthma. Meniere's has proved to be a general physiological disturbance as many investigators have observed.

Adaptation (or the lack of it) is an important factor in all physiologic or pathologic processes. Hence, all maladies to some extent involve maladaptation — failure to deal with stress. The ever increasing stress of civilization is a factor in many ophthalmological and otorlaryngological conditions. In this context, a nervous breakdown is the inability to adapt to nervous stress. In our treatment we do not employ tranquilizers or sedatives. As an adjunct to our program, we balance the autonomic nervous system with stabilizers, particularly Bellergal.

I am here to demonstrate that an ENT man treats more than specific conditions mentioned in the texts. I personally know that Dr. Goldman is a specialist interested in migraine, emotional disturbances and other conditions such as anxiety neuroses, which seem far afield from his designated specialty. No one of you can claim he treats only eyes, ears or noses.

At the present time Josephson is prescribing breathing and the good life; nevertheless, he was the first to demonstrate in 1935 that adrenocortical extract could relieve glaucoma.[2] Sam Roberts, the late Professor Emeritus of ENT at Kansas State School of Medicine, preached nutrition, and restoring the individual to as near normal health before attempting to correct a specific otolaryngologic condition.[3]

There has fortunately been a growing tendency to disregard the limitations of one's specialty and to visualize the clinical conditions as and end result dependent upon changes in physiology and body chemistry of the organs of an organism which is essentially *one unified whole.*

One of your members, Dr. William D. Currier,[4] in successfully treating a patient for Meniere's, was challenged by the internist to explain why he left his specialty to treat a mutual patient for rheumatoid arthritis which had heretofore been unresponsive to conventional therapy.

For the sake of credibility we have previously stated that about 16% of the population has some moderate-to-severe degree of hypoadrenocorticism with hypoglycemia but in actuality, the figure should read 67%, if all the arthritics, asthmatics and hay fever sufferers, alcoholics and other related groups are included. Indeed, no family, I believe, actually escapes the ravages of hypoglycemia resulting from stress induced hypoadrenocorticism. Even the coronary patient shortly after his attack will have a reactive hypoglycemia the severity of which depends on the adrenal response to stress. This reactive hypoglycemia may clear within a few months but it may persist and later be diagnosed as diabetes or latent diabetes. A sudden drop to hypoglycemic levels, it has been reported, may produce another coronary spasm and infarction.

We have observed many interesting physiological and psychological aspects of the hypoadrenocortic such as pinna ossificans which labels the patient addisonian in many endocrinologists' minds. Only as recently as 1967, Henkin et al., of the National Institute of Health showed that patients with untreated adrenocortical insufficiency exhibit markedly increased detection sensitivity of taste and smell. In particular, they found that the auditory threshold returned to normal after administration of adrenal cortical hormones and ACTH. Desoxycorticosterone decreased the serum potassium level but did not alter the auditory threshold.[5]

Neither the mechanism of the increased sensitivity to sound nor its locus of action in the nervous system is known but the phenomenon is not confined to the auditory system. All three sensory modalities investigated responded similarly to replacement with carbohydrate active steroids and in our cases, to ACE.

The olfactory sensitivity in adrenal insufficiency was found to be roughly 100,000 times (10^3 - 10^5) more acute than in normal subjects. Treatment with prednisolone returned the olfactory threshold to normal in the first day.[6]

In our cases, this sensitivity has been modified by allergic or vasomotor rhinitis, but with ACE, the extreme sensitivity which often causes nausea and vomiting, were quickly brought under control. Henkin and Solomon found an increased taste sensitivity to salt and many other substances in hypoadrenocortic patients as well as in hypopituitarism.[7]

The controlled testing was done by means of the electrogustometer and a lowered threshold was found in all of the hypoadrenocortic patients. Again, moderate doses of prednisone abolished this sensitivity in most of these patients in 1 to 3 days. The authors recommend that electrogustometry be widely used for diagnostic purposes in primary and secondary adrenal cortical insufficiency.

Allergy

In the course of treating several thousand patients for specifically an underlying glandular disorder, i.e., adrenocortical dysfunction, a sizeable proportion of these patients presented myriad allergic symptoms. In the process of correcting the basic glandular dysfunction, it was early noted that when the general condition improved, the allergic manifestations either subsided, or entirely cleared up.

In reviewing the patients who presented themselves primarily with allergic complaints, it was found that in all of them many of the criteria were present essential for a diagnosis of hypoadrenocorticism relating to ophthalmologic, rhino-otolaryngologic conditions. Hypoadrenocorticism must be taken to imply a derangement of many hormones produced by the adrenal gland and not necessarily be thought of as under-function of the entire gland. That is to say, that a disproportion exists among the three groups of adrenocortical steroids, namely, the glucosteroids, the mineralosteroids, and the 17-ketosteroids. Most of the patients fit into the picture of hypoadrenocorticism as previously described elsewhere.[8-15] But indeed, allergic patients have also been relieved whose diagnosis was adrenocortical hyperplasia, indicating an overactivity of one zone and a hypofunction of another. When the hypersecreting cells were inhibited through appropriate hormonal administration, a state of homeostasis was attained and symptoms alleviated. Carryer and Miller in a study of 101 patients with Cushing's Syndrome, secondary to adrenal tumor, or cortical hyperplasia, found two cases with a previous history of asthma and hay fever. Striking remissions occured with the development of Cushing's Syndrome but recurred after surgical extirpation of a major portion of the functioning adrenal cortex. These men also suggest that defects in the metabolism of adrenal steroids, congenital or acquired, may be the basis for the so-colled allergic diathesis.[16] It is a reasonable assumption that adrenocortical dysfunction provides the basis for all allergies but for practical purposes, we shall assume that there exists a state of hypofunction of the adrenal cortex involving the zona fasciculata and compromising carbohydrate metabolism whether the condition is inherited or subsequently induced by unusual stress.

Generally speaking, most allergies become manifest in their most severe form following a markedly stressful situation whether it be emotional or physical. Acute infections, including meningococcic meningitis, puerperal sepsis, and lobar pneumonia may be associated with necrosis of the adrenal cortical cells. The probably relationship between adrenal cortical damage and circulatory collapse in such diseases suggests the use of Eschatin.[17-61] In a review of the clinical uses of adrenal cortical hormones, references are made to a specific loss of the cortical factor in

overwhelming infections as being important in shock associated with such conditions.

Perla and Marmorston[62] used cortical hormone as part of the treatment in severe infections including bronchopneumonia, therapeutic malaria and severe influenza. This plan of treatment resulted in maintenance of normal blood pressue, decreased signs of toxicity, avoidance of circulatory collapse, maintenance of appetite and shortening of convalescence.

When one or both parents are hypoadrenocortic with allergic manifestations, a child may be premature and shortly after birth show evidence of adrenal exhaustion such as electrolyte imbalance, projectile vomiting, eczema or severe diaper rash. An older individual may not have exhibited any allergic tendencies until subjected to surgery, emotional shock or other stressful situations.

Recently, a common more severe form of adrenocortical dysfunction is encountered in patients who have been treated with individual steroids for allergies or other unassociated conditions. It is quite obvious how cortisone or any of its derivatives may upset the intricate hormonal balance of the cortex by suppression of the zona fasciculata. On the other hand, the same may be said of ACTH, but this adrenocorticotropic hormone is specific for cortisone and to a lesser degree for the other cortical components and thus, the balance of total steroids is upset. I see no reason why individual steroids should be used except in an acute emergency when a life-saving situation is presented and even then, larger doses of ACE will usually alleviate the condition without derangement of the normal balance.

The effects of cortisone, and hydrocortisone include neutrophilia, lymphopenia, eosinopenia, reticulocytosis, increased gastric secretion, inhibition of membrane permeability, decreased fibroblastic proliferation, alteration of immune reactions, alteration of central nervous system excitability and disturbance of melanin pigmentation.

Cortisone and hydrocortisone have important effects upon carbohydrate, protein and fat metabolism. They cause decreased peripheral utilization of glucose and increased gluconeogenesis from protein. This explains the decreased tolerance to carbohydrates when excessive cortisone or hydrocortisone is administered.

Cortisone has been employed empirically for many symptoms common to hypoadrenocortical patients and as a consequence, the treatment of the allergic manifestations is further complicated since a state of homeostasis cannot be attained through the use of the whole adrenal cortex extract without great difficulty. Indeed, the only failures with ACE therapy have occurred after indiscriminate use of individual steroids has created an irreversible situation.

Our concept of disease has been materially augmented by Selye's exposition of his General Adaptation Syndrome. The allergic patient presents many of the manifestations described in the general adaptation syndrome including physical and laboratory findings as described by Selye. The allergic individual is one who is unable to respond to stress in a normal fashion.

John P. McGovern of Houston, President of the American College of Allergists, was quoted in the September 9, 1968 issue of "Medical Tribune." He said in part: "In many asthmatic patients, attacks repeatedly reoccur or become worse at night, generally between 11 p.m. and 4 a.m., a time coinciding with minimum excretion of urinary corticoids. These manifestations suggest that nocturnal physiological hypofunction of the adrenal gland certainly might be one of the factors favoring precipitation of an attack. Study of temporal relations between circadian as well as other cyclic control mechanism and recurrent allergic manifestations, such as asthma, might help provide a more satisfactory interpretation of certain of the allergic phenomena and thus perhaps lead to improved methods of treatment."

It has been indicated that the allergic state is one of the constitutional manifestations of "Hypoadrenocorticism" whether inherited or acquired. Rackemann followed a number of asthmatic patients for twenty to thirty years and found some to have two distinct episodes separated by a long symptom-free interval. The first episodes occurred in the teens or twenties and these he attributed to allergy or "extrinsic" causes, i.e., infections or other stressful situations. His interpretation is that the allergy and the infection are merely exciting causes which produce asthma in a patient who suffers from a definite constitutional disease and gives as one theory of explanation, a disturbance of adrenal function.[63]

In our large series of cases manifesting allergic symptoms, several findings have been constant with modifications, if in addition to the adrenal cortices, other glands are involved. The most important of these general findings may be enumerated as follows:

1. Relative lymphocytosis
2. Eosinophilia
3. Low, flat glucose tolerance curve or reactive hypoglycemia
4. Hypometabolism — low B.M.R. — normal P.B.I., T-3 and RaI uptake
5. Hyponatremia

Hypometabolism has generally been attributed to an atypical hypothyroidism since the B.M.R. usually ranges from minus 10 to as low as minus 26, even though the P.B.I. is normal. Patients, although asthenic and exhibiting none of the classical symptoms of myxedema or thyroid

dysfunction, were placed on thyroid medication and often responded with an exacerbation of their symptoms or showed marked sensitivity to the extract. On the other hand, minimal doses of proloid (1/4 gr.) stimulated the adrenal-thyroid axis with gratifying but not necessarily permanent results. If any improvement occurred, it could be explained on the basis of the response of the thyroid-adrenal axis. Within the past several years, the advocates of this thyroid hypometabolism were thrown into consternation when the now common P.B.I., T-3 and RaI determinations indicated normal thyroid levels.

Again, an explanation had to be forthcoming for the enterprising investigators who postulated that the fault lay at the "cellular level." Cytomel (triodiothyronine) was employed, again, with some success, in a few individuals, since in these particular cases, the thyroid-adrenal axis was, at least, partially intact. The failures naturally occurred in those individuals whose adrenals could not stand the further abuse of stimulation from the thyroid following the employment of the potent fraction of its hormone. The most that can be said for triodiothyronine, is that its action is rapid in onset and ceases suddenly when withdrawn. Dessicated thyroid is less expensive and equally effective if at all indicated but dosage should be in the range of 1/4 gr.

Returning to Selye's Adaptation Syndrome,[64] the criteria for adrenal insufficiency are the persistence of the thymus and a relative lymphocytosis. Most frequently, the allergic patient, unless experiencing an acute episode of an allergic reaction, shows a relative lymphocytosis and absolute eosinophilia.

Briefly, in 1936 Hans Selye demonstrated by a series of animal experiments that the organism responds in a "sterotypical" manner to a variety of widely different factors such as infections, intoxications, trauma, nervous strain, heat, cold, muscular fatigue, etc. The specific actions of all of these agents are quite different. Their only common feature is that they place the body in a state of general or systemic stress. The infection initiating an asthmatic attack, or the contact with an allergen in the nasopharynx causing symptoms of hay fever, or the chemical producing cutaneous reactions are all stressor agents.

During the stress reaction, all the organs of the body show involutional or degenerative changes while the adrenal cortex actually flourishes. This accounts for a normal or low normal value of steroid determinations when obtained in practice on allergic patients. We now are distinguishing between the effects of adrenal cortical insufficiency and adrenal cortical imbalance. It has been shown that groups of hormones from one of the zones may be normal while the others may be present in deficient or abundant concentrations. This is the alarm reaction or

the first stage of the more prolonged general adaptation syndrome, which comprises three distinct stages:

1. Alarm reaction — adaptation has not been acquired
2. Stage of resistance — adaptation is optimal
3. Stage of exhaustion — acquired adaptation is lost again

In the General Adaptation Syndrome the most outstanding features of this stress response are:[64]

1. Adrenocortical enlargement with histological signs of hyperactivity — both hypertrophy and hyperplasia.
2. Thymico-lymphatic involution with concomitant blood changes.
   a) Eosinopenia
   b) Lymphopenia
   c) Polymorphonuclear leukocytosis
3. Gastro-intestinal ulceration.
4. Shock or other manifestations of damage. Recent work seems to indicate that the thymus plays an important role in immunological development which does not end with adolescence but persists throughout life.
5. Electrolyte imbalance — actual wasting of sodium.

Experimentally it has been shown that thymico-lymphatic involution and typical blood count changes could be produced by adrenal cortical extracts even in the absence of the adrenals. Production of these hormones is therefore considered to be the indirect result of stress. On the other hand, adrenal cortical extracts lessen shock and gastrointestinal changes and therefore these conditions are combatted by an adequate adrenocortical response. Additionally, Selye showed in 1937 that the only procedure which could prevent an adrenocortical response to stress was hypophysectomy. Stress stimulates the adrenal cortex through the pituitary tropic hormones, or ACTH. Clinically, most allergic states have responded well to the adrenal cortical extract, individual steroids and ACTH.

Pottenger and Pottenger in 1938, were the first to report the effects of adrenal steroids in allergies using a crude adrenal cortical extract. The percentage of improvement in intractable asthma was very high (85%). These findings were substantiated by other clinicians using the crude extract. Since the appearance of the purified extracts of Parke-Davis (Eschatin) and Upjohn (ACE), the literature is repleat with beneficial results.[17-61]

More recently, of course, the individual steroids, starting with cortisone and hydrocortisone and going on to the newer products, prednisone and prednisolone, and finally, hexamethasone, have proved to be effective in anaphylactic shock, status asthmaticus and other acute allergic condi-

tions. However, these should *not* be used because of the severe side effects, unless ACE proves to be ineffectual, which is unlikely. Even topical use on the eye has proved disastrous as indicated by several recent medical reports. These substances are used as replacement therapy in a sense, since the patient has to be given maintenance doses. When medication is suspended the symptoms more often than not return and generally, in a more severe form. Thus, we may see a simple case of hay fever progress into fulminating asthma.

Our experience has been that previous steroid medication renders the patient much more difficult to treat successfully with adrenal cortical extract because the dosage of individual steroids necessary for a favorable response is above the physiologic level of what the adrenals normally produce. Hence, even though individual steroids are often miraculous in their immediate effect, aggravation of the underlying cause is precipitated if continued for any length of time. Prolonged use not only produces a furthere dysfunction of the adrenal, but it very often leads to actual atrophy of the gland.

ACTH, likewise, may produce dramatic relief of symptoms but continued treatment, again, leads to an imbalance of the three groups of steroids produced by the adrenals. In addition, ACTH is a protein and in allergic patients one always runs the risk of producing anaphylactic shock. ACTH is the specific tropic hormone for hydrocortisone which will be produced in larger amounts *if* the adrenal is capable of response. ACTH is not specific for the mineralosteroids (aldosterone) although there is some overlapping in the stimulatory effect of ACTH on the zona glomerulosa as evidenced by the production of moon facies, increase in blood pressure, etc.

The 17-ketosteroids also are indirectly stimulated by ACTH but depend primarily on the gonadotropic hormones for their elaboration. It is readily foreseeable, therefore, that the employment of either individual steroids or ACTH will eventually cause a disruption of the balance of all of the adrenal cortical hormones.

Why then does ACE have a more beneficial effect than either cortisone or ACTH. Assume that there is a deficiency of glucocorticoids from the zona fasciculata. The stressor factor in this case is a pollen or other antigen which starts in motion the events enumerated for the general adaptation syndrome. Histamine is released stimulating the autonomic nervous system to produce adrenalin which, in turn, activates the hypothalamus which through humoral reactive hormones and nervous pathways to the pituitary causes the latter to secrete ACTH and other tropic hormones. Since the cells of the adrenal cortex which produce cortisone are deficient, there occurs a further imbalance with overproduction of

mineralosteroids and 17-ketosteroids. The introduction of the whole adrenal cortical extract supplies a sufficient amount of glucosteroids to bring their level to normal and thereby the body reacts physiologically in neutralizing the antigen through the release of antibodies from the lymphocytes and small white cells of the lymph. At the same time, if an overabundance of mineralosteroids is being produced, the introduction of aldosterone in the extract will lower the amount being produced through its feedback mechanism. Again, theoretically, if the adrenal production of 17-ketosteroids is subnormal or normal, the addition of another small amount is not going to produce any appreciable effect one way or the other, since it will have no effect upon the lymphocytes but will further assist in establishing normal balance.

In other words, the introduction of ACE tends to produce a state of homeostasis which is possible in no other conceivable manner. The intracacies and interactions of the 32 or more adrenal hormones are infinite since we know some are antagonistic and others synergistic with one another. There is an astronomical number of combinations necessary to catalyze the myriad enzymatic reactions which are going on constantly in order to maintain homeostasis in the whole organism. Variations in this process account for the differences exhibited by each patient and treatment must be modified accordingly.

French K. Hansel, in discussing respiratory allergy from the standpoint of the otolaryngologists, states that — "In the management of allergy of the respiratory tract, it is quite impossible to separate, for purposes of diagnosis and therapy, the upper from the lower types. Nasal allergy may exist alone or in association with bronchial asthma. Conversely, asthma rarely exists without some concomitant nasal involvement. When allergy affects all of the respiratory tract, the process must be considered as a whole and not as two separate units.[65]

Along these lines, I see patients with indications of hypoadrenocorticism such as undue fatigue, muscle pains, orthostatic hypotension, all relative to a fall in blood sugar, who at the same time present signs and symptoms of what has been diagnosed as sphenoid sinusitis, scintilating scotomata, nystagmus and "eye aches." In the treatment of the underlying adrenal insufficiency, in addition to the restoration of normal physical activity, the glabellar headaches are relieved. The hyperactive pituitary in its attempt to stimulate the under-functioning adrenal, becomes hypertrophied or hyperplastic and cannot be contained within the confines of the sella turcica without pressure and resulting symptoms. Intravenous injections of 10 to 20 cc. of ACE relieve this situation by its feedback mechanism and the glabellar headaches (eye aches), nystagmus, and misdiagnosed sphenoid sinusitis disappear concomitantly. The severe

migraine glabellar headache is often dramatically relieved by the parenteral injection of about 1,500 i.u. of gonadotropic or anterior pituitary like hormone derived from human placenta.

It is important to realize that the employment of ACE is not simply replacement therapy since discontinuation of this treatment does not result in the immediate return of symptoms. Adequate dosage of this extract will first of all supply a sufficient amount of the lacking hormones to combat the stressful situation. At the same time, the feedback inhibition of the pituitary provides a four-hour refractory period in which the faltering cells may return to normal. When the pituitary inhibitory effect wears off these cells can function more efficiently usually for about a week at the beginning of treatment.

A very common condition presenting itself today, especially in women, is iatrogenic hyponatremia. Almost every pharmaceutical house has joined the campaign to eliminate NaCl through indiscriminate use of diuretics or "water pills." The possibility of hypokalemia or hyperkalemia is often mentioned but the critical wasting of sodium is overlooked and patients are placed on a low salt diet, with no regard for physiological principles.

It is well known that hypoadrenocortics waste sodium, potassium and chlorides. We have devised an electrolyte clearance test which promises to be more definitive than any of the present day procedures for the detection of adrenal insufficiency. A twenty-four hour urinary excretion of the electrolytes is first determined, then the determination is repeated after a sodium chloride loading of 15 gm. So far these tests show an astonishing above normal increase over the first twenty-four hour specimen. As a result of these observations, we have instituted, as a standard procedure, the administration of 10 to 20 gr. NaCl every day of the year, increasing to as much as 70 to 80 gr. on hot or humid days. There has been gratifying alleviation of the most common complaint, fatigue. For the allergic patient, salt tablets are far superior to any energizer yet devised. Data on this test are not complete but preliminary evidence is most encouraging.

Treatment

These patients are in a state of negative nitrogen balance which is enhanced by the use of cortisone. Anabolic agents are therefore indicated. ACE is in itself anabolic. The most effective specific agent we have is "Durabolin." Mild secondary anemia is a frequent finding. B_{12} and B_6 have been used because of the erythropoietic and adrenal saving effect. Usually the anisocytosis, poikilocytosis, and microcytic and macrocytic anemias are alleviated by ACE.

It is clear that adrenal hormones are able to forestall the alarming signs and symptoms of allergies but the mechanism is little understood. The high incidence of lymphocytosis in allergic states must have some significance. It was shown by Daugherty and White that the administration of ACE destroys the lymphocytes with the release of antibodies.[66]

In our experience scratch or patch-testing is only of academic interest and so-called desensitization shots seem to be of little or no value.

Androgens induce significant retention of calcium and potassium. In correlation to this a disproportionate amount of sodium is not retained. As a matter of fact, some patients increase the amount of sodium excreted. Therefore, to establish homeostasis even with a deficiency of anabolic hormones, the entire adrenal cortex spectrum must also be employed including aldosterone or DOCA to establish electrolyte balance.

Most of the anabolic steroids can cause hepatotoxic changes but when using them in conjunction with ACE we have never encountered difficulty on that score. (Fluoxymesterone (Halbestin - Upjohn) is roughly five times as anabolic and androgenic in its activity as methyltestosterone.) One gram daily of Ascorbic Acid in divided doses is recommended as the only oral vitamin supplement. The adrenal cortex reacts properly only in the presence of adequate Vitamin-C and cholesterol.

As we have seen in Selye's General Adaptation Syndrome, a normal response of the adrenals is necessary to avoid shock and other factors injurious to the organism. The release of the cortical hormones has an immediate action on the lymphocytic system. Almost invariably in allergies we find a relative lymphocytosis and eosinophilia but ACE reduces the lymphocyte count and many of the lymph nodes decrease in size or disappear. The lymphocytes, therefore, must be involved in this stressful situation. Although the role of the eosinophils is at present unclear the Thorn test is based on the fact that ACTH or epinephrine reduces the eosinophil count. A drop of 50% is said to be significant proof of adrenal insufficiency but this is not an entirely reliable indicator.

The standard explanation for many years regarding the allergic response is that symptoms of hay fever, asthma and eczema result from the contact of the allergen with the antibody. Much is left unexplained if one adheres to this idea. This antibody-antigen reaction is supposed to take place on the surface of the cell, injuring it and releasing histamine. This would indicate that treatment be directed toward preventing this reaction when in reality, the normal individual is constantly protected because of this reaction, since he has sufficient antibodies to neutralize the antigens constantly bombarding all tissues. True, there is a release of histamine in all allergic reactions. Our approach to the neutralization of this reaction is to use histamine azoprotein (Hapamine).

Antibodies against histamine should alleviate the allergic state, but histamine acts as a haptin and is not antigenic in itself and must be coupled to a protein to form an antigenic complex. This was accomplished in 1943 by Gell[67] who was successful in coupling histamine to despeciated horse serum. Histamine azoprotein has been used to great advantage in effecting a quicker response to ACE in asthma, vasomotor or allergic rhinitis, physical allergy (heat, cold, light), gastrointestinal allergy, contact dermatitis, atrophic eczema, vertigo, periodic headache, liver extract sensitivity, and infantile eczema.

The allergic individual is one whose adrenals cannot meet the demands of the stressful antigens and reacts pathologically. Tissues react in a stereotyped manner to any antigen or injury and histamine is released for the protection of the organism as a whole. A chain of events follows: the vegetative nervous system reacts to the histamine and releases hormones from the adrenal medulla to stimulate the hypothalamus and pituitary which, in turn, causes the elaboration of the protective hormones from the adrenal cortex.

We have shown elsewhere that "hypoadrenocorticism" may be an inherited characteristic with typical physical findings, or normal adrenals may be injured to produce secondary manifestations. From the above precepts, the management of the allergic state would involve the prevention of further damage to the adrenals or assistance in the restoration of the malfunctioning adrenal cortical cells to normal. This is accomplished by giving adequate amounts of all the adrenal steroids in the form of an extract which also helps maintain a normal electrolyte level.

We know that all hypoadrenocortics have faulty carbohydrate metabolism as revealed by the glucose tolerance test which may show a low, flat curve or a reactive hypoglycemia. We also know all sugars and starches act as stressor agents.

Therefore, we consider the elimination of all *readily* available carbohydrates from the diet (high protein, moderate fat, minimal carbohydrate) more essential than local treatment and equally as important as supplying the needed steroids in their naturally occurring balanced concentration as found only in the extract.

The storage of carbohydrate is largely under adrenal control. Adrenalectomy decreases glycogen storage in the liver and muscles, while mineralocorticoids raise the glycogen concentration, especially in the liver. Adrenalin depletes the hepatic glycogen reserves, since it transforms glycogen into blood glucose. There is also a simultaneous diminution of muscle glycogen.

However, after a prolonged fast, and in other conditions, which cause depletion of hepatic glycogen stores, adrenalin may actually raise

the liver glycogen. This is due to the fact that the lactic acid, formed by the hormone from muscle glycogen, is reconverted into hepatic glycogen through the "Cori Cycle." Thus, adrenalin transforms muscle glycogen into lactic acid and the latter is converted into hepatic glycogen, which, in turn, is broken down into blood glucose by the same hormone through the activation of specific enzymes.

The lactic acid content of the blood and muscles tends to diminish after adrenalectomy, apparently because of decreased lactic acid formation. On the other hand, adrenalin increases the lactic acid content of the blood due to the above mentioned conversion of muscle glycogen into lactic acid.

In susceptible individuals abnormal accumulation of lactate in the blood may produce muscular and emotional symptoms which we have observed for many years and were recently described by Pitts and McClure of St. Louis.[68] In cases where there is derangement of the glycogen-lactate-glucose cycle, a post prandial rise in blood sugar may result in an excess of blood lactate. This produces a state of anxiety — the "Non-neurotic Anxiety Neurosis." This is attended by fearfulness, feelings of impending doom, fear of going insane or fear of a heart attack. The physical symptoms attending such an episode include shortness of breath, chest discomfort, dizziness, faintness, shakiness, palpitations, and paresthesias. Later, muscular aches may appear in the calves of the legs, the thighs and temporal muscles. The last may present a challenge to the otolaryngologist. However, all the aches are markedly alleviated by intravenous injections of calcium preferably in the form of gluconate.

The temporal muscular involvement may be accompanied by a sensation of fullness in the ears. This latter phenomenon may also be produced by birth control pills as a result of the fluid retaining propensities of the progesterone as discussed at your last meeting in 1967.

On June 28, 1968, H.E.W. dispatched a bulletin on the adverse reactions observed in patients receiving oral contraceptives, citing a significant association in the development of thrombophlebitis and pulmonary embolism. An association was also implied, which has neither been confirmed nor refuted, with serious adverse reactions such as cerebrovascular accidents and neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis. I have had patients who prior to my treatment reported many ocular and auricular symptoms particularly scintillating scotomata. When placed on oral contraceptives given in conjunction with ACE there have been no adverse side effects because the combination of steroids in the extract has the capability of correcting most hepatic conditions. The liver is then able to metabolize or detoxify both the estrogens and progestins and their precursors.

There are many EENT conditions dependent on the release of histamine and its subsequent involvement in tissue edema and interactions of antigens and antibodies. However, I will limit my discussion to only a few of the more salient conditions encountered most frequently, namely, glaucoma, Meniere's Syndrome, asthma and glabellar headaches.

Glaucoma

In the course of consultations during the past several weeks with patients being treated primarily for hypoadrenocorticism, there have been at least a score who when first examined had some degree of glaucoma. In almost all cases, the condition has been arrested or in the earlier cases, appears to be progressing to a complete remission. I have not attempted to modify treatment prescribed by the ophthalmologist in any way. The improvement in the eyes is dependent upon the restoration of normal function of the total organism together with the focal assistance of the specialist, being cognizant, however, that the adrenal plays an important role in the recovery.

Dworetzky classifies the allergic diseases of the eye anatomically.[69]

- Extraocular lesions
  - Acute allergic conjunctivitis
  - Eczema of the eyelids
  - Angioedema of the eyelids
  - Vernal catarrh
- Ocular lesions
  - Cornea
    - Phlyctenular keratoconjunctivitis
    - Recurrent marginal ulcers
  - Uveal tract
    - Non granulomatous uveitis
    - Granulomatous uveitis
    - Sympathetic ophthalmia
    - Endophthalmitis phacoanaphylactica
  - Lens - cataract

To this list, of course, we would add glaucoma.

ACTH and corticosteroids have assumed considerable attention but I am sure you are aware of the devastating side-effects, both systemic and topical from these agents. Both systemic administration of corticosteroids and their topical use in the eyes can cause serious, often irreversible, ophthalmic complications. These include exacerbation of Herpes Simplex Keratitis; also bacterial and fungal infections of the eyes, posterior subcapsular cataract, and glaucoma.

Josephson was the first to cmploy ACE in glaucoma with astonishing improvement in all cases.[2] He attributed the improvement to the normalization of the capillary permeability which eliminated edema of the ocular tissues. There is evidence that glaucoma represents an allergic state in which circulation through the canal of Schlemn is disrupted. Since all allergies, in my estimation, stem from adrenal cortical insufficiency it is logical to expect ACE to be beneficial. Josephson found that the administration of ACE caused a sharp drop in tension with a remarkable rise in visual acuity in primary simple glaucoma which had not responded to the ordinary treatment. He stated that ACE offers a test of the secretory function of the eye as well as acting as a therapeutic agent of remarkable value. He was impressed by the promptness of response. Within 20 minutes after the administration of ACE the vision rose from 20/100 plus to 20/30 without correction in one of his cases.

Complete relief from pain and discomfort has generally been observed even in cases which have advanced to blindness. ACE therapy usually halts the drop in vision and reduces cupping of the disc. Injections of ACE (usually 10 cc., i.v.) may be required as often as every 3 to 4 days but gradually, the intervals are increased to once weekly, thence bi-weekly, etc. The patient usually has some other manifestation of allergic diathesis, i.e., hay fever, conjunctivitis or asthma.

Meniere's Syndrome

Bauer describes Meniere's Disease as characterized by recurrent attacks of sudden vertigo of the "special" type that passes off after several minutes or hours, sometimes days.[70] These attacks may be accompanied by temporary tinnitis and impaired hearing on the affected side. In severe cases, a widespread disturbance of the autonomic nervous system may occur with vomiting, abdominal pain or diarrhea. Anatomical studies revealed the commonly described "endolymphatic" hydrops without any signs of inflammation or hemorrhage. The similarity and combination of Meniere's attacks with migraine are highly suggestive of vasomotor origin. Intermittent labarinthic angioneurotic edema seems to fit best the underlying pathologic process. Vasomotor imbalance, specific allergy or a chronic disease of thee inner ear are often identified as inciting factors in these patients. Vasoconstricting or vaso-dilating drugs are capable of producing an attack; therefore, Bellergal with its ability to neutralize both propensities is a vital component of the overall regimen recommended for autonomic nervous system instability together with the rest of the regimen employed for any allergic condition.

In our experience, Meniere's Syndrome is found only in patients evidencing an underlying adrenal cortical insufficiency. Therefore, our

approach to diagnosis and trcatment lies in the area of allergy. The texts say that acute symptoms of Meniere's can be brought on by infections and emotional distress. On this premise alone, one can readily see the connection with hypoadrenocorticism. Stress, from whatever source, evokes acute symptoms of the various systems including that of the ear.

Our approach to Meniere's emphasizes evaluation of the carbohydrate metabolism; study of salt and potassium handling via the electrolyte clearance test; careful search of the patieent's history for other allergic manifestations such as eczema, hay fever and the like, and for recent infections or emotional stress.

Treatment consists of elimination of readily absorbed carbohydrates, increase of salt in the diet (including extra salt in tablet form), frequent small feedings, and Eschatin (Adrenal Cortical Extract) 10 cc. on a once a week schedule. Desensitization should be limited simply to injections of histamine azoprotein, in very small doses initially and gradually increasing to one cc.

As we feel, Meniere's along with other problems, falls into the group of symptoms of adrenal cortical insufficiency, treatment of the existing adrenal cortical pathology effects relief of symptoms and usually eliminates the entire syndrome.

We are well aware that the texts suggest the elimination of salt because of its "fluid retaining property". However, these patients are in a state of negative nitrogen balance and require salt for proper metabolism of protein, and also, the adrenal cortical insufficiency involves failure of the zona glomerulosa in handling sodium and excessive amounts are lost in the urine and perspiration. Increasing salt in these patients improves the sodium-potassium balance and decreases the production of aldosterone.

It is generally accepted that allergic problems are aggravated by stress from whatever source, be it physical or emotional. This implicates the adrenal cortex. In a previous paper, "The Hypoadrenocortical State and Its Management," 1955, we categorized the hypoadrenocortic according to symptoms. Dizziness and an uncomfortable feeling in the head are noted in a very large percentage of the patients. Treatment as described eliminates these complaints. We should like to point out also that in patients who show a slightly elevated blood pressure with Meniere's it is our conclusion that this elevation usually indicates a compensatory action of the zona glomerulosa resulting from excessivee stimulation from the pituitary because of the failure of the zona fasciculata. Again, treatment of the adrenal cortical insufficiency effects a reduction in blood pressure without the use of anti-hypertensive drugs and withdrawal of salt. The anti-hypoglycemia diet with the Eschatin acts to

regulate the entire adrenal cortical function, suppressing the overactivity of the zona glomerulosa and increasing the efficiency of the zona fasciculata and zona reticularis.

Meniere's Syndrome then falls into the picture of adrenal cortical insufficiency and is relieved permanently by adherence to the anti-hypoglycemia diet, use of salt, and periodic injections of adrenal cortex extract plus any other hormonal adjuvant indicated by deficiency in a target organ. The intricacies of the hydrops of the vestibular system together with modifications of treatment — hormonal, dietetic and nervous stabilization — have been amply described by Dr. Goldman in several articles, the most recent and detailed of which appeared in 1965.[71]

Asthma, hay fever, and many of the allergic dermatidides are treated in like manner and respond even after the outmoded desensitization therapy has failed provided the patient has not been thrown completely out of balance by previous therapy with individual steroids.

Summary

Our clinical experience and Selye's fundamental research lead us to the conclusion that a very large number of pathological conditions become apparent only when bodily defense is "derailed" because the adrenal cortex is exhausted by excessive stress or the adrenal cortex is inherently deficient. These conditions can be forestalled or alleviated through supporting and resting the cortex and reducing internal and external stress. This can be accomplished with diet and ACE and by stabilizing the autonomic nervous system and controlling any associated endocrine dyscrasia.

REFERENCES

1. Sidney Smith: Letter to Dr. Holland, June 1835; FAMILIAR MEDICAL QUOTATIONS, Page 12-13, Edited by Maurice B. Strauss, M.D., Little, Brown and Company, copyright 1968.
2. E. M. Josephson, M.D.: ADRENAL CORTEX HORMONE IN INTRA-OCULAR TENSION, The Eye, Ears, Nose and Throat Monthly, Vol. 13, Page 453, 1935.
3. Sam E. Roberts, M.D.: EXHAUSTION: CAUSES AND TREATMENT: Published by Rodale Books, Inc., Emmaus, Pennsylvania, 18949, copyright 1967.
4. W. D. Currier, M.D., Pasadena, California 91101: Personal Communication
5. Henkin, R. I., and G. F. Powell: INCREASED SENSITIVITY OF TASTE AND SMELL IN CYSTIC FIBROSIS; Science, 138:1107, 1962.
6. Henkin, R. I., J. R. Gill, and F. C. Bartter: STUDY IN TASTE THRESHOLDS IN NORMAL MAN — PATIENT WITH ADRENAL CORTICAL INSUFFICIENCY: The Role of Adrenal Cortical Steroids and of Serum Sodium Concentration; J. Clin. Invest. 42:727-735, 1963.
7. Henkin, R. I., and Solomon, D. H.: SALT-TASTE THRESHOLD IN ADRENAL INSUFFICIENCY IN MAN; J. Clin. Endocr., 22:856, 1962.

8. Tintera, John W., M.D. and Goldman, Herbert B., M.D.: HYPOADRENOCORTICISM IN OTOLARYNGOLOGIC SURGICAL PROCEDURES; New York State Journal of Medicine, Vol. 56, No. 6, March 15, 1956.
9. Goldman, Herbert B., M.D., and Tintera, John W., M.D.: HYPOADRENOCORTICISM IN OTOLARYNGOLOGY; A.M.A. Archives of Otolaryngology, Vol. 64, pp. 381-389, November, 1956.
10. Goldman, Herbert B., M.D. and Tintera, John W., M.D.: STRESS AND HYPOADRENOCORTICISM: The Implications in Otolaryngology; Annals of Otology, Rhinology and Laryngology, Vol. 67, No. 1, Page 185, March, 1958.
11. Goldman, Herbert B., M.D.: HYPOADRENCORTICISM AND ENDOCRINOLOGIC TREATMENT OF MENIERE'S DISEASE; New York State Journal of Medicine, Vol. 62, No. 3, Page 377-382, February 1, 1962.
12. Tintera, John W., M.D.: THE HYPOADRENOCORTICAL STATE AND ITS MANAGEMENT; New York State Journal of Medicine, Vol. 55, No. 13, pp. 1869-1876, July 1, 1955.
13. Tintera, John W., M.D.: STABILIZING HOMEOSTASIS IN THE RECOVERED ALCOHOLIC THROUGH ENDOCRINE THERAPY: Evaluation of the Hypoglycemia Factor; Journal of the American Geriatrics Society, Vol. 14, No. 2, pp. 126-150, February, 1966.
14. Tintera, John W., M.D.: ENDOCRINE ASPECTS OF SCHIZOPHRENIA: Hypoglycemia of Hypoadrenocorticism; Journal of Schizophrenia, Vol. 1, No. 3, pp. 150-181, 1967.
15. Tintera, John W., M.D., and Lovell, Harold W., M.D.: HYPOADRENOCORTICISM IN ALCOHOLISM AND DRUG ADDICTION: Geriatrics, Vol. 6, No. 1, pp. 1-11, January-February, 1951.
16. Carryer, Haddon M. and Miller, Archie, W.: THE OCCURRENCE OF ALLERGIC DISEASES IN PATIENTS WITH CUSHINGS SYNDROME; (Mayo Clinic and Foundation), Journal of Allergy, 29:485-492, November, 1958.
17. Tintera, John W., M.D. and Lovell, Harold W., M.D.: ENDOCRINE TREATMENT OF ALCOHOLISM; Geriatrics, Vol. 4, No. 5, pp. 274-280, September-October, 1949.
18. Tintera, John W., M.D.: OFFICE REHABILITATION OF THE ALCOHOLIC, New York State Journal of Medicine, Vol. 56, No. 25, pp. 3896-3901, December 15, 1956.
19. Panos, T. C., M.D.: ADRENOCORTICAL INSUFFICIENCY IN INFANTS; (University of Texas) Texas State Journal of Medicine, 52:9, January, 1956.
20. McKenna, Robert D.: EMERGENCY TREATMENT OF ADRENOCORTICAL INSUFFICIENCY; J.A.M.A., 152:1494, August 8, 1953.
21. Taylor, F. S., and Essig, L. L.: ESCHATIN IN ADRENAL CORTICAL FAILURE; Amer. Jour. Obstet. Gynec., 65:720, April, 1953.
22. Loehner, Conrad A., (Salem, Oregon): FURTHER OBSERVATIONS ON THE USE OF ADRENAL CORTEX EXTRACT IN THE PSYCHOTIC AND NON-PSYCHOTIC PATIENT; Endocrinology, Vol. 27, September, 1940.
23. Weille, Francis L., M.D.: HYPOGLYCEMIA IN MENIERE'S DISEASE; (Boston) Arch. Otolaryng., Vol. 87, pp. 129-131, May, 1968.
24. Goldzieher, Max A. (Endocrinologist — St. Clare's Hospital, 55 East 86th Street, New York, New York 10028): THE ADRENAL GLANDS IN HEALTH AND DISEASE: Chapter XIV; Cortical Function in Metabolism, pp. 160-301, F. A. Davis Company, 1944.

25. Soffer, Louis L., M.D., F.A.C.P., Dorfman, Ralph I., Ph.D., and Gabrilove, J. Lester, M.D., F.A.C.P.: THE HUMAN ADRENAL GLAND: Cushing's Syndrome; pp. 506-511, Publ. Lea & Febiger, Philadelphia, Penn., 1961.
26. Venning, Eleanor H., M.Sc., Ph.D.: MEDICAL CLINICS OF NORTH AMERICA - CHICAGO NUMBER: ENDOCRINOLOGY: Evaluation of Adrenal Cortical Function In Man; Publ. W. B. Saunders Company, Philadelphia and London, January, 1948.
27. ADRENAL CORTEX THERAPY IN PSYCHOSES; Therapeutic Notes, pp. 47, February, 1939.
28. THE ADRENAL HORMONES; Therapeutic Notes, pp. 136-141, (Endocrinology Issue) April, 1935.
29. Werner, August A., M.D., F.A.C.P.: ENDOCRINOLOGY: CLINICAL APPLICATION AND TREATMENT: The Adrenal Cortex; pp. 677-693, pp. 478-484; Publ. Lea & Febiger, Philadelphia, Penn., 1942, Second Edition.
30. Hartman, Frank A., Ph.D., and Brownell, Katharine A., Ph.D.: THE ADRENAL GLAND: Adrenal Cortex and Energy Metabolism; pp. 233-239, Publ. Lea & Febiger, Philadelphia, 1949.
31. Wolf, William, M.D., M.S., Ph.D.: ENDOCRINOLOGY IN MODERN PRACTICE: Adrenal Preparations; pp. 1029-1030, Publ. W. B. Saunders Company, Philadelphia and London, Second Edition, Completely Revised, 1940.
32. Gordon, G. S., M.D., Ph.D., Escamilla, R. F., Goldberg, M. B., and Lisser, H., M.D.: ENDOCRINOLOGY IN CLINICAL PRACTICE - Useful Endocrine Preparations: Adrenal Cortex; pp. 383-385, Publ. The Year Book Publishers, Inc., Chicago, Illinois, 1953.
33. Turner, C. Donnell, Ph.D.: GENERAL ENDOCRINOLOGY - The Adrenal Glands: Physiologic Specificity of Cortical Compounds; pp. 240-243, Publ. W. B. Saunders Company, Philadelphia and London, 1948.
34. MERCK MANUAL OF DIAGNOSIS AND THERAPY: Adrenocortical and Related Therapy;; pp. 484-491, Publ. Merck & Co., Inc., Rahway, New Jersey, Ninth Edition, 1956.
35. Hoffman, Jacob, A.B., M.D.: FEMALE ENDOCRINOLOGY: Including Sections on the Male: Relation of the Adrenal Cortex to the Sexual Sphere; pp. 254-259, Publ. W. B. Saunders Company, Philadelphia and London, 1944.
36. Swingle, W. W.; Pfiffner, J. J.; Vars, H. M.; Bott, P. A., & Parkins, W. M.: Science 77:58, 1933.
37. Thomas, Jr., H. M.: J.A.M.A. 123:264, 1943.
38. Weil, P., & Browne, J. S. L.: Science 90:445, 1939.
39. Sarason, E. L.: Arch. Int. Med. 71:702, 1943.
40. Thorn, G. W.: J.A.M.A. 123-10, 1944.
41. Greenblatt, R. B.: Office Endocrinology, Charles C. Thomas, Springfield, Illinois, 1945.
42. Cheney, W. C.: J.A.M.A. 139:1077, 1949.
43. Sheldon, D. E.: Am. J. Obst. & Gynec. 49:269, 1945.
44. Williams, R. H.: Clinics 5:775, 1946.
45. Gordon, E. S.; Sevringhaus, E. L., & Stark, M. E.: Endocrinology 22:45, 1938.
46. Reed, A. C.: Am. J. Trop. Med. 22:127, 1942.
47. Wolff, W. A.; Rhoads, J. E., & Lee, W. E.: Nebraska M. J. 27:369, 1942.
48. Webb, Jr., A.: North Carolina M. J. 3:220, 1942.
49. Rhoads, J. E.; Wolff, W. A., & Lee, W. E.: Ann. Surg. 113:955, 1941.
50. Rich, A. R.: Bull. Johns Hopkins Hosp. 74:1, 1944.

51. Freeman, W.; Melick, J. M., & McClusky, D. K.: Am. J. Obst. & Gynec. 33:618, 1937.
52. Solomon, E. P.: Kentucky M. J. 39:58, 1941.
53. Dorsey, C. W.: Am. J. Obst. & Gynec. 58:1073, 1949.
54. Sapeika, N.: Arch. Int. Med. 82:263, 1948.
55. Perera, G. A.: Bull. New York Acad. Med. 26:75, 1950.
56. Pines, K. L.; Perera, G. A.; Vislocky, K., & Barrows, A. D.: Proc. Soc. Exper. Biol. & Med. 68:286, 1948.
57. Perera, G. A., & Pines, K. L.: Proc. Soc. Exper. Biol. & Med. 71:443, 1949.
58. Goldfarb, A. I., & Berman, S.: Quart. J. Stud. on Alcohol 10:415, 1949.
59. Smith, J. J.: Proceedings of the First Clinical ACTH Conference, The Blakiston Company, Philadelphia, Pa., 1950, pp. 566.
60. Smith, J. .: N. Y. State . Med. 50:1704, 1950.
61. Lapin, Joseph H., M.D.; Stanley F. Goldman, M.D., and Alex Goldman, M.D., New York City: THE CLINICAL USE OF ADRENAL CORTEX HORMONES; N. Y. State J. Med. 43:1964, 1943.
62. Perla, David and Marmorston, Jessie: SUPRARENAL CORTICAL HORMONE AND SALT IN THE TREATMENT OF PNEUMONIA AND OTHER SEVERE INFECTIONS; The Eyes, Ears, Nose and Throat Monthly, Vol. 13, pp. 453, 1935.
63. Rackemann, F. M.: ASTHMA IS A CONSTITUTIONAL DISEASE, J. Allergy 29:535, 1958.
64. Selye, Hans: STRESS, Acta, Inc., Med. Publishers, Montreal, Canada, pp. 82, 1950.
65. Hansel, French K.: COSEASONAL INTRACUTANEOUS TREATMENT OF HAY FEVER, J. Allergy, 12:457, 1941.
66. Daugherty, T. F., and White, A.: INFLUENCE OF HORMONES ON LYMPHOID TISSUE STRUCTURE AND FUNCTION, Endocrinology, 35:1, 1944.
67. Gell, P. G. H., and Benacerraf, B.: DELAYED HYPERSENSITIVITY TO SIMPLY PROTEIN ANTIGENS, Advances Immunol., 1:319-343, 1961.
68. Pitts, Ferris N., Jr., M.D., and McClure, James N., Jr., M.D.: LACTATE METABOLISM IN ANXIETY NEUROSIS, New England . Med., Vol. 277, No. 25, pp. 1329-1336, December 21, 1967.
69. Dworetzky, Murray, M.D. (The Allergy Clinic, N. Y. Hospital) New York City: ALLERGIC DISEASES OF THE EYE, N. Y. State . Med., Vol. 57, No. 4, pp. 765-769, February 15, 1957.
70. Bauer, Julius, M.D., F.A.C.P.: DIFFERENTIAL DIAGNOSIS OF INTERNAL DISEASES: Clinical Analysis and Synthesis of Symptoms and Signs of Pathophysiologic Basis; Chapter 8: VERTIGO, NAUSEA AND VOMITUS; Meniere's Disease, Page 289; published by Grune & Stratton, Inc., 381 Park Avenue South, New York, New York 10016, Third Revised Edition, 1967.
71. Goldman, Herbert B., M.D.: TREATMENT OF THE HYPOGLYCEMIA OF MENIERE'S SYNDROME, Transactions Indiana Academy Ophthalmology and Otolaryngology, 48:7-25, 1965.

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ENDOCRINE ASPECTS OF SCHIZOPHRENIA: HYPOGLYCEMIA OF HYPOADRENOCORTICISM

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Endocrine Aspects of Schizophrenia: Hypoglycemia of Hypoadrenocorticism[1]

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A GROWING BODY OF DATA LENDS STRENGTH to the conviction that schizophrenia can no longer be considered a purely mental disease. Like alcoholism, schizophrenia must be approached with the whole human organism in mind. This attutude was proposed more than forty years ago by Meyer (1948). Our mission is to coordinate and harmonize the "psyche" and the "soma" through the principles of genetics, biochemisty, enzymology and especially endocrinology. This can be no surprise even to the psychoanalyst. Over two thousand years ago the ancients described the pineal gland as the seat of the soul and in the seventeenth century Descartes agreed with them (Harvard, 1891. Freud himself was speaking of endocrinology when he said, "These mental disturbances are open to therapeutic influence only when they can be identified as secondary effects of some organic disease (Freud, 1943)".

In recent years psychiatry has come to sense some limitation as a descriptive science. Mere manipulation of the psyche left something to be desired. Other disciplines were invoked. Surgery seemed too brutal. Convulsive therapy was helpful as a last resort. The success of Hoffer (1957) with nicotinic acid and diet is a promising step. The steady increase in mental hospital population in the U.S. reversed itself abruptly in 1955 with the advent of tranquilizers and antidepressants. By 1963 the mental hospital census in the U.S. was 135,000 less than had been projected (Simpson, 1966). Although they may have been spared hospitalization, the picture of 135,000 numbed and somewhat toxic and sometimes addicted citizens is not entirely a satisfactory one to contemplate.

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Studies attempting to correlate psychotic states with adrenal function are well known. Bunney et al, 1965a; Bunney et al, 1965b; Suwa et al, 1962; Curtis et al, 1960; Persky et al, 1959). Other investigators (Simon & Gillies, 1954; Larsen, 1964) tried to associate mental aberration with such physical attributes as bone and muscle measurements, fat distribution and blood pressure, all of which may certainly carry endocrine connotations.

My firm belief in the vital importance of the endocrine system in pathological mentation was sparked in the early forties when I first insisted on 3-4 hour glucose tolerance tests. The laboratories apologized for seemingly incorrect readings although they had double-checked their techniques. What mystified them was the low flat curves derived from disturbed early adolescents. This laboratory procedure had been previously carried out only for patients with physical findings presumptive of diabetes.

Dorland's definition of schizophrenia (Bleuler's Dementia Praecox) includes the phrase, "often recognized during or shortly after adolescence", and further, in reference to hebephrenia and catatonia, "coming on soon after the onset of puberty".

These conditions might seem to arise or become aggravated at puberty, but probing into the patient's past will frequently reveal indications which were present at birth, and during the first year of life, and through the pre-school and grammar school years. Each of these periods has its own characteristic clinical picture. The picture becomes more marked at pubescence and often causes school officials to complain of juvenile delinquency or underachievement. A glucose tolerance test at any of these periods could alert parents and physicians and could save innumerable hours and small fortunes spent in looking into the child's psyche and home environment for maladjustments of questionable significance in the emotional development of the average child. The negativism, hyperactivity, and obstinate resentment of discipline are absolute indications for at least the minimum laboratory tests: urinalysis, complete blood count, P.B.I. determination and the 5-hour glucose tolerance test. A glucose tolerance test can be performed in a young child by the micro-method without undue trauma to the patient. As a matter of fact, I have been urging that these four tests be routine for all patients, even before a history or physical examination is undertaken.

In almost all discussions on drug addiction, alcoholism, and schizophrenia, it is claimed that there is no definite constitutional type that falls prey to these afflictions. Almost universally the statement is made that all of these individuals are emotionally immature. It has long been our goal to persuade every physician whether he is oriented toward psychiatry,

genetics or physiology to recognize that one type of endocrine individual *is* involved in the majority of these cases—the hypoadrenocortic. In most instances he has an inborn error of metabolism, with failure in the production of certain adrenal cortical hormones which initiate and control the interaction, activation and inhibition of certain enzymes. Alcohol dehydrogenase, for example, has definitely been incriminated in the alcoholic and the barbiturate addict. In the schizophrenic, time and again various peculiar metabolites have been demonstrated in the blood or urine. These metabolites have been shown to be related to carbohydrate intake and reflect a breakdown in the cycle in which the cerebral cortex activates the vegetative nervous system which in turn stimulates the production of catecholamines necessary to mediate the hypothalamic-adrenohypophiseal-adrenocortical complex (Kaplan, Inf. Comm.).

Hypoadrenocortical Syndrome

I first described the hypoadrenocortical syndrome in 1949 (Tintera & Lovell, 1949) in connection with alcoholism and later, in 1955 (Tintera, 1955) summarized the typical findings in 200 selected cases. The chief complaints were as follows:

Excessive fatigue	94%
Nervousness & irritability	86%
Mental depression	79%
Apprehensions	71%
Excessive weakness	65%
Light headedness	47%
Faintness & fainting spells	42%
Insomnia	40%
Inability to concentrate	100%

Other findings according to organic systems are listed with their frequencies in these papers. It is germane, however, to give here the chief physical and laboratory findings.

Postural hypotension	93%	
Generalized cervical lymphadenitis	93%	
Skin thin and dry	93%	
Perspiration scanty	91%	
Hair sparse	83%	Physical
Crowded lower incisors	80%	
Asthenic habitus	78%	
Positive Rogoff's sign	71%	
Erythema of thenar and hypothenar eminences	28%	
Blanching on exposure to cold	21%	

Low basal metabolic rate		
(average-minus 14)	85%	
X-Ray: J-shaped stomach and visceropotosis	73%	
Eosinophilia	58%	
Relative lymphocytosis	51%	Laboratory
Low, flat Glucose Tolerance curve	51%	
(if relative or reactive hypoglycemias are included, the total approaches 100%)		
17-ketosteroids-low		
Male: 2.4 to 29; average 10.9 mg./24 hrs. (N=8-25 mg./24 hrs.)		
Female: 1.2 to 22; average 7.7 mg./24 hrs. (N=5-15 mg./24 hrs.		

With more recent advances in laboratory procedures, a normal PBI is almost invariably found in spite of decreased metabolism. These patients are hypometabolic but not necessarily hypothyroid and thyroid medication must be used with caution.

We need not, and indeed should not, limit our consideration to the first manifestation of schizophrenia in the pubescent child since even at birth such ominous stigmata may be present as hyponatremia, hypoglycemia, hypomyotonia, and hyperreflexia. The frequently premature offsping of parents who exhibit allergies or other hypoadrenocortic indicia may have gastric symptoms such as projectile vomiting or pylorospasm, often severe enough to be fatal. Later we see the hyperactive preschool child and the underachiever in grade school. His chief scholastic barrier is the inability to concentrate on mathematics, and finally he fails algebra and/or geometry. Then there is the negativistic adolescent with failure in development of secondary sex characteristics.

In typical sequence the colicky newborn develops diaper rash followed by frank eczema. Later (after T. & A.), hay fever often arises which may eventually lead to asthma (post-appendectomy) and finally schizophrenia intervenes, at which time the allergies disappear. Incidentally, the post-appendectomy asthma is an argument for the recticuloendolthelial function of the appendix. Mesenteric adenitis mimics appendicitis; 85% of the removed appendices are innocent.

Improvement in the schizophrenic is usually attended by a return of asthma. We have demonstrated elsewhere that hypoadrenocorticism is the basis of the allergic response (Blaine, 1965). Stress may activate the hypothalamus-pituitary-adrenal axis to such an extent that sufficient steroids are elaborated to control the allergy but at the same time the

balance is disturbed since ACTH is specific for glucocorticoids, but not for mineralocorticoids and 17-ketosteroids to an equal degree. For this reason it is illogical to prescribe individual steroids such as cortisone or cortisol without regard to the synergistic and antagonistic hormonal relationship.

The endocrinologist is not mystified by the striking clinical improvement in many psychiatric patients following electro-convulsive therapy. In addition to interrupting the mental processes, this electrical insult to the organism stimulates the adrenal cortex to pour out tremendous quantitiès of properly proportioned corticosteroids (Graham & Cleghorn, 1951). This is beneficial if the adrenal is able to respond but when the adrenal is already exhausted, the result may be disappointing. E.S.T. has a definite place in the psychiatric armamentarium, provided the patient has been conditioned previously with A.C.E. (adrenal cortex extract) but *not* with individual steroids which only create imbalance among the 32 or more steroids involved. Employing these principles of pre-treatment with A.C.E., Connason and Ryberg (1957) obtained remarkable results, even in long-standing cases. In their series, the milder foreign protein stimulus was used instead of electroshock.

Carbohydrate Metabolism

The only definitive gauge of impaired carbohydrate metabolism in the schizophrenic and/or hypoadrenocortic is the five-hour glucose tolerance test. In young individuals with hypoadrenocorticism or pituitary-adrenal insufficiency, a low flat curve is observed. This moderate hypoglycemia induces a craving for carbohydrates, alcohol or drugs which afford temporary relief of symptoms such as nervousness and feelings of unreality. Hepatic damage results from prolonged abuse of these agents. Fatty infiltration follows glycogen depletion and the G.T.T. curve then will be characterized by a sudden initial rise to a high plateau followed by an abrupt drop, technically reactive hypoglycemia. In the pituitary-adrenocortic with obesity the rise reaches hyperglycemic levels and eventually declines to hypoglycemic values. Without dietary indiscretions, the curve may remain flat until the climacteric when again a further disturbance in the steroid balance may arise as a result of gonadal failure. The adrenal produces 65% of the male hormone in the man but only 15% of the female hormone in the woman during the child-bearing years. The absolute shut-down of the gonads puts a greater load on the already deficient adrenals and many acute episodes are encountered at this age,

especially in the female when the adrenals are required to produce 100% of the estrogens.

Cortisone, or its derivatives, is not the answer to adrenal deficiency, as evidenced by a 13 year old girl who developed chronic nephrosis with marked edema. Hospitalized at one of our local university medical centers, she was given the generally approved dose of 60 mg. prednisone to which she did not respond. The dose was doubled to 120 mg., then to 240 and finally to 320 mg. per day, at which point this shy, unobstrusive child became a manic schizoid, destroying so much hospital equipment she had to be restrained. The 4+ proteinuria persisted and she, along with seven

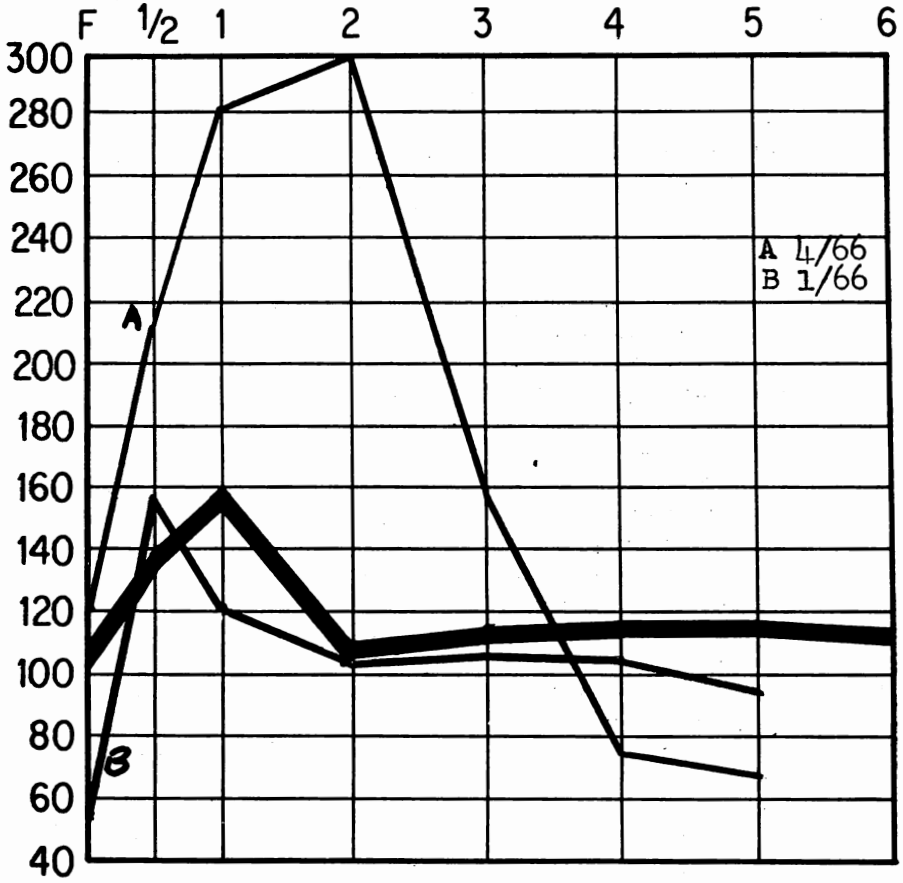

FIG. 1. *Glucose tolerance curves of 13-year old patient.*

other children, were considered failures on prednisone and as a last resort, an untried experimental drug was proposed, whereupon the protesting parents sought other advice.

When I first saw her, the urine boiled solid in the test tube. The day after the initial dose of Eschatin the urine was absolutely clear. She made a stormy but complete ambulatory recovery with A.C.E., diet, etc. The G.T.T. showed a severe diabetic curve. After recovery, a normal curve was obtained, except for an exceptionally low fasting level, as shown in Figure 1. What was the cause of schizophrenia in this case? Evidentally, it was a derangement of cerebral carbohydrate metabolism. During intensive A.C.E. treatment, she was a good student, but now on maintenance doses cannot concentrate as well, failing most subjects, notably algebra, but she is alive.

Case Histories

The following case histories represent patients, who on the average had previously been treated by 10 physicians and 2 psychiatrists. All demonstrated moderate to severe emotional disturbances but no specific psychiatric diagnosis is offered:

Case 1

Patient: T. H. First seen 6/5/62; Age 35; White female.
Always tired, born tired. Quite upset, cries for no reason. Difficulty in concentrating. Good marks in school but had to study lying down. On and off thyroid (Proloid) for 12 years. 2 children (never felt better than when pregnant. Put on Dexedrine 1960, followed by hypoglycemia collapse Feb. 1960. On low-carbohydrate diet for 4 months, then returned to regular diet. Same year spent 6 weeks in psychiatric hospital for overdose of Librium where the diagnosis was made of anxiety, neurocirculatory asthenia. Still on amphetamines. Saw 12 MDs in past year. Blood pressure has been 80/40. Craves sweets. Gets rose fever and vasomotor rhinitis. Adores pickles.

P.E.: Long index fingers, hypoadrenocortical teeth, positive Rogoff.

G.G.T.: 1960: F-81, ½-136, 1-167, 2-133, 3-108, 3½-123, 4-91, 4½-95, 5-87. P.B.I.—11.8 mcg%.

Diagnosis: Hypoadrenocorticism, hypo-ovarianism (mild), autonomic nervous system instability, orthostatic hypotension.

RX: Adrenal Cortical Extract, (A.C.E.) B6, B12, Theelin, Durabolin, Bellergal.

Course: Short periods of slight improvement through 7/28/62. Patient not faithful to diet at first and continued to take tranquilizers, but by 10/16/62 patient stated enthusiastically that she was functioning once more as a human being. Discharged to family physician.

Admitted to hospital 8/1/64 with acute pyelitis; discharged 8/6/64. Admitted to hospital 1/29/65 with diagnosis of neurotic depression and conversion hysteria; discharged 2/7/65. Admitted to hospital 4/13/66 in a hypoglycemia collapse, at which time the glucose tolerance test was: F-60, ½-112, 1-127, 2-94, 3-56, 4-48, 5-46. Discharged 4/20/66. 11/23/66—First consultation since 10/26/62. In and out of hospital four times. Had not been following diet. Taking Eskatrol twice a day. Patient returned to hypoglycemic regimen. 11/28/66—"felt like a zombie." Crying, depressed, can't concentrate. 12/13/66—Patient is beginning to have periods of "feeling decent" but can be thrown into panic by being forced to make a "decision." Referred back again to family physician in a manageable state.

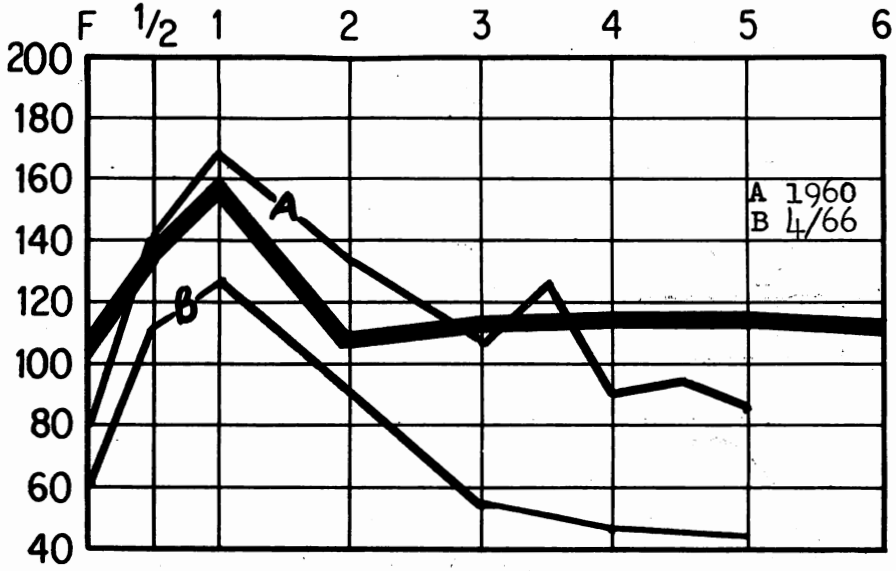

FIG. 2. *Glucose tolerance curves for Case 1.*

Case 2

Patient: H. J. First seen 4/14/58; Age 21; White female.
Fears and anxiety (worse in crowds). Afraid to leave her house. Dizzy spells. Saw psychiatrist 2-3 times a week for 3 years. Was "afraid" of him. Had ambulatory shock treatment Oct. 1956 (3 electroshock—5 insulin). Received increasing doses of Sodium amytal each visit—couldn't talk otherwise. Less nervous driving car; short periods of

employment. Took tranquilizers—also Dexamyl. Perspires profusely: started to gain weight at 5 or 6. Always a tom-boy. Used depilatory last 3-4 years upper lip, chin, side of face.
Menstrual difficulties. No sex activities. Sighing respiration. Trochanteric obesity at 12 or 13. Candy binges.

P.E.: Unremarkable, except for separation of upper incisors, high palatal arch, mild hirsutism, long index fingers, 3-4 interspace tenderness, positive Rogoff. Blood pressure 152/90. Ht. 5'5", Wt. 135.

G.T.T.: April, 1958: F-90, ½-116, 1-86, 2-96, 3-80, 4-82.

Diagnosis: Mild hypopituitarism with secondary hypo-ovarianism and hypoadrenocorticism.

RX: Diet, A.C.E., Benadryl, Theelin, B6, B12, Bellergal, Menagen, Norlutin.

Course: Very slow improvement with gradual increase in activities outside the the home. Employment status also improved. Many periods when symptoms returned—shaking, anxiety, panic, depression but by 1½ years was married and moved to Wyoming. Works steadily and reports good general condition. Blood pressure normal. Death of 18-month old baby 1966 brought on period of "exhaustion." Determines own need for A.C.E.—5-10 cc per month. Leads comparatively extravertive life even withstanding the collapse of her dream to run dude ranch.

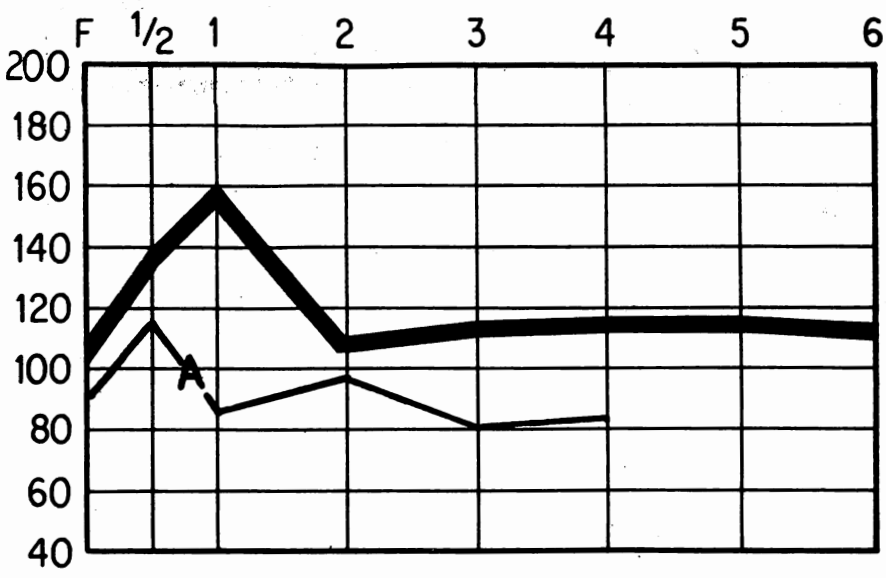

FIG. 3. *Glucose tolerance curves for Case 2.*

Case 3

Patient: P. M. First seen 4/4/47; Age 32; White female.
Depressed, confused, irritable. Tired and too weak to stand. Migraine since age 17, mild allergies. Fingers blanch with mild cold. Vague fears for self. Cries often, "impossible to live with."

P.E.: Wt. 105, Ht. 65", blood pressure 136/82, positive Rogoff (rt), dermographia.

Diagnosis: Hypoadrenocorticism, hypo-ovarianism.

RX: Diet, A.C.E., Theelin, Gynergin, Hepthis, Cortate Pellets-DOCA, Proloid, Presidon, Bellergal.

Course: Slow recidivous progress as activity increased. Much improved with gain in weight. Patient not seen between Dec. 1956 and Jan. 28, 1964, during which period she had required psychiatric hospitalization. Now in a stormy menopause. Rogoff strongly positive. Slow progress again. Course of shock treatments recommended 7/65. Tranquilizers and also Bellergal, diet, A.C.E. (increased doses, Theelin, Valium, B6, B12, Norlutate, Menagen. Within a month shopped. Now back at work and coping with unusual stress.

G.T.T.: Jan. 30, 1964: F-90, -137, 1 -98, 2½-; 3½-65, 4½-79, 5½-79.

FIG. 4. *Glucose tolerance curves for Case 3.*

Case 4

Patient: L. R. First seen 11/20/61--Age 11.5—White female. Tired, no energy, allergies. Can't concentrate, gets dizzy in math. class. Colic and projectile vomiting as an infant. Intense early family trauma. High I.Q. Under psychiatric care. An emotionally disturbed child. Difficult to manage.

P.E.: Wt. 77, Ht. 54", blood pressure 110/70, allergic conjunctivitis, Vasomotor Rhinitis, mod. positive Rogoff. P.B.I. 5.3 mcg%.

G.T.T.: 11/1/61: F-110, ½-188, 1-183, 2-150, 3-112, 4-110, 5-102.

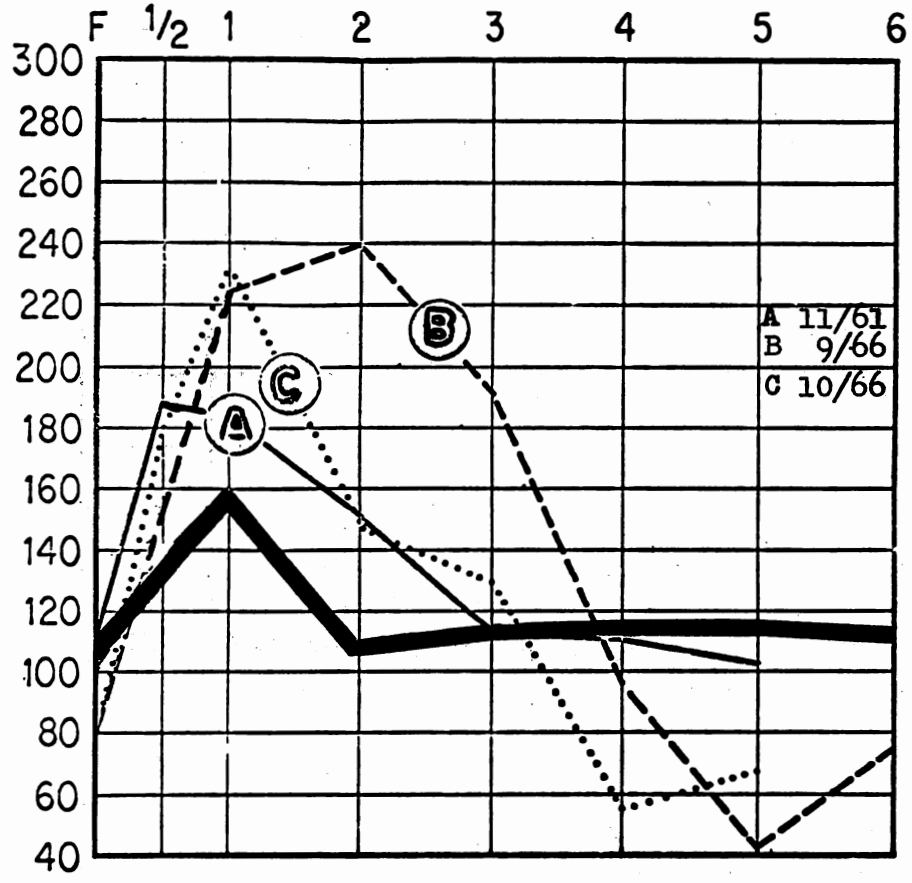

FIG. 5. *Glucose tolerance curves for Case 4.*

Diagnosis: Mod. hypoadrenocorticism, sexogen insufficiency, "emotional disturbance."

RX: Diet, Lipo, A.C.E., Bellergal, API., Theelin, B6, B_{12}. Will need Proloid and progesterone.

Course: Steady dramatic improvement in school work, family relationships, life interests and energy output. Discharged 10/64 and regular regimen stopped and invented own diet. Menarche marked by irregularity at age 15. Day of repeat Glucose Tolerance Test Oct. 1966 made a tentative attempt to slash wrists and was hospitalized and given intensive endocrine therapy with prompt favorable response. Outside school privileges as in-patient.

G.T.T.: Sept. 1966: F-80, 1-224, 2-240, 3-191, 4-95, 5-42, 6-74.
Oct. 1966: F-80, ½-180, 1-230, 2-148, 3-130, 4-55, 5-67.

Case 5

Patient: P. H. First seen 12/11/63; Age 37; White female.
Depression, agitation, tiredness since childhood. Life seemed bleak, lived front day to day. Saw endocrinologist in 1961 for weight when she was told her Glucose Tolerance Test was normal. (In 1957 it had been: F-88, ½-83, 1-87, 2-80, 3-71.7, 4-57). Has temper tantrums and screams at her 3 children. No interest in sweets but likes pickles and pickle juice. Tried suicide by sleeping pills 9 years ago. Intermittent treatment of psychiatrist. His two siblings, one in mental hospital, other has "nervous stomach."

P.E.: Wt. 130, Ht. 5'1", blood pressure 120/62. Hyperactive reflexes, mild girdle and lower trochanteric obesity, mild hirsutism, 4th interspace tenderness. P.B.I.—3 mcg%.

Diagnosis: Mild hypopituitarism, hypoadrenocorticism, hypo-ovarianism and hypothyroidism.

RX: Diet, Bellergal, Menagen, Proloid, Theelin, A.C.E., B6, B_{12}. Later Durabolin, Norpramin.

Course: At first patient did not stay on diet and progress was very slow. In 9 months felt very well and engaged in wide array of activities. Depression and fatigue followed series of serious stress situations but is now enjoying life.

G.T.T.: Oct. 12, 1966: Afternoon G.T.T.: F-105, ½-175, 1-206,2-108, 3-88, 4-101, 5-95.

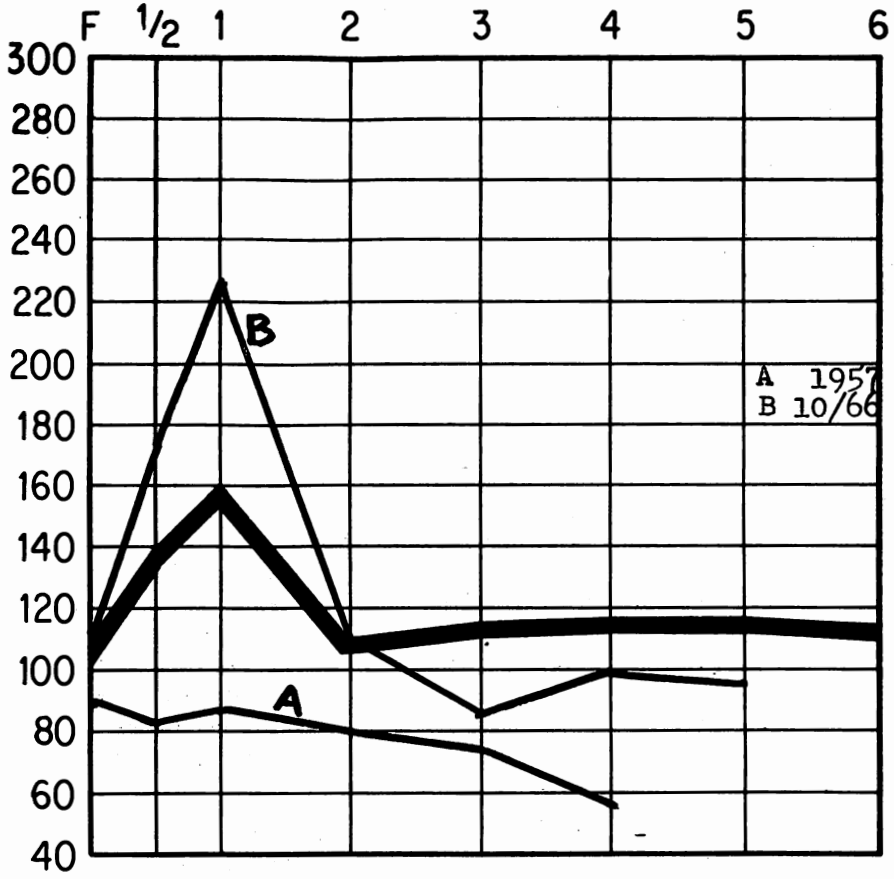

FIG. 6. *Glucose tolerance curves for Case 5.*

Case 6

Patient: K. B. First seen 6/23/59; Age 44; White female.
Depression at the smallest challenge; unable to handle decisions, cries for no reason; no self-confidence; no interest in anyone or anything. Very attached to mother. Hospitalized at 6 for overactive thyroid. Father died April 1948; 3 electroshock treatment at this time. Balked in panic twice at approaching matrimony. Married Dec. 1948. Three children. Well during pregnancy, depressed post-partum. Minimal sexual pleasure. Wanted whole family to live with mother. Intolerable alcoholic husband.

P.E.: Wt. 131, Ht. 65", blood pressure 152/85. Crowded lower incisors, long index fingers, exaggerated reflexes, such trochanteric obesity, 4th interspace tenderness. P.B.I.—6.8 mcg%.

G.T.T.: F-90, ½-139, 1½-117, 2 -71, 3½-67, 4½-59.

Diagnosis: Hypoadrenocorticism, hypo-ovarianism, autonomic nervous system instability.

RX: Bellergal, Menagen, A.C.E., Theelin, Testosterone, Benadryl, B6, B12, Durabolin, Deprol, Valium, Heparin and diet.

Course: Very slow undulant progress. Constant severe marital aggravation. Took handful of Bellergal and Phenobarbital Feb. 1960. 4 electroshock treatments April 1963. Very slow progress since then, not always diet-faithful. Still "up and down" but excursions less wide, anxieties less specific and able to work quite steadily. Still living under extreme uxorial stress. Blood pressure drops with sense of well-being. Working steadily with increased ambition. Highest Civil Service rating.

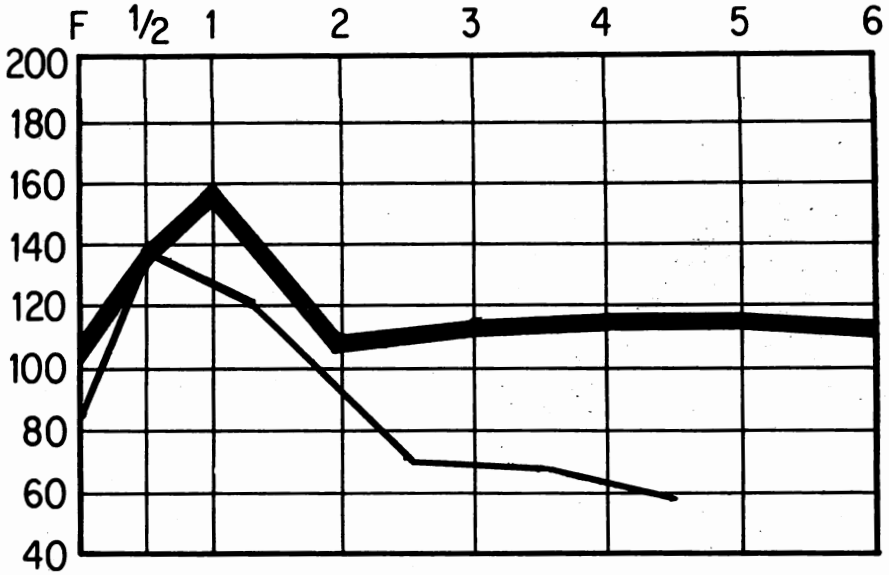

FIG. 7. *Glucose tolerance curves for Case 6.*

Case 7

Patient: H. M. First seen 11/7/56; Age 23; White female.
Nervous-crying spels. Felt like an outcast at school. "Nervous breakdown" at 15. Thought her food was poisoned. Shock treatments. Closely

attached to mother. Eggs made her vomit. Married two years. Baby eight months old. Cried all the time after baby was born. Didn't nurse it—afraid her breasts would sag. Afraid her mother would hurt the baby. Had shock treatments again. Depressed. Cries. Can't sleep. Irrational with nembutal. Cowered in corner at sight of sphygmomanometer. "I don't want any more shock treatments."

P.E.: Wt. 106, Ht. 62", blood pressure 132/90. Swollen turbinates, long right index finger, adrenal teeth, positive Rogoff, exaggerated reflexes.

G.T.T.: F-100, ½-180, 1-155, 2-110, 3-95, 4-75.

Diagnosis: Hypoadrenocorticism, hypo-ovarianism (mild).

RX: Diet, A.C.E., Benadryl, B6, B12, Theelin, Bellergal, Noludar.

Course: Dramatic improvement with first treatment. Uneventful normal delivery 2/29/60. Felt well afterwards. Nursed the baby. Discharged. Felt very well during next pregnancy but went into severe post-partum depression 6/27/61. Recovered at once with A.C.E. and is feeling very well.

FIG. 8. *Glucose tolerance curves for Case 7.*

Case 8

Patient: D. H. First seen 3/13/61; Age 44; White female.

Year ago felt she was losing her mind and has not felt right since. Was afraid she would strike people—would have to leave any social situation in panic; couldn't look in a mirror, couldn't face strangers; couldn't take a bath; afraid of harming children. Saw 3 psychiatrists—told cure would take 3 years. Taking Librium.

P.E.: Wt. 133, Ht. 65", blood pressure 100/70. Crowding of lower incisors, 4th interspace tenderness, liver enlarged and tender. P.B.I.—5.1 mcg%.

Diagnosis: Hypoadrenocorticism, hypo-ovarianism.

RX: Librium, A.C.E., Theelin, B6, B12, Bellergal, Menagen.

Course: Progressed slowly, by 2 months was having more good days than bad. Good periods lengthened slowly. Specific phobias lessened greatly. Patient now performing quite normally with only occasional bouts of fearfulness under severe stress situations, as when unwed daughter became pregnant.

G.T.T.: 2/2/61: F-92, ½-135, 1½-94, 2½-87, 3½-70, 4½-84.

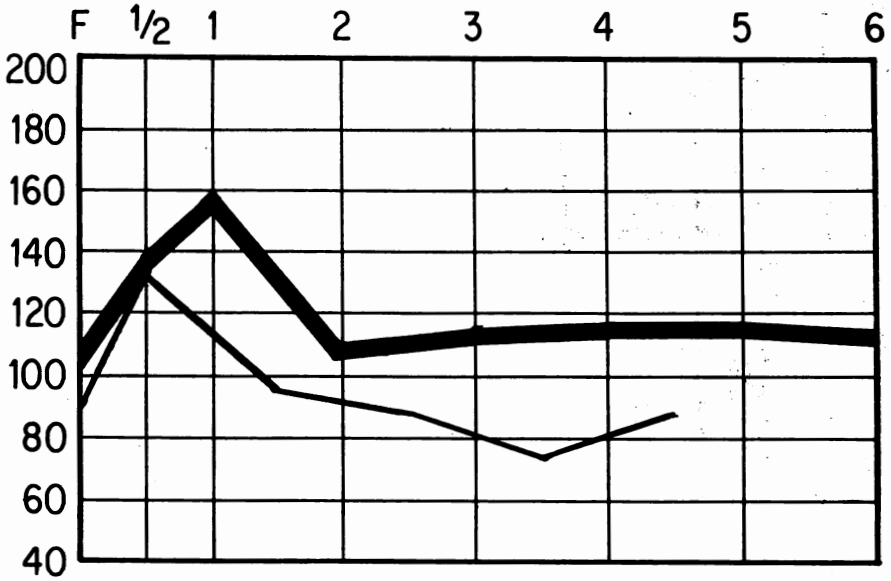

FIG. *9. Glucose tolerance curves for Case. 8.*

Case 9

Patient: T. L. First seen 5/10/66; Age 31; White female.

Nervous breakdown, disturbed, anxiety, depression for one year. (Diagnosed by psychiatrist—schizophrenia with paranoid tendencies.) Tofranil made her feel worse. Also had hepatitis. Thinks often of suicide.

P.E.: Weight 120, Ht. 64", blood pressure 110/70, conjunctivitis, spots of pigmentation on neck, long index fingers, Rogoff tenderness, exaggerated reflexes. P.B.I.—4.8 mcg%.

G.T.T.: 2/6/66: F-88, ½-153, 1-135, 2-78, 3-78, 4-65, 5-68, 6-85.
7/62 post-hepatitis: F-124, ½-200, 2-202, 3-120, 4-120.
(hepatic curve)

Diagnosis: Hypoadrenocorticism.

RX: A.C.E., B6, B12, Estrogens.

Course: Gradual definite improvement in mood. Increased energy and complete absence of all original complaints as of 12/66.

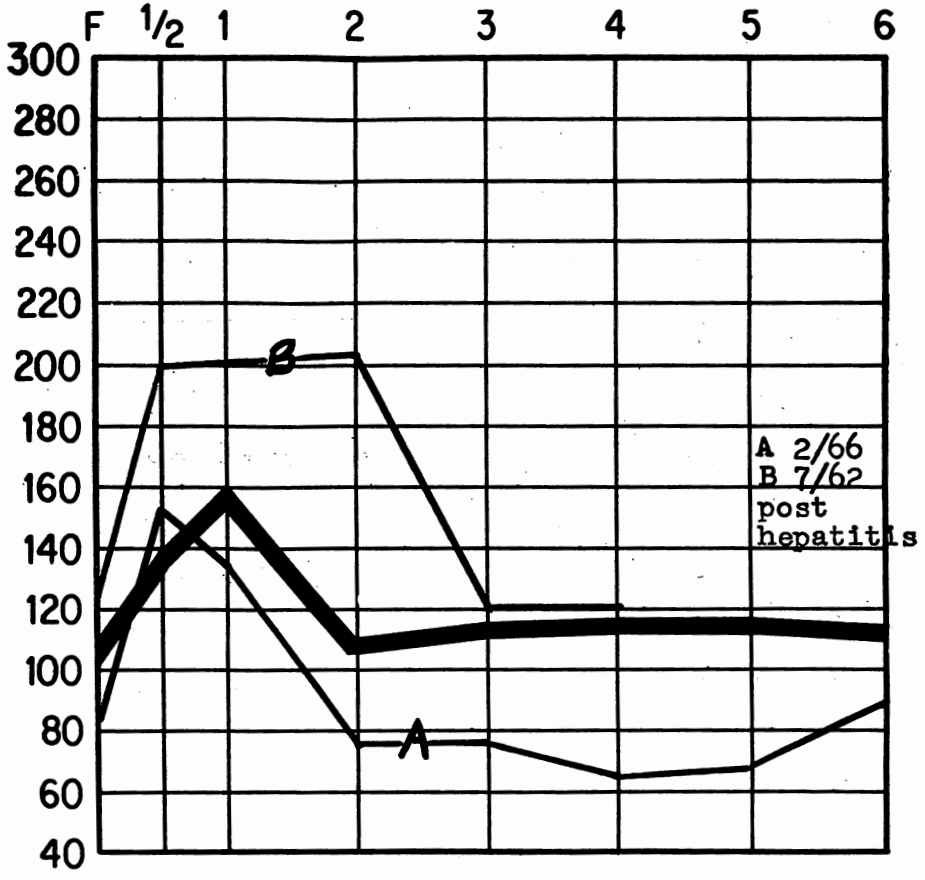

FIG. 10. *Glucose tolerance curves for Case 9.*

Case 10

Patient: C. S. First seen 9/25/62; Age 42; White female.
Referred with diagnosis hypoglycemia. Nervous, doesn't sleep. Deep sense of inadequacy, afraid of losing her job. (even when employer promotes her and pays her more). No energy. Ten years ago had a "nervous breakdown" described as paranoid schizophrenia. Recent consulting psychiatrist thinks psychotic exacerbation possible. Gets rose fever. Already on hypoglycemia diet and tranquilizers.

P.E.: Wt. 136, Ht. 63", blood pressure 110/70. P.B.I.—6.2 mcg%. Swollen turbinates, sl. crowding lower incisors, long index fingers, moderate trochanteric obesity.

G.T.T.: F-96; ½-159, 1-135, 2-136, 3-125, 4-77, 5-97.

Diagnosis: Hypoadrenocorticism, Mild hypo-ovarianism.

RX: Decreased tranquilizers, A.C.E., Menagen, Bellergal, B6, B12, Durabolin, Theelin.

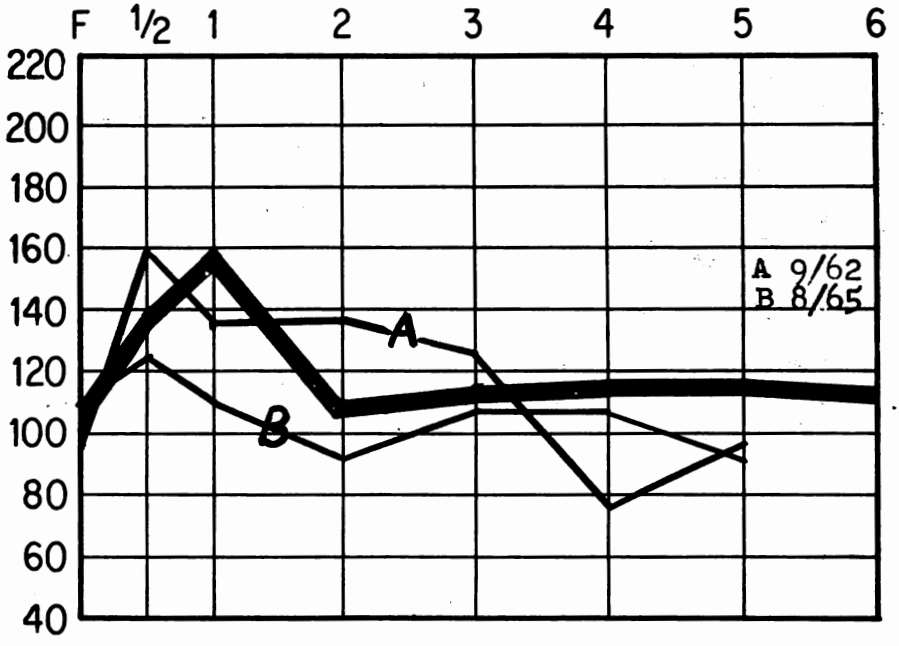

FIG. 11. *Glucose tolerance curves for Case 10.*

Course: General improvement was rapid. Emotional state and energy output good. Fear of losing job and sense of inadequacy in that respect kept returning in various degrees. Had 7 electroshock treatments in July 1963. The "job fixation" has been reduced and other wise the patient feels very well.

G.T.T.: 8/3/65: F-111, ½-125, 1-108, 2-92, 3-108, 4-108, 5-92.

Case 11

Patient: S. B. First seen 10/22/58; Age 33; White female.
Eczema at five. Asthma since six--severest with first pregnancy. Recently every morning. Always controlled with Tedral and Phenobrab. Food allergies during emotional upheavals. Depressed, nervous, snaps at people. Pain in her chin since adolescence—worse with nervous spels. Chews her lips until they are sore. Had a short "nervous breakdown" —screaming nude in the street, thought husband wanted to kill her. Had psychotherapy but no shock treatment. Has no feeling for her 10 year old son "effeminate."

P.E.: Wt. 133, Ht. 65", blood pressure 118/72. Allergic rhinitis, adrenocortical teeth, high narrow palatal arch, 4th interspace tenderness, pos. Rogoff on rt., exaggerated reflexes. Mod. trochanteric obesity.

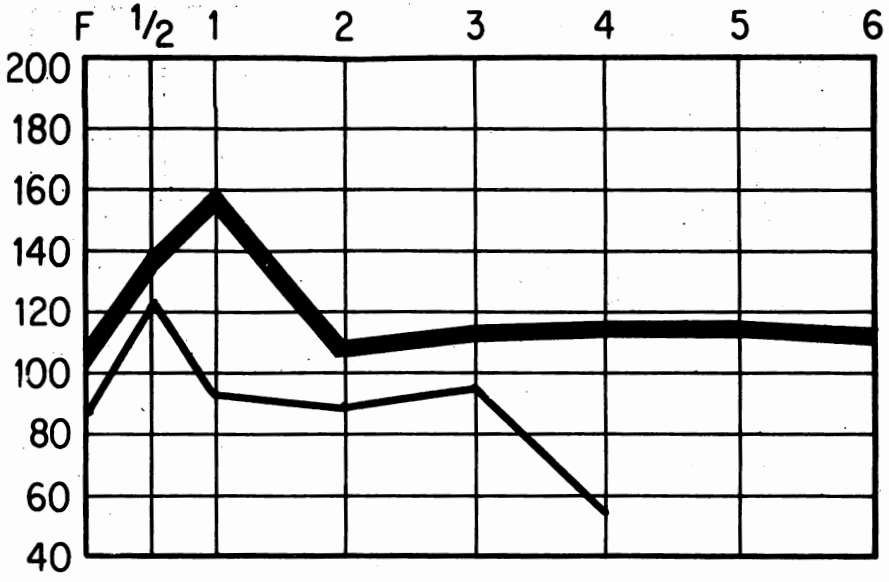

FIG. 12. *Glucose tolerance curves for Case 11.*

Diagnosis: Hypoadrenocorticism, hypo-ovarianism.

G.T.T.: F-89, ½-123, 1-92, 3-98, 4-54.

RX: Diet, A.C.E., Benadryl, Bellergal, Menagen, B6, Theelin, Norlutin, Diuril, Aldactone.

Course: Rapid improvement until wheezing attacks became rare. Two or three acute hypoglycemic episodes with severe schizoid manifestation associated with diet lapses. Dramatic instantaneous recovery during intravenous injections of Eschatin by family physician. Great improvement in mood. Activities extended to include water skiing and travel to Europe. Has gone through hay fever seasons without any asthma.

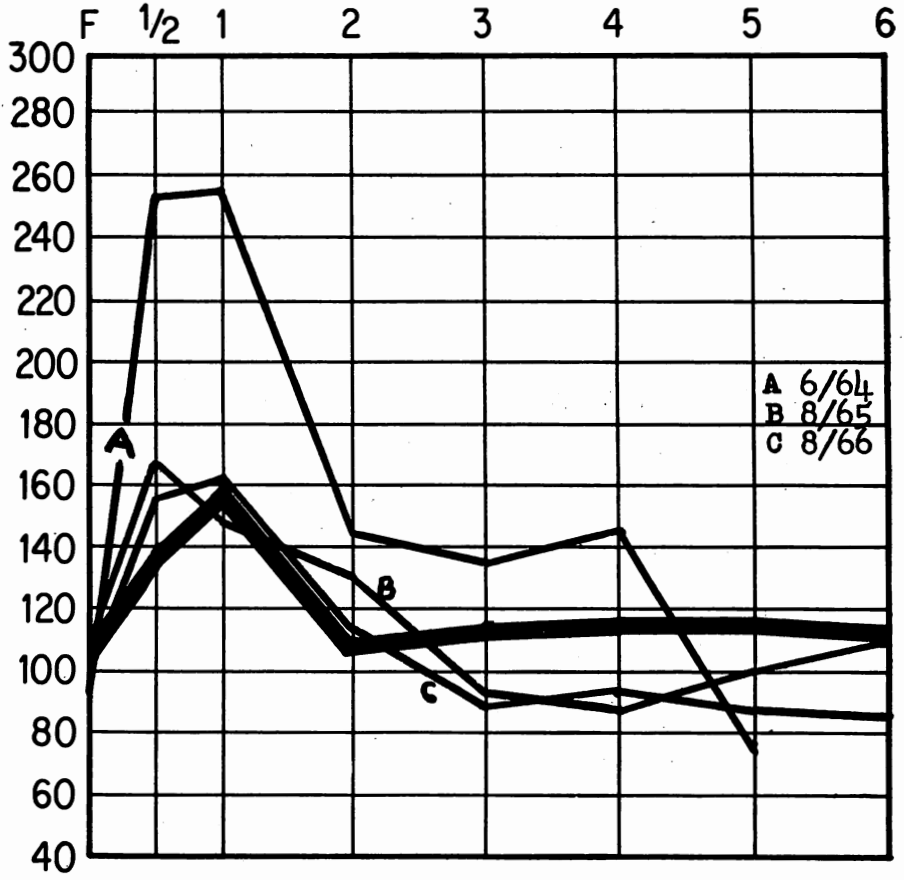

FIG. 13. *Glucose tolerance curves for Case 12.*

Case 12

Patient: L. C. First seen 6/20/62; Age 11; White female.
Bright, fidgety and nervous, inattentive in school. Gaining weight. Steals money and useless trinkets, mostly from family. Impossible to reason with. Was thumb-sucker when younger, also some colic and projectile vomiting as an infant.

P.E.: Wt. 97, Ht. 60", blood pressure 100/50, P.B.I. 4.8 mcg%. Swollen turbinates, crowded lower incisors, long right index finger, sluggish reflexes.

Diagnosis: Inborn error in metabolism, hypoadrenocorticism (mild), hypothyroidism (mild).

RX: Diet, Intramuscular A.C.E. (in oil), Proloid, Bellergal, B12, Theelin in small doses.

Course: Gradual improvement in personality and school-work. Went from failing student to honor student. At age 17 however, indulged in sexual reveries almost hallucinatory in degree. Reported imaginary sexual debauches as fact. This has since cleared up.

G.T.T.: 8/5/65: F-90, ½-168, 1-150, 2-127, 3-91, 4-85, 5-100, 6-109.
8/30/66: F-90, ½-155, 1-160, 2-105, 3-90, 4-90, 5-87, 6-85.

Case 13

Patient: C. M. First seen 5/11/60; Age 66; White female.
Repeated periods of profound depression starting with menopause in 1943. Two courses of electroshocks—last one in 1954. Now on Nardil. Referred by psychiatrist as a "hopeless case."

P.E.: Wt. 150, Ht. 64", blood pressure 134/70. Crowded lower incisors, long right index finger. Some pigmented moles. Positive Rogoff. Some pitting edema of ankles. Strongly exaggerated reflexes. marked Kraurosis vulvae.

G.T.T.: 4/28/60: F-81, ½-143, 1½-67, 2 -67, 3½-70, 4½-84.

Diagnosis: Hypoadrenocorticism, post-menopausal syndrome, autonomic nervous system instability, allergic diathesis.

RX: Diet, A.C.E., Menagen, Bellergal, Theelin, Benadryl, B6, B12. Reduce Nardil. Librium later prescribed.

Course: Steady progress with fewer more shallow periods of depression at greater intervals until at the present she leads a very full life with much activity in the arts, education and travel. Endures severe stress extremely well. She has recently been awarded a high public honor.

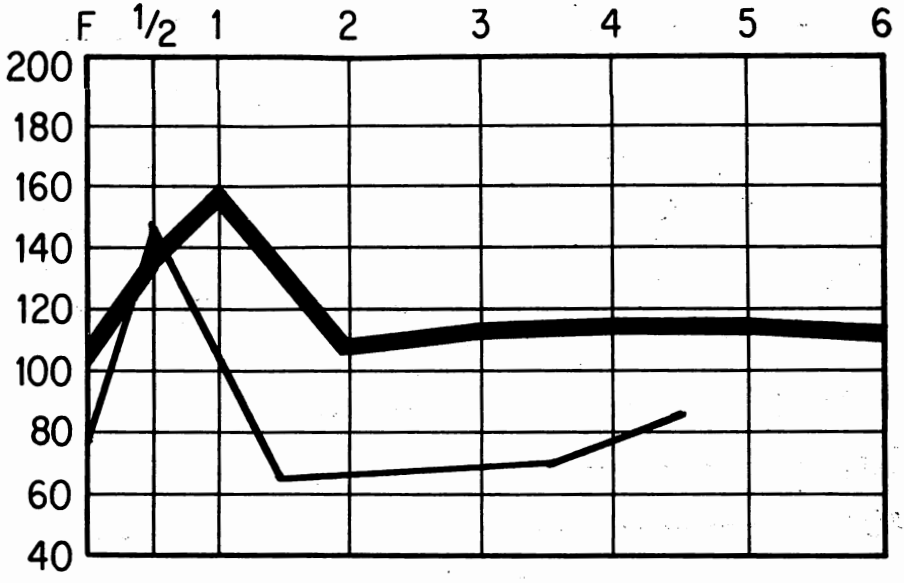

FIG. 14. *Glucose tolerance curves for Case 13.*

Case 14

Patient: V. C. First seen 4/10/65; Age 17; White female.
Tired and depressed. Frequent headaches, no interest in anything. Gets dizzy dressing, has to sit on bed. Cries for no reason. Can't concentrate. Panicked at college boards. Feels something terrible is going to happen to her. Hay fever history, also enuresis.

P.E.: Wt. 126, Ht. 64", blood pressure 118/74. Marked vasomotor rhinitis, some crowding of lower incisors, some hair upper lip, long index fingers, 4th interspace tenderness, positive Rogoff, overactive reflexes. P.B.I.—6.2 mcg% (taking 1 gr. thyroid daily).

G.T.T.: F-87, ½-115, 1-96, 2-115, 3-95, 4-78, 5-95.

Diagnosis: Moderate hypoadrenocorticism. Slight estrogen deficiency.

RX: Diet, A.C.E., Progesterone, Theelin, B6, B12, Norpramin, DOCA, Proloid, Librium.

Course: Stormy slow progress with candy binges and spells of depression, withdrawal, and banging head on the floor. Attitude at times has approached catatonia. Has been able to work as a salesgirl and is better able to manage her depressions. Wants to go to college and has been admitted.

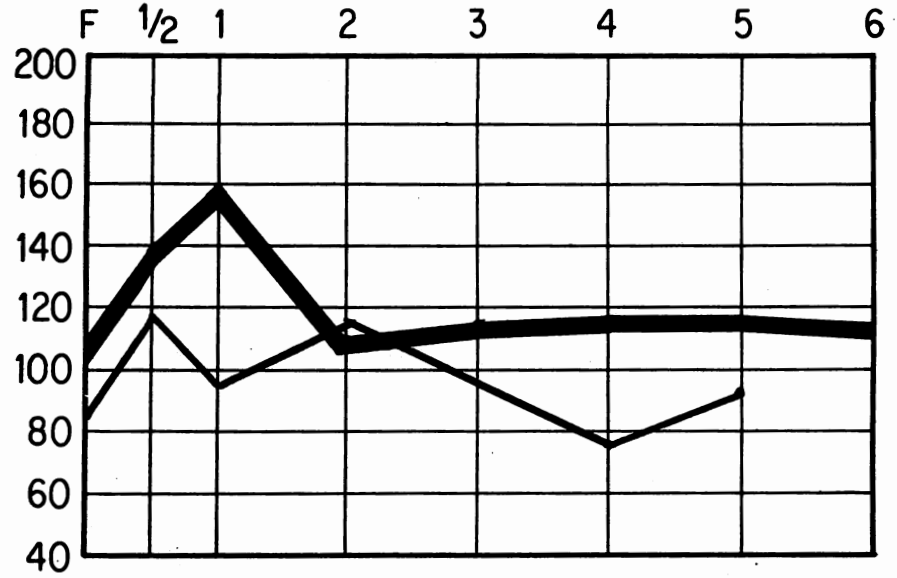

FIG. 15. *Glucose tolerance curves for Case 14.*

Case 15

Patient: H. W. First seen 1/19/66; Age 43; White female.
Asthma, hay fever, "skin condition", rhinitis, started 22 years ago, Called "shrimp" as a boy. Sense of nervous compulsion. Colchesine etc. for got one year ago. Lost sense of taste several years ago. Craves sweets. Haunted by continuous sense of anxiety.

P.E.: Wt. 137, Ht. 68", blood pressure 110/84. P.B.I.—8.7 mcg%. T_3 1.09. Long index fingers, gouty deformation of the hands. crowded lower incisors, skin lesions back. scalp and left sternum, engorged thyroid, pigmented nevae, Rogoff sign mod. pos., exaggerated reflexes.

G.T.T.: 1/8/66: F-84, ½-98, 1½-56, 2 -46, 3 -50, 4 -53, 5 -70.
PM Test: 11/4/66: F-73, ½-165, 1½-96, 2½-75, 3½-44, 4½-48, 5½-56.

Diagnosis: Marked adrenal insufficiency, autonomic nervous system instability, severe seborrheic dermatitis of scalp and torso, gouty arthritis.

RX: Diet, A.C.E., Bellergal Spacetabs, Bellergal, B6, B12, Vitamin C, Testosterone, DOCA.

Course: Marked improvement in mental outlook, upsurge in ambition and energy output. Got very much improved. Rare headaches. Sense of smell returned. Asthma disappeared. Gave up smoking without noticing

it. Seborrhea cleared completely and only pigmented areas remain on chest wall and lumbar area.

The aspect of the patient's present gratifying sense of general well-being is most important to him is at the same time the most interesting to the physician. For twenty years the patient has been operating successfully, writing books, mastering difficult engineering techniques and carrying a heavy teaching load. Now to his amazement the realization comes that throughout his adult life he had been driving himself mercilessly in the face of terrifying anxieties and discomfort. His present life is such a new and different experience that he doesn't see how he ever survived.

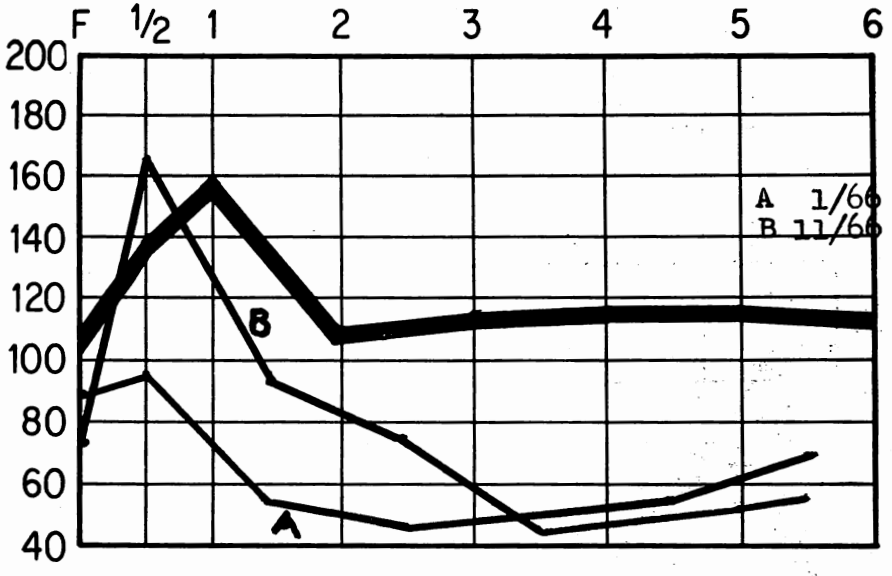

FIG. 16. *Glucose tolerance curves for Case 15.*

Case 16

Patient: L. E. First seen 12/9/64; Age 44; White female.

Referred—already under treatment for hypoglycemia. Shaking and nauseated. Wakes at 3 AM with pain and severe palpitation. Two courses of electroshocks in July, 1964. First one helped, second one made her feel worse—couldn't stand them. Thorazine makes her scream, kick and pound. At various times has been dizzy, weak,

nauseated. She has had shaking of the arms and legs, quivering inside. Crying, worried, depressed. Felt like screaming or dying. Masturbated as often as 30 times in one day. Treated in 1964 for hyperglycemia with orinase. Normal blood curve returned. Now "cries all the time, can't stand people or radio." Can't drive a car now—used to relax her. Can't take Bellergal. Inactive pulmonary turerculosis.

G.T.T.: 1962: F-115, ½-189, 1-147, 2-147, 3-94, 4-42, 5-74.
11/21/66: F-92, ½-168, 1-144, 2-112, 3-76, 4-84, 5-84, 6-92.
Aug. 1964: F-81, ½-158, 1-153, 2-129, 3-119.

P.E.: Wt. 136, Ht. 66", blood pressure 128/82 T-3 1.06.
Crowded lower incisors, long index fingers, 4th interspace tenderness, positive Rogoff sign. Progesterone obesity.

Diagnosis: Marked hypoadrenocorticism, hypo-ovarianism (estrogen and progesterone deficiency), marked vagal involvement (damaged by TBC chest surgery).

RX: Diet, A.C.E., Theelin, Durabolin, B6, B12, Belladonna, Quinidine, Menagen, Norlutin, Quinaglute, Norpramin, Valium, Calcium, Benadryl, Ascorbic acid.

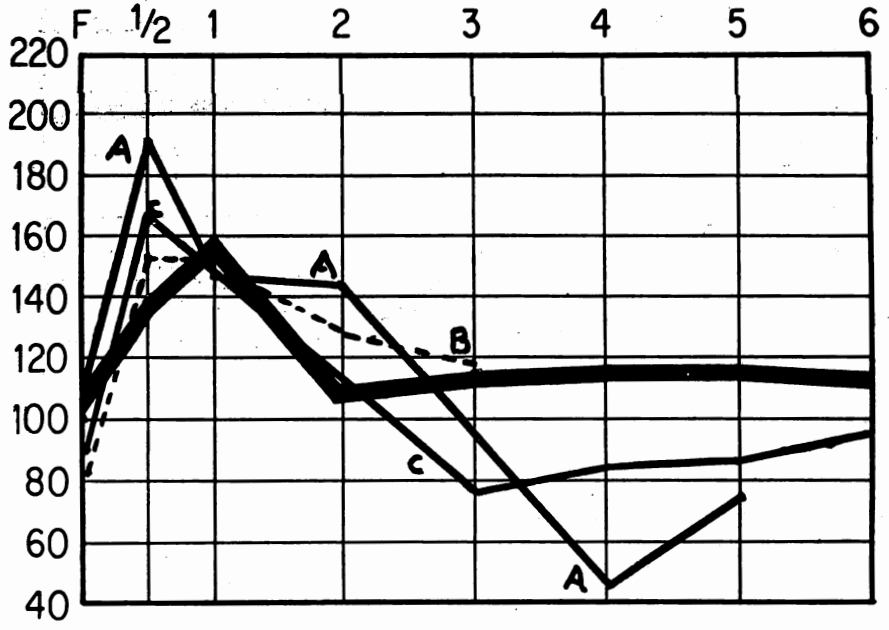

FIG. 17. *Glucose tolerance curves for Case 16.*

Course: Signs and symptoms dropped away one by one. Shaking and quivering ceased. Mood improved and crying stopped. Masturbation ceased. Took up automobile driving again. Fondness for music returned. Took part in an amateur entertainment and was offered some professional contracts. This after being certified for long-term complete disability.

Discussion.

More than twenty years ago Selye (1946), Long (1940) and Britton (1932) reported animal experimentation with A.C.E. that convinced the writer that the hypoglycemia which follows glucose intake is caused primarily by failure of the adrenocorticosteroids to inhibit insulin activity and influence the rate of insulin catabolism (Ingle, 1944). This hypothesis has been corroborated recently by experiments which indicate that insulin-induced hypoglycemia stimulates the production of glucosteroids by the adrenal cortex (Plager & Matsui, 1966). The insulin level reached is not high enough to justify the use of the term hyperinsulinism. It was concluded that the activation of the hypothalamic-pituitary-adrenal system is not so much a function of the fall in blood glucose below an absolute level as it is of the rate of glucose fall. This reaction is modified by the initial level of blood glucose. The G.T.T. is therefore a delicate indicator of the ability of the C.N.S. and especially of the hypothalamus to activate neural and humoral pathways to the pituitary. In pituitary failure there is no response to insulin administration even though the rate of blood glucose fall could be sufficient to produce adrenal response in cases with intact pituitaries.

Within the past year, Plager and Matsui (1966) have demonstrated *in vitro* what has been postulated *in vivo* that there is a graded antagonism between various dose levels of cortisol and insulin. Unfortunately, current animal experimentation does not deal with the whole extract since cortisol is generally presumed to be the principal ingredient in such a preparation and therefore there is a dearth of recent laboratory data on the obvious synergistic-plus-antagonistic activity of the whole extract. However, this writer has reported repeatedly and at some length on the highly beneficial results obtained in 25 years of clinical use of A.C.E. (Tintera & Lovell, 1949; Tintera, 1955; Tintera, 1966).

As we know, the human organism operates for the most part on glucose which must be supplied by the blood at the appropriate concentration. It is understood that the adrenal cortex, through the operation of the glucocorticoids plays a major role in regulating this concentration but

there are many intricate systems involved in carbohydrate metabolism; particularly enzyme systems of the "Kreb's cycle". These operate in all tissues at the cellular level, especially in the muscles and the liver. The enzymes of the liver necessary for glycogenolysis and gluconeogenesis have been identified. Alcohol dehydrogenase and other enzymes implicated in psychopathological conditions have been less thoroughly investigated although they play a role in alcoholism and drug addiction.

The other organs participating in carbohydrate metabolism have received too little attention. For instance, the prostate is responsible for the metabolism of fructose. Chronic benign prostatic hyperplasia is a frequent concommitant of schizophrenia and is not necessarily an erotic manifestation. Roberts (1966) has pointed out that the intactness of the testis, the pituitary and the adrenal is necessary for accelerated prostatic growth. Prostatic hyperplasia can be exaggerated by the increased elaboration of growth hormone, adrenocortical steroids and pituitary prolactin or interstitial-cell stimulating hormone under the repeated stimulus of recurrent hypoglycemia. Androgens exert a diabetogenic effect as do these counter-insulin responses. The high zinc, fructose and enzyme content of the prostate favors the production of insulin and thus may induce hypoglycemia.

The kidney contributes perhaps 15-20% of the inflow of glucose as calculated from arteriovenous differences and renal blood flow (Cahill, 1964). This will be discussed below:

Treatment

The importance of diet in the treatment of hypoglycemia (Physician's Guidlines, 1966) cannot be overemphasized. There must be strict elimination of all rapidly absorbable carbohydrates. This forestalls the sudden rise and subsequent fall in blood sugar levels. The heightened protein intake is beneficial in its own right since the individual amino acids evoke rises in circulating glucose (Fagans, Unp. Lecture).

Vitamin intake should be monitored to facilitate proper liver (B6) and adrenal function (BI, 3, 6, 12 & C). Ascorbic acid is particularly important since adrenal requirements for this vitamin are greatly increased by stress.

In most instances if tranquilizing agents have been prescribed they may be reduced in dosage when agents influencing the autonomic or vegetative nervous system are prescribed. The A.N.S. undoubtedly plays a major part in converting emotional stimuli into symptoms. In order to minimize the role of emotions in the production of functional symptoms in patients with adrenal insufficiency, it has been found advisable to prescribe a combination (Bellergal) of l-hyoscyamine,

ergotamine tartrate and phenobarbital. Large doses of this preparation are not required because of a synergistic action with adrenal cortical extract. Patients are generally started on three tablets a day, one on arising, one at about two o'clock in the afternoon before the expected fall in blood sugar, and then one between dinner and retiring. Portis has demonstrated that paralysis of the right vagus nerve with large doses of atropine will prevent the inevitable afternoon fall in blood sugar (Portis, 1950; Portis & Zitman, 1943). After approximately one to two months the Bellergal may be reduced to two tablets daily. This dosage has been continued for as long as six years. This autonomic system-oriented preparation helps reduce the intensity of emotional stimuli, thus acting to prevent the development of functional disturbances. In my estimation this is one of the most valuable drugs available to the physician.

In mild cases at least 10 cc of A.C.E. are given intravenously (or if impractical, intramuscularly) at least once a week for one to two months. In severe, acute cases 10 cc injections may be required as often as every four hours for the first 24 hours; then q. 8 hr. until it seems clinically possible to give daily injections which may be continued for 1-2 weeks. After that, weekly injections may be given indefintely until the interval between treatments may be progressively increased to two weeks, three weeks, etc. Pyridoxine, 1.0 cc (50 mg.) is added to the solution of A.C.E. at least once a week because of the role of this vitamin in the enzyme systems involved in regulating carbohydrate metabolism. Also for its synergistic and antihistaminic sedative effect, the optional addition of 1 to 5 cc of Benadryl hydrochloride solution to the intravenous infusion is sometimes desirable.

The use of A.C.E., especially if given intravenously, produces a temporary feedback inhibiting the pituitary from whiplashing an already exhausted adrenal and gives a refractory period of about four hours to the cells in the zona fasciculata and zona reticularis. At the same time, the level of circulating glucosteroids is elevated so that restorative processes can take place in the liver. With stabilization of the blood sugar, the over-stimulated pancreas is also given a period of respite. However, if cortisone or one of its derivatives is given in place of A.C.E., this steroid would have to be given in divided doses of at least 100 mg. or its equivalent, which would completely inhibit the pituitary and thus the secretion of glucosteroids by the cells of the zona fasciculata and if given over an extended period, atrophy of these cells would occur and further adrenal insufficiency would result. In fact, continued use of individual glucosteroids will invariably increase the level of blood glucose so that diabetic levels develop.

ACTH is also contraindicated in these patients since it would tend to whip the already exhausted adrenal cortex, producing hypertrophy and possibly hyperplasia of the cells of the zona fasciculata, but with little beneficial effect upon the mineralosteroid-producing cells in the zona glomerulosa save for further slight water retention.

For males—Testosterone proprionate 50 mg. I.M. once a week initially and methyl testosterone (Oreton) 10 mg. b.i.d.—p.c. daily buccal administration—

no more than 2 Gm. over a 3 month period. To help restore nitrogen balance and further reduce demands on the adrenals—Adroyd or Maxibolen may be used. When intervals have been increased to one month, 1 cc Decadurabolin may suffice to maintain a positive nitrogen balance.

For females—after negative Pap smear and culpocytology—Theelin or conjugated 5 mg. (50,000 i.u.) weekly injections, and natural estrogens (Menagen or Premarin) orally daily (during child-bearing years from the 3rd through the 26th day of the menstrual cycle). If there is a history of fibroids or dysmenorrhea, progesterone may be beneficial in addition to the estrogen (from the 12th through the 26th day of the menstrual cycle).

Some comment is indicated on the various medicaments mentioned in the foregoing resumes. There seems to be some misunderstanding as to the use of the whole natural adrenal cortical extract (A.C.E.). It is uniquely valuable and safe (Mod. Drug Encyl., 1965). In addition, it is effective for long term use and in many cases should replace the corticosteroids. To our personal knowledge more than 50,000 individual doses (10 cc or more) have been administered over 20 years with no report of undesired side effects and with consistent reports of beneficial results, often dramatic. In extreme cases or in conjunction with surgery, dosage may range as high as 200 cc so long as salt intake is maintained. Lipo Adrenal Cortex is also a vailable for intramuscular use. One cc of this preparation is equal to 10 cc of the aqueous extract.

Bellergal has been dealt with elsewhere at some length. Other drugs are of special interest mainly because of possible unwanted or toxic side effects. Large doses of chlorpromazine for instance over a long period will substantially reduce the secretion of ACTH (Bass, 1965) Hepatic toxicity (jaundice) (Fajans Unpl. Lecture) has been reported from isocarboxazid (Marplan), phenelzine sulfate (Nardil), imapramine hydrochloride (Tofranil), and desipramine hydrochloride (Norpramin, Pertofrane). Many reports have dealt with hypertensive reactions resulting from the ingestion of cheese while taking any of the monoamine oxidase inhibitors: Marplan, Nardil, nialamide (Niamid), tranylcypromide (Parnate). The antidepressants should not be prescribed for patients with epilepsy or impaired kidney function.

The minor tranquilizers, chlordiazepoxide (Librium), chlormezanone (Trancopal), diazepam (Valium), and meprobmate (Miltown-Equanil, etc.), can cause less severe but definite adverse hepatic and renal effects.

Since hypoadrenocorticism is characterized by hyponatremia and hypo-kalemia, these side-effects must be kept in mind. Hyponatremia, a factor in the "Inappropriate Antidiuretic Hormone Syndrome," causes headache, disorientation, somnolence and other cerebral symptoms. Severe headaches often accompany the alkalosis associated with hypokalemia. Pending electrolite adjustment these can be relieved by glutamic acid-hydrochloride in doses large enough to acidify the urine. As we have seen, the kidney in man contributes perhaps 15-20% of the inflow of glucose. Any agent which would depress renal glucogenesis could theo-

retically result in symptomatic hypoglycemia within an hour (Roberts, 1966). It is well therefore when prescribing any of these drugs to be alert to possible toxicity for the liver, kidney and cerebrum.

When the hypoglycemia of hypoadrenocorticism associated with schizophrenia has been recognized, the administration of A.C.E. and the institution of appropriate diet and supportive medication will fill only the immediate needs of the patient. At this point the talents of the psychiatrist are vital. His approach may be altered somewhat but the guidance of the physician-psychiatrist is of prime importance in the restoration and maintenance of the desired homeostatic state, the reflection of the nutritional, hormonal and nervous function of the body. The psychiatrist must lead these physiologically inadequate and often emotionally immature individuals to full maturation by regulating their activities and guiding them in their adjustment to society and in the acceptance of their limitations and in the avoidance of stressful situations.

Summary

The individual with constitutionally inadequate carbohydrate metabolism has been described as the potential and genetic candidate for schizophrenia.

Recognition is most easily made through correlation of symptoms and readings during a five-hour glucose tolerance test, and the interpretation of the curve (Tintera, 1966).

Although many mentally or emotionally disturbed individuals seem to make adjustment through diet alone, the underlying hypoadrenocorticism must be treated. The regime of choice includes A.C.E., ancillary hormonal therapy, supportive medication, and personal counseling.

References

Bass, Allan D. *Drugs Affecting adrenocortical function.* Postgraduate Medicine, 1965, 37, 82.

Blaine, T. R. *Goodbye allergies.* New York; Citadel Press, 1965.

Britton, S. W. & Silvette, H. *The effects of cortico-adrenal extract on carbohydrate metabolism in normal animals.* American Journal of Physiology, 1932, 100, 693-700.

Bunney, W. E., Jr., Mason, J. W., Roatch, J. F., & Hamburg, D. A. *A psychoenhavioral variables and urinary 17-Hydroxy-corticosteroids in depressed patients.* Psychosomatic Medicine, 1965, 27, 299-308.

Bunney, W. E., Jr., Mason, J. W., & Hamburg, D. A. *Correlations between bedocrine study of severe psychotic depressive crises.* American Journal of Psychiatry, 1965, 122, 72-80.

Cahill, G. F. *Advances in enzyme regulations.* Vol. 2. New York; Macmillian Company, 1964.

Connason, B. F., & Ryberg, R. A. *Stress conditioning in schizophrenia and neurotic disorders.* Diseases of the Nervous System, 1957, 18, 7.

Curtis, G. C., Cleghorn, R. A., & Sourkes, T. L. *The relationship between affect and the excretion of adrenialine, noradrenaline and 17-hydroxycorticosteroids.* Journal of Psychosomatic Research, 1960, 4, 176-184.

Fajans, S. S. *Unpublished Lecture.*

Freud, S. *A General introduction to psychonanalysis* (translated by Joan Riviere) Garden City, New York; Garden City Publishing Co. 1943.

Graham, B. F., & R. A. Cleghorn, R. A. *Changes in the circulating leukocytes following electrically induced convulsions in man.* Journal of Clinical Endocrinology, 1951, 11, 1469.

Harvard Encyclopedia, 1891 Volume 23.

Hoffer, A., Osmond, H., Callbeck, M. J., & Kahan, I. *Treatment of schizophrenia with nicotinic acid and nicotinamide.* Journal of Clinical and Experimental Psychopathology, 1957, 18, 131-158.

Ingle, D. J. *The chemistry and physiology of hormones.* Washington, D. C.; American Association for the Advancement of Science, Smithsonian Institution, 1944.

Kaplan, M. *Informal Communication.*

Larsen, Virginia L. *Physical characteristics of disturbed adolescents.* Archieves of General Psychiatry, 1964, 10, 55-64.

Long, C. N. H., Katzin, B. & Fry, E. G. *The adrenal cortex and carbohydrate metabolism.* Endocrinology, 1950, 26, 309.

Meyer, A. *Commonsense psychiatry.* New York: McGraw Hill, 1948.

Modern drug encyclopedia and therapeutic index, 1965.

New Drugs. Chicago, Illinois: *American Medical Association,* 1966.

Persky, H., Maroc, J., Conrad, E. & Den Breeijen, A. *Blood corticotropin and adrenal weight-maintenance factor levels of anxious patients and normal subjects.* Psychosomatic Medicine, 1959, 21, 379-386.

Plager, J. E. & Matsui, N. *In vitro demonstration of the anti-insulin action of cortisol on glucose metabolism.* Endocrinology, 1966, 78, 1154.

Portis, S. A. *Life situation, emotions and hyperinsulinism.* Journal of the American Medical Association, 1950, 142, 1281.

Portis, S. A. & Zitman, I. H. *Mechanism of fatigue in neuropsychiatric patients.* Journal of the American Medical Association, 1943, 121, 569.

Physician's guidelines to diagnosis and treatment of hypoglycemia or the hypoadrenocortical state. The Hypoglycemia Foundation, Scarsdale, New York, 1966.

Roberts, H. J. *The roles of diabetogenic hyperinsulinism in pathogenesis of prostatic hyperplasia and malignancy.* Journal of the American Geriatrics Society, 1966, 14, 795.

Selye, H. *The general adaptation syndrome and the diseases of adaptation.* Journal of Clinical Endocrinology, 1946, 6, 117.

Simon, G. B., & Gillies, S. M. *Some physical characteristics of a group of psychotic children.* British Journal of Psychiatry, 1964, 110, 104-107.

Simpson, G. M. *Drug therapy in mental illnesss* Effective participation by general practitioners. Postgraduate Medicine, 1966, 39, 557.

Suwa, N., Yamashita, I., Owada, H., Shinohara, S., & Nakazawa, K. *Psychic state and adrenocortical function*: A psychophysiologic study of emotion. Journal of Nervous Mental Diseases, 1962, 134, 268-276.

Tintera, J. W. *The hypoadrenocortical state and its management.* New York State Journal of Medicine, 1955, 55, 1869.

Tintera, J. W. *Stabilizing homeostasis in the recovered alcoholic through endocrine therapy*: Evaluation of the hypoglycemia factor. Journal of the American Geriatrics Society, 1966, 14, 126.

Tintera, J. W., & Lovell, H. W. *Endocrine treatment of alcoholism.* Geriatrics, 1949, 4, 274.

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STABILIZING HOMEOSTASIS IN THE RECOVERED ALCOHOLIC THROUGH ENDOCRINE THERAPY: EVALUATION OF THE HYPOGLYCEMIA FACTOR

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The recovered alcoholic, regardless of the number of years of sobriety, nonetheless still presents a complex symptomatology of hypo- and hyperactivity of the various endocrine organs of the body. We have delineated in several previous communications (1–4) this symptom complex, which revolves around hypoadrenocorticism. This concept had led to the conclusion that alcoholism is a manifestation of an adrenocortical insufficiency; it is not a disease per se, but an aggravation of this endocrine insufficiency engendered by the injudicious use of alcohol. In February 1952 the World Health Organization concluded that the basic cause of alcoholism is congenital, due to a "slight deficiency of carbohydrate metabolism, of the enzyme system or of certain endocrine relations."

An understanding of just what our present concept of hypoadrenocorticism, or relative adrenal insufficiency, entails at the current level of our knowledge of adrenal function requires a brief explanation. We have come a long way from the sterile thinking that the adrenal cortex functions "all-or-none." The multifaceted activity of the cortex can hardly be comprehended when one considers the symbiotic and antagonistic activities of the 32 hormones produced by these little power-houses. Our contentions and bases for treatment depend upon these interrelations of the many steroids thus elaborated, inhibited, or augmented.

GENETIC INFLUENCES

First, however, mention should be made of the genetic influences in alcoholism (5). Conceivably, any person through prolonged use and abuse of alcohol may eventually succumb to its use in an addictive manner. But, for many years we have maintained that in predisposed individuals there is adrenocortical deficiency (possibly an inborn error of metabolism) which should be considered as much of a genetic factor as is the well-established diabetic factor. Persons manifesting this genetic influence, as others also have pointed out, characteristically show a decreased metabolism, marked hypotension and orthostatic changes in blood pressure, a characteristic hair distribution, and a fondness or even a real craving for salt and carbohydrates.

In children whose parents have shown this deficiency, we often find similar traits plus lack of concentration, even though the child has a high intelligence quotient. These children have a marked craving for sweets, but when they are given a low-carbohydrate diet alone they show marked changes in personality.

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Their schoolteachers' reports disclose a complete reversal of inattentiveness, uncooperativeness, and poor scholastic standing.

In the case histories of alcoholics, many of these patients refer to their progressive carbohydrate or candy binges in childhood or early adulthood, which incidentally induced greater adrenal involvement. To substantiate this contention further, McCandless and Dye (6) demonstrated that a particular intestinal flora develops in animals with a pituitary-adrenal insufficiency when fed a high-carbohydrate diet, with the liberation of acetaldehyde, acetylcholine and acetic acid rather than glycogen. A progressive adrenal deficiency is observed even before maturity.

Our alcoholic patients have furthermore stated that these binges lifted them from periods of depression to temporary periods of well-being. Very soon, however, these same persons discovered that emotional depression could be alleviated more effectively by the consumption of alcohol. But this respite from depression and craving was of short duration, so that continued drinking seemed to be the only answer. In a previous communication, Lovell and Tintera (2) demonstrated that this craving is a physiologic attempt to increase the subject's blood sugar. The clinical signs of hypoglycemia often appear to be more severe than the blood sugar values warrant, but as Thorn (7) has demonstrated, even minor drops in the blood sugar level will cause marked symptoms of hypoglycemia even with the so-called low flat glucose tolerance curve. At this point the craving for carbohydrates or alcohol may become intense.

It is so often found that the offspring of alcoholic parents either become alcoholics themselves or teetotalers because they realize their inability to handle or tolerate alcohol. These persons are the ones who retain their leanness and asthenia throughout life since they are not able to metabolize carbohydrates properly. Like their teetotaler forebears, they may expect longevity much beyond the average with the assurance that senility due to arteriosclerotic changes will not usually ensue. Their predecessors with this hypoadrenocorticism often reached 80, 90 or even 100 years of age, and still maintained their mental acuity.

CLASSIFICATION OF ADRENAL STEROIDS

The original statement that an inherited or induced adrenocortical deficiency plus alcohol ingestion are primary factors in the production of the alcoholic state, cannot be denied. The thirty-odd hormones of the adrenal cortex are conveniently divided into three groups, and symptomatology and treatment definitely are based on their relative activity or inactivity. Current research has indicated involvement of one or another of these groups.

Group I. Glucosteroids

Briefly, recent observations have been centered upon the marked hypoglycemic reactions following ingestion of alcohol, implicating the glucosteroids.

Adrenal, and specifically the pituitary-adrenal axis, function is necessary to counteract insulin-induced hypoglycemia. The adrenal cortex secretes the 11-

oxygenated glucosteroids which are essential in opposing the action of insulin. Thus the adrenal steroids attempt to maintain a state of homeostasis by antagonizing the hypoglycemic activity of insulin. Early in alcoholism the release of glycogen from the liver by alcohol stimulates a sensitized pancreas to produce insulin, but the hypoadrenocortical state allows a fall to hypoglycemic levels since the normal glucosteroid response has been diminished. Therefore in hypoadrenocorticism there is a period of reactive hypoglycemia attributed to reflex production of insulin in the absence of counteracting glucocorticoids (8).

Adrenocortical hormone insufficiency is characterized by a depletion of the carbohydrates of the blood and tissues. The specific changes in carbohydrate metabolism in relationship to the factors involved in these changes are as follows:

Intake of food or alcohol
Rate of absorption from the gut
Rate of deposition in the tissues
Rate of glycogenolysis
Gluconeogenesis from protein
Mobilization of endogenous protein
Deamination of amino acids
Conversion of deaminized acids to glucose
Rate of insulin catabolism
Inhibitory effect on insulin action
Direct inhibitory effect on peripheral utilization of carbohydrate, and
Direct effect on oxidation of fat and protein.

Long et al. (9) demonstrated that adrenocortical hormones increase body carbohydrate stores. The rises in liver glycogen and blood sugar were attributed to gluconeogenesis. Glucosteroids also inhibit the utilization of carbohydrates, and this may be more important than gluconeogenesis in elevating carbohydrate levels. Eisenstein et al. (10) recently demonstrated the *in vitro* effects of certain adrenal steroids and synthetic analogs on hepatic gluconeogenesis. They showed that both triamcinolone and cortisol stimulated hepatic carbohydrate formation in 10^{-7} M concentration; however, the rise induced by triamcinolone was significantly less than that due to cortisol or hydrocortisone. Dexamethasone caused a greater increase in carbohydrate synthesis than did triamcinolone but, in a slightly decreased concentration, failed to cause a significant alteration in gluconeogenesis. It was also found that the amount of hormone which will enhance carbohydrate synthesis *in vitro* is about the same as plasma corticoid concentration in man.

In alcoholism, as in any stress situation which alters or interferes with the normal concentration of any of the cortical steroids, definite changes in the levels of hepatic and blood sugar are to be expected. The degree of involvement will depend upon which, and to what extent, each of these hormones is involved.

Group II. Mineralosteroids

Following the withdrawal of alcohol, a definite state of hyperaldosteronism exists, with its resultant hypertension, electrolyte imbalance and edema. Aldosterone secretion is increased when blood sodium is low, blood potassium is high or the patient is dehydrated. On the other hand, aldosterone secretion is diminished when blood sodium is high, potassium is low, or the patient is well hydrated or edematous. Evidence of hypokalemia is often noted in the form of negative T-waves in the electrocardiogram; these waves generally return to normal within a few days after beginning treatment with adrenocortical extract. The patient with hyperaldosteronism also continues to secrete large amounts of potassium despite the hypokalemia. Edema is rare in primary hyperaldosteronism but is much more common in hyperaldosteronism associated with alcoholism, hepatic cirrhosis or the nephrotic syndrome. A prompt rise and return to normal of the serum potassium level occurs upon administration of spironolactone (Aldactone-A) in doses of 25 mg three or four times daily for about three or four days. Alkalosis also is corrected and an acid urine is excreted.

Possibly a substance called adrenoglomerulotropin from the pineal gland normally stimulates the adrenal to produce aldosterone, but in cases of increased stress further aldosterone secretion may be stimulated by ACTH.

Group III. Ketosteroids

It has long been recognized that protracted drinking in the male results in hypogonadism. This is a result of fatty infiltration of the liver with consequent failure of detoxification of the estrogens by the hepatic cells, leading to "neutralization" of the androgens. Thus gynecomastia develops along with atrophy of the male gonads.

BASIS FOR HORMONAL THERAPY IN ALCOHOLISM

In our experience, by far the greatest percentage of women who become alcoholic are housewives at the menopausal age. During the childbearing years the ovaries produce about 85 per cent of the circulating estrogens and the adrenal cortex produces the remaining 15 per cent. With the waning of ovarian function the adrenals are called upon to produce more and more estrogens. If there is a pre-existent hypoadrenocorticism, the adrenals are unable to withstand this excessive onslaught and a severe adrenal insufficiency results with its concomitant hypoglycemia. Moderate social drinking then often becomes a suddenly compulsive alcoholic pattern. There is increasing evidence that both estrogens and progestins should be maintained cyclically by oral medication from the time of the menopause onward (11). No woman manifesting even moderate menopausal symptoms should be denied oral or parenteral estrogen therapy. We strongly recommend that treatment with estrogens be started immediately in every woman subjected to hysterectomy, regardless of whether or not an oophorectomy was performed. The uterus itself appears to be neces-

sary for the normal metabolism of estrogens; the endogenous steroids seem to be inadequate. McGavack (12) stated that when estrogen deficiency occurs normally at the menopause, it involves the loss of one of the stimulants to the production of corticoids by the adrenal. The climacteric represents an imbalance which normally takes place without manifestations, except the cessation of menses. One of these imbalances is the maintenance of overstimulation of corticoid production by the pituitary or some other source. Estrogens are corticomimetic in that they cause a retention of sodium and chloride in normal and adrenalectomized animals (13) and exert a glycogenic effect in intact animals (14). Plasma corticosterone responses to ACTH or stress are enhanced in rats (both male and female) given estradiol as well as cortisone. These data are explained by the stimulatory effects of estradiol on both pituitary and adrenal function (15).

The ultimate objective in endocrinology is the achievement of a state of homeostasis. Effective as the new tranquilizers may be, the results are merely the temporary alleviation of emotional or mental symptoms. Indeed, even if alcoholism is considered as a psychopathologic condition, treatment should be aimed primarily at the functional disorder with the subsequent relief of psychic manifestations. However, in order to attain this goal there is no objection to the immediate relief of the disturbing presenting symptoms through the use of some of the modern drugs such as chlordiazepoxide (Librium), diazepam (Valium) or chlorpromazine (Thorazine), but only as adjuncts to the therapy which will eventually restore the normal physiologic state.

With the recognition of the validity of our original thesis that an endocrine imbalance exists in alcoholism, various interpretations and modifications of treatment were instituted through the use of individual steroids or other hormones. Some reports appeared which apparently contradicted our findings. Therefore an explanation of a hypothetical situation, with a description of the action of whole adrenal cortical extract (ACE), may be in order even though it may appear elementary.

Figure 1 represents the state of the adrenal cortex in most chronic alcoholics, i.e., a rather severe deficiency of glucosteroids, a moderate overproduction of aldosterone, and a mild decrease in the production of 17-ketosteroids.

Under basal conditions it may be assumed that the normal adrenal produces the equivalent of about 15 mg of cortisone-like activity in twenty-four hours. A 10-ml dose of adrenal cortical extract (ACE) contains 1 mg of cortisone-like activity. ACE, especially if given intravenously, will produce a temporary feedback action to inhibit the pituitary from whiplashing an already exhausted adrenal and cause a refractory period for the cells in the zona reticularis and zona fasciculata, lasting about four hours. At the same time the concentration of circulating glucosteroids is increased so that corrective processes are proceeding in the fatty infiltrated liver, and with the stabilization of the blood sugar level the overstimulated pancreas is also given a period of respite. However, if cortisone or one of its derivatives is given, a divided dose of 100 mg or its equivalent is usually deemed necessary. There is a resultant complete shut-

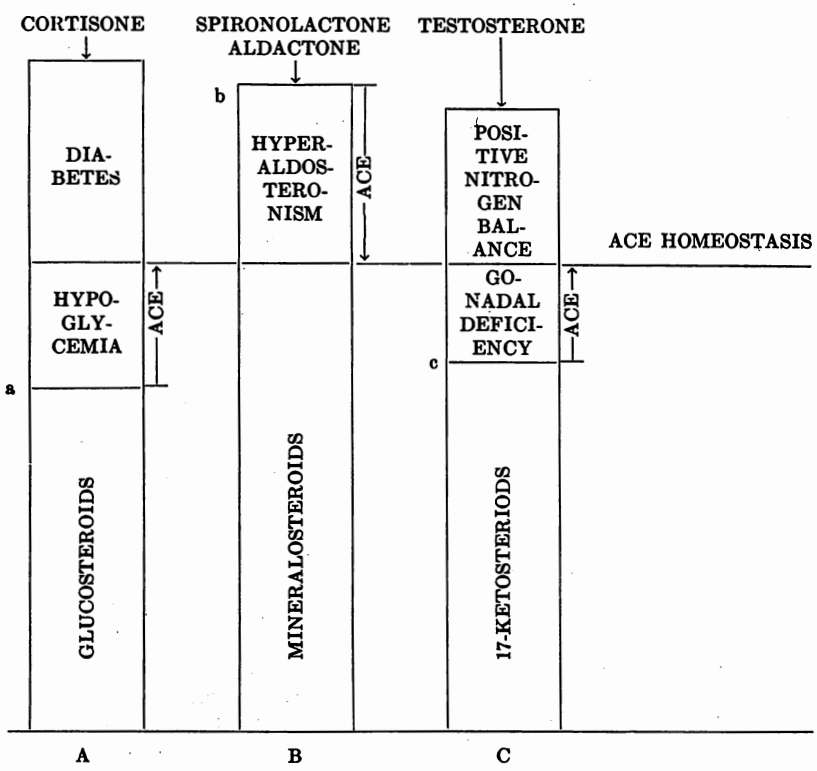

FIG. 1. Normal level of glucosteroids (A), mineralosteroids (B) and 17-ketosteroids (C) —Homeostasis. In chronic alcoholism, glucosteroid activity is reduced to (a) through pre-existing relative adrenal insufficiency, enzyme interference, unresponsiveness of the pituitary, and exhaustion of the zona fasciculata cells; mineralosteroid levels (b) rise above normal; and 17-ketosteroids (c) fall—Estrogenic "neutralization" and failure of the zona reticularis. Cortisone raises the concentration of glucosteroids from hypoglycemic to diabetic levels. Adrenal cortex extract (ACE) is usually sufficient to counteract hyperaldosterone levels, by its feedback mechanism in relation to the pineal gland and anterior pituitary, but spironolactone will counteract the aldosterone directly in the presence of cirrhosis. Supplemental testosterone, in the presence of gonadal deficiency, will raise the negative nitrogen balance to a positive one.

down of glucosteroid production from the cells of the zona fasciculata. If given over a protracted period, atrophy of these cells and further adrenal insufficiency results. Continued use will invariably increase the concentration of blood sugar but at a diabetic level.

Hormones are useful in treating the deficiency states resulting from the absence of, damage to, or functional failure of, the organ which secretes the hormone. Since the cortical hormones are capable of restoring normal vigor to the

patient in adrenal deficiency states, attempts have been made to engender a greater-than-normal response from undamaged glands. Homeostasis is achieved with the recommended doses of the hormones present in the extract, since the amount of these hormones are kept well within the physiologic range, but definitely unfavorable physiologic effects occur with the usual massive doses of individual steroids.

Pituitary ACTH will also whip the already exhausted adrenal cortex, causing hypertrophy and possibly hyperplasia of the cells of the zona fasciculata, but with little beneficial effect upon the mineralosteroid-producing cells in the zona glomerulosa save for further slight water retention. Consequently, little is accomplished and ACTH should be reserved for special situations such as relieving the symptoms of delirium tremens.

The observation has often been made that rarely do diabetics become alcoholic, but alcoholics do become diabetic. These are the patients who experience reactive hypoglycemia. The glucose tolerance curve is higher than normal and there is a delay in the fall of blood sugar concentration, hypoglycemic levels being reached three to four hours after the ingestion of glucose. Plasma insulin levels are higher than normal, but the peak is reached later than in the state called functional hypoglycemia. These patients may be considered prediabetic, since repeated episodes of hyperglycemia eventually result in destruction of the beta cells in the islands of Langerhans and finally the development of true diabetes unless there is proper dietary control.

Hyperaldosteronism, as a consequence of alcoholism, accounts for the marked hypertension and fluid retention often observed during continuous drinking or upon withdrawal of alcohol. The administration of spironolactone (Aldactone-A) usually causes diuresis and a reduction in blood pressure. The small amount of aldosterone contained in the "amorphous fraction" of ACE is sufficient to reduce secretion of this hormone to normal through moderate injections of ACE. This probably accounts for the welcome sedative effect experienced shortly after intravenous administration of ACE.

The concentration of circulating aldosterone is elevated in ascitic animals with liver disease (16), due to adrenal hyperfunction and also to the failure of the liver to inactivate the aldosterone. Moreover, Lalonde et al. (17) concluded from their observations that the inability of the liver to metabolize aldosterone contributes significantly to the development of ascites in patients with alcoholic cirrhosis.

EOSINOPHILIA

In 1944 Dougherty and White (18) reported the occurrence of lymphopenia in mice following administration of ACE or ACTH. These findings were confirmed in man four years later by Hills et al. (19), who also observed a pronounced fall in the eosinophil count. These changes in the blood have since been widely used as an index of adrenocortical activity.

An interesting case in which improper conclusions were drawn from laboratory testing is exemplified by the report of Oltman and Friedman (20). They

attempted to evaluate adrenocortical function in alcoholics by measuring the reduction in circulating blood eosinophils following subcutaneous injection of epinephrine, which stimulates the production of ACTH and adrenocortical hormones. All the patients were suffering from some acute complication of alcoholism. The first test was made twenty-four to forty-eight hours after admission to the State Hospital, and repeated after about fifteen days. The initial eosinophil count was below 100 per cu mm in 54.2 per cent of the patients; and below 200 per cu mm in 87.3 per cent. About 46 per cent showed a 50 per cent reduction in eosinophils in both tests. This, according to these authors, does not confirm the presence of deficient adrenocortical function in alcoholic patients. However, the initial total counts of eosinophils were lower than those found in normal controls. In the presence of adrenocortical insufficiency or stress secondary to chronic alcoholism, no other response could be expected if the patient were to survive.

Prior to this report, Gabrilove (21) showed that surgery or other trauma or stress caused a marked decrease of the circulating eosinophils; in the case of surgery, this persisted for two to four days or longer. The reduction was followed by a rise to levels above those present before surgery. Thus stress, ACTH, cortisone, epinephrine or insulin can cause eosinopenia. Morever, continuous stress as induced by chronic intake of alcohol, or continuous corticosteroid therapy, does not cause the adrenal glands to atrophy completely. The pituitary cells, however, cease to respond adequately to subnormal levels of circulating glucosteroids.

In the Interim Report, 1957, of the California Alcoholic Rehabilitation Commission the data available at that time reflected secondary changes in the activity of the adrenal gland, i.e., a significant decrease in the number of circulating eosinophils and a marked increase in the glucose and acetone content of the urine during the period immediately following the commitment of the alcoholic. In addition, eosinopenia appears to be more marked in patients who are still in the inebriated condition.

HYPOGLYCEMIA

Greenblatt (23) in his recent book entitled "Search the Scriptures," describes Esau (in the Old Testament, the first recorded case of hypoglycemia) as saying, "Behold, I am at the point to die," and selling his birthright for a high-protein lentil soup which he knew would relieve his symptoms.

"Even today, its diagnosis (hypoglycemia) is often missed because of the extreme variability of its manifestations. The occurrence of functional hypoglycemia, although frequent enough, is understood so poorly that the disorder has earned the soubriquet, *stepchild of medicine.*"

Functional hypoglycemia is marked by an increased output of, or more properly, increased sensitivity to, endogenously-produced insulin. This sensitivity is intensified by emotional turmoil and stress, by constant pressure, and by violent exercise. The hypoglycemic syndrome can stem from various endocrine disorders—pituitary gland failure, severe hypothyroidism, exhaustion of

the adrenal glands—but the most severe cases are caused by the rare insulin-producing tumors of the pancreas.

In 1924 Harris (24) drew attention to the presence of hypoglycemia in non-diabetic patients and prescribed a low-carbohydrate diet. He attributed this form of hypoglycemia with its symptoms of nervousness, weakness and hunger, to hyperinsulinism. He also noted that the blood pressure readings in all but two of his patients were low, and thought it possible that "hypoadrenalism" was associated with "hyperinsulinism." Recently, however, "hyperinsulinism" has been found to be a misnomer, since there is no evidence of any excessive secretion of insulin. Indeed, in a number of the patients studied, the blood insulin activity was entirely within normal limits. In the past few years many observers have referred to this condition as "relative hypoglycemia" (25).

In a discussion on hypoglycemia, the important thing to remember is that it is not true hyperinsulinism, except in the rare cases of pancreatic adenoma; rather, it is a failure of certain glucosteroids to antagonize or catabolize insulin. In a psychiatrically disturbed patient, when there is an apparently normal glucose tolerance curve, these steroids are being produced by the adrenal through an overstimulation via the pituitary to such an extent that a situation of relative *hyperadrenocorticism* exists, presenting an imbalance between the normally synergistic and antagonistic adrenal steroids. Thus, a severe asthmatic may be relieved of his physical complaints with the initiation of psychic manifestations; and conversely, as the mental or emotional signs and symptoms are alleviated, there is usually a return of his allergic disorder.

In 1942 Portis and Zitman (26), in a preliminary report, suggested that the mechanism of fatigue in neuropsychiatric patients was that of spontaneous hypoglycemia as a result of a vagal stimulation. Portis (27) later reported that the hypoglycemia of these anxious, depressed neuropsychiatric patients was successfully treated by a low-carbohydrate diet and administration of atropine sulfate which paralyzed the right vagus nerve. The low flat glucose tolerance curve returned to a near-normal slope after treatment, and there was improvement in the emotional state with a return of zest and enthusiasm, and increased efficiency.

Some of the symptoms described by these writers are similar to those we found originally in the hypoadrenocortical state (3). In addition, we observed low or low-normal 17-ketosteroid excretion, eosinophilia, relative lymphocytosis, and a normal PBI level. A definite constitutional type was described. It is this pre-existing genetic constitutional type that reacts abnormally to stress with increasingly severe symptoms referable to hypoglycemia.

In addition to this pre-existing hypoglycemia, alcohol itself can produce hypoglycemia, even in normal persons. Cummins (28) was one of the first to realize that alcohol was the cause of convulsions with hypoglycemia (in a 6-year-old male patient). Hypoglycemia in alcoholism is due to depletion of hepatic glycogen supplies. Increased levels of circulating insulin seem to have nothing to do with alcoholic hypoglycemia; rather, it is the result of depletion of the glycogen stores and impaired gluconeogenesis (29).

It is quite evident that this type of person, when he obtains relief of his symptoms by temporarily raising his blood sugar, will eventually become addicted to alcohol. This individual is the potential alcoholic. Through continued use of this intoxicant, alcohol dehydrogenase is diminished. Thus larger amounts of alcohol can be consumed, with an apparent increased tolerance. However, after further abuse of the endocrine system controlling the oxidation of this substance, the final state of exhaustion is reached. The patient either dies or recovers, and if he recovers, a permanent deficiency state results unless measures are taken to correct it. Permanent sobriety is not the sole answer. Steps must be taken to correct the abnormal metabolic processes.

NUTRITION

The first step is the prescribing of an adequate diet rich in vitamins, not so much to correct vitamin deficiencies as to supply adequate vitamins for normal adrenal and liver function. Ascorbic acid is essential for adrenocortical activity, since adrenal ascorbic acid is depleted during stress. By far the most important aspect of dietary measures for the prevention of hypoglycemic episodes is the restriction of readily available carbohydrates. Sufficient protein for anabolic restoration is also necessary. Since our original report in 1948 on the necessity of a moderately high-fat diet, many other reports have appeared. Mindrom and Schiff (30) in 1955 demonstrated that patients with a fatty liver can absorb and utilize large amounts of dietary fat. During the period of high-fat intake, these patients showed progressive clinical improvement along with disappearance of excess liver fat and a return to normal values for liver function test.

Disturbances of the mineral content of the body, frequently found in patients with liver disease, help to perpetuate hepatic damage (31). The hypertension, ascites and associated debility are largely due to hyperaldosteronism, which responds to a temporary regimen of spironolactone (Aldactone; 25 mg four times daily).

Every recovered alcoholic requires at least 10 ml of adrenal cortex extract (Eschatin—Parke, Davis & Co.) intravenously once a week for one to two months. Then the intervals may be gradually increased to two weeks, three weeks, and so forth. Particularly at the beginning of treatment, 1–2 ml of diphenhydramine (Benadryl) solution is usually added to the intravenous injection for its sedative effect.

In addition, 50 mg of pyridoxine (vitamin B_6) is also added to the ACE injection, at least on alternate visits. In a special study, pronounced B_6 deficiencies were found in every one of 18 patients with delirium tremens. This deficiency has been attributed to the increase in protein metabolism secondary to the delirium (32).

One of the most common symptoms of the recovered alcoholic is the persistence of epigastric distress years after complete abstinence. Many cases are diagnosed as duodenal ulcer or hypertrophic gastritis. Bercovitz (33) reviewed 1,500 cases with a diagnosis of duodenal ulcer and found a spastic condition of this portion of the gut which he referred to as the post-bulbar duo-

denal spasm syndrome. His patients responded to adrenal cortical extract and atropine or one of its derivatives. This method of treatment is also effective in relieving symptoms of pylorospasm and hypertrophic gastritis. In our original report (1) in 1947 we recommended the use of Bellergal tablets three to four times daily. These tablets contain ergotamine tartrate, belladonna derivatives and phenobarbital, and have the effect obtained by Bercovitz on the gastrointestinal system and by Portis on the blood sugar level.

Long before the adrenal cortex was implicated in the production of alcoholism, it was well known that chronic alcoholics exhibit decreased libido and low sperm counts, but not necessarily infertility. The full head of hair and lack of secondary sex hair on the body has been attributed to a preponderance of estrogens. Since the adrenals normally produce such an abundance of male hormones and their analogues, it would appear that the adrenocortical extract would be sufficient to restore this balance to normal. In practice it has been found advantageous to use androgens orally or parenterally, in addition to ACE. This induces a positive nitrogen balance; otherwise a negative nitrogen balance may persist even after years of sobriety alone.

Malnutrition and avitaminosis have been alleged to be the precipitating causes of alcoholism. But anyone who has been treating the victims of this disorder knows that the majority of these patients, especially in the middle- or upper-income brackets, have had an adequate supply of calories, including all of the essential vitamins. Why should the recovered alcoholic, whose diet conceivably was deficient, still complain of the same symptoms that precipitated his alcoholism, long after he has been receiving a well balanced diet? One reason is that many of these people continue the onslaught against the adrenals by substituting readily available carbohydrates for the alcohol. Even so, others who follow a low-carbohydrate, moderate-fat, high-protein diet may be relieved of such symptoms as the "dry-jitters" (hypoglycemic crises) but still suffer from other mental and emotional symptoms due to an erratic blood sugar level, since the liver and adrenals are not yet functioning normally.

Alcoholics Anonymous has performed a very commendable service in reclaiming many lost souls through their twelve-step program, and these rehabilitated persons have maintained their sobriety by helping others to remain sober. However, the maintenance of sobriety is an empty goal if they are unable to do anything with their newly won achievement. Their purpose now should be to use their long-latent talents for their own betterment and to the advantage of society. Our purpose is to make them feel like normal people, regardless of their association with a drinking society. But how can they achieve these goals when the symptoms that initiated their abnormal drinking pattern persist, and to a much greater degree? Their thinking is confused, often with depression, engendering suicidal tendencies. A feeling of inadequacy is common, and this interferes with the normal performance of, and satisfaction with their occupation.

Liver disease. The prolonged abuse of alcohol precipitates many functional disturbances which cannot be corrected by mere abstinence from this substance. Most notable is the occurrence of reactive hypoglycemia years after

drinking has been terminated. In addition, fatty infiltration of the liver has been augmented by the natural tendency to substitute readily available carbohydrates for alcohol. It is common to find A. A. members carrying a candy bar or a lump of sugar to be ingested in case they have an attack of the dry jitters. If left to their own resources, recovered alcoholics naturally adopt a diet high in carbohydrates. In no instance have we found these patients to be free of hypoglycemia. The hypoglycemia is preceded by hyperglycemia, the severity of which depends upon the amount and duration of damage imposed upon the liver and adrenals through the consumption of alcohol and, later, carbohydrates. Indeed, Banting once stated that more cases of hepatic cirrhosis are produced in hard soft-drinkers than in hard hard-drinkers.

In a controlled study (34), a group of rats was given enough alcohol to supply 22 per cent of their caloric intake. The intoxicated rats accumulated 36 per cent more fat in their livers than did the control group, even though the total diet was adequate to maintain normal liver function and to promote good growth. Choline chloride and vitamin B_{12} were effective in preventing fatty livers if given in large doses. It would thus appear that alcohol per se, and not a reduction of protein intake or an excess of calories with relation to lipotropic substances, causes the liver damage.

Factors other than poor nutrition are involved in the pathogenesis of the many forms of liver disease seen in alcoholic subjects. The exact role of nutrition and alcohol in the development of fatty liver or Laennec's cirrhosis remains to be determined. In the metabolism of alcohol the first step is its oxidation by alcohol dehydrogenase to acetaldehyde. Figueroa and Klotz (35) reported a significant decrease in liver alcohol dehydrogenase in liver biopsy specimens obtained from patients with cirrhosis.

The increased tolerance for alcohol in the chronically addicted patient may be due to an adaptive increase in the activity of alcohol dehydrogenase and acetaldehyde dehydrogenase. Further studies are being carried out at several institutions.

THE GENERAL ADAPTATION SYNDROME

In 1936 Selye (36) demonstrated by a series of animal experiments that the organism responds in a "stereotypical" manner to a variety of widely different factors such as infections, *intoxications*, traumas, nervous strain, heat, cold, and muscular fatigue. The specific actions of these agents are quite different. Their only common feature is that they place the body in a state of general or systemic stress, which is essentially the rate of wear and tear within the body at any one time. Some stressor agents are: 1) an infection that initiates an asthmatic attack, 2) contact with an allergen in the nasopharynx that causes symptoms of hay fever, 3) chemicals that produce cutaneous reactions, or 4) alcohol, which can lead to addiction. Alcohol in itself is a stressor agent in stimulating the adrenal cortex, but it may also act as an antigen in the addiction concept of Randolph (30).

During stress reactions all the organs of the body show involutional or degenerative changes while the adrenal cortex actually flourishes—which ac-

counts for normal steroid values usually obtained on alcoholic patients. The initial response to alcohol is the Alarm Reaction or the first phase of the more prolonged General Adaptation Syndrome (G.A.S.), which has three distinct stages:

1. Alarm Reaction. (Adaptation has not been acquired.)
2. State of Resistance. (Adaptation is optimal.)
3. Stage of Exhaustion. (Acquired adaptation is lost again.)

In the General Adaptation Syndrome the most outstanding features of this stress response are: adrenocortical enlargement with histologic signs of hyperactivity, both hypertrophy and hyperplasia; thymico-lymphatic involution with concomitant blood changes (eosinopenia, polymorphonuclear leukocytosis); gastrointestinal ulceration; and finally shock or other manifestions of damage when the adrenal cortex is no longer able to withstand the onslaught.

Experimentally, thymico-lymphatic involution and typical blood-count changes can be produced by adrenocortical extracts, even in the absence of the adrenals. These hormones are therefore considered the indirect results of stress. On the other hand, adrenocortical extracts lessen the shock and the gastrointestinal changes; thus these conditions are combatted by an adequate adrenocortical response. Additionally, Selye showed in 1937 that the only state which could prevent an adrenocortical response to stress was hypophysectomy; he therefore concluded that stress stimulates the adrenal cortex through the pituitary adrenocorticotropic hormone (ACTH). Clinically most acute alcoholic states have responded better to adrenocortical extract than to the individual cortical steroids or to ACTH.

The typical patient we have described as being potentially alcoholic is the tall and linear, with a low blood pressure, few or no secondary sex characteristics, lymphocytosis, eosinophilia, a low basal metabolic rate, a normal serum level of protein-bound iodine, and a low flat glucose tolerance curve falling off to hypoglycemic levels. 17-Ketosteroid values in such patients, not subjected to stress, are low or low-normal. However, the adrenal cortex is capable of stimulation as described by Selye in his General Adaptation Syndrome. Thus we find that this person is extremely sensitive to alcohol when first exposed (alarm reaction), but with further alcoholic exposure and stimulation the state of resistance ensues; this may last as long as fifteen years (more or less), and during which time large quantities of alcohol may be consumed and fairly well tolerated. However, the third state—exhaustion—finally develops in which the acquired adaptation is again lost, and the result is a typical example of chronic alcoholism. Even after years of sobriety the glandular aberrations thus produced present a new set of findings of deterioration. Instead of the low flat glucose tolerance curve there is now a high initial rise, and the curve falls to a hypoglycemic level at about the third hour.

RELATIONSHIP BETWEEN ALCOHOLISM AND DRUG ADDICTION

Alcohol dehydrogenase activity was measured by Fazekas et al. (37) in liver homogenates from 15 intact and 15 adrenalectomized rats killed six hours

after the operation. In the adrenalectomized animals, activity was reduced by 16 per cent. Addition of adrenal cortex extract increased the enzymic activity of the homogenates from normal and adrenalectomized rats to an equal degree. It was concluded that adrenal cortex hormones have a stimulating effect on alcohol dehydrogenase activity and thus promote the oxidation of alcohol in the blood. More recently Wallace (38) of the U.S.A.F. demonstrated that all barbiturates exert an inhibitory effect on alcohol dehydrogenase, which apparently explains the danger in the use of these sedatives in intoxicated persons. It also offers a clue to the relatively high incidence of barbiturate addiction in alcoholics, particularly after control of the acute phase has been achieved. The marked increase of adrenocortical hormones during stress can reduce the effectiveness of depressant drugs on the organism (39).

Jellinek (40) stated emphatically that there is ample evidence to show that large alcohol intake exerts an exorbitant stress upon the adrenals, and that there is a fairly high incidence of adrenal damage in alcoholics. He states further that endocrinopathies may play a role in the withdrawal symptoms in alcoholism, but since these symptoms are the same as in drug addiction, it would have to be known whether such addictions also cause adrenal changes. We have shown that such changes do occur in various drug addictions not associated with alcohol, and that they respond to ACE therapy.

As a point of interest, a legal dilemma exists in an Eastern State hospital where a young heroin addict was committed by the courts because he was convicted of stealing to support his habit. Since his mother had a long arduous history of hypoglycemia and his father had a history of severe chronic alcoholism, the psychiatrists agreed to perform a glucose tolerance test. The test revealed a marked hypoglycemia, with the following blood sugar concentrations: fasting 71 mg, half-hour 154 mg, one hour 105 mg, two hours 100 mg, three hours 39 mg, four hours 60 mg, and five hours 62 mg per 100 ml. The patient was given a low-carbohydrate, high-protein diet and when there was a noticeable improvement in his psychiatric condition little further persuasion was needed to institute ACE therapy. Now that psychiatric and endocrine therapy are no longer required, the problem is whether he should remain in the State hospital, be committed to prison, or be set free.

PSYCHIATRIC SYMPTOMS: RELATION TO HYPOGLYCEMIA

Many patients obtain considerable relief of symptoms by following a high-protein, moderate-fat, low-carbohydrate diet. However, the most challenging situation is presented by the recovered alcoholic who, even after maintaining sobriety and following such a diet, still has a myriad of so-called psychiatric symptoms. Undoubtedly such tranquilizing agents as Thorazine, Librium, Valium, and even Bellergal help to keep many of these feelings in abeyance, but this is not the ultimate solution. So far as we have been able to ascertain, only one course of treatment can prevent this vicious hyperglycemic-hypoglycemic reaction from occurring, and that is through the use of the whole adrenal cortex extract plus any other adjunctive endocrine preparations which may be indicated by a careful history, physical examination, and a minimum of laboratory procedures.

The following glucose tolerance curve for a man with a 9½-year record of sobriety, is typical.

	Blood Sugar (mg/100 ml)	Urine Sugar (qual.)
Fasting	106	Neg.
1 hr.	226	Neg.
2 hrs.	138	2-plus
3 hrs.	103*	Trace
4 hrs.	82	Neg.
5 hrs.	59	Neg.

* Onset of hypoglycemia.

In such cases the physiologic mechanism in the response to glucose is extreme during the glucose tolerance test, indicating an extremely erratic regulation of blood sugar. This factor is perhaps the most important of all in the regulation of the sensorium. A feeling of well-being goes with nourishment and the consequent increase in the blood sugar level. We think more clearly, and experience better physical and mental activity when our blood sugar levels are substantial. In the foregoing table the asterisk indicates the onset of symptoms of hypoglycemia which later develop into the full-blown picture of fatigue, nervousness, apprehension, irritability, faintness, blackouts, mental confusion, cold sweats, and even stupor. Usually the patient feels the need for such physiologic support as alcohol or sweets might give. It is the rapidity of the fall in blood sugar concentration which produces these reactions, and not the level from which, or to which, it may have fallen (41). In patients who receive adequate treatment with ACE, the blood sugar curve approaches normal, and in practically every instance the glycosuria is eliminated. In contradistinction, cortisone has a tendency to produce a blood sugar curve similar to that of the diabetic, and to induce glycosuria.

Alcohol is practically the only foodstuff that is absorbed immediately from the gastrointestinal tract and utilized as energy. Upon entering the blood stream there is a release of adrenaline. This causes palpitation, flushing, sweating and syncope, which sets the pituitary-adrenal axis in motion, resulting in liberation of glycogen from the liver into the blood and the consequent hyperglycemia. It is obvious, therefore, why an alcoholic may have the physiologic urge to take that first drink, particularly a few hours after a high-carbohydrate meal when the blood sugar inevitably has dropped down to hypoglycemic levels. The same mechanism holds true following such emotional stimuli as sorrow, grief or fear—or any situation which may trigger the release of adrenaline.

These circumstances are exemplified in the following case history:

P. W., a lawyer aged 51, had been active in Alcoholics Anonymous for eight years, having been a periodic "stress and strain" drinker between the ages of 32 to 43. He was now reputedly a successfully controlled case of alcoholism. He took his obligations seriously, and gave the customary talks to A. A. on how, according to his experience, one could throw off the shackles of alcoholism by helping others to gain sobriety.

By talking to others and helping them in their battle with alcohol, he helped to talk himself into maintaining sobriety and convinced himself that he was satisfied with his lot. He stated that it had become an acceptable, but rather mechanical approach to life. The whole business of living had become a sort of battle—but since it was clearly a battle of survival, he had better keep his guard up. There was, however, a yearning for something which he could not define. He also tolerated certain physical disabilities which he could have borne much more easily if he could have taken a drink. Nevertheless, he was a disciplinarian, and tolerated his nervousness and essential lack of satisfaction with a determined handling of the day-to-day problems.

The complaints which finally prompted him to seek medical aid were nervousness, lack of the power of concentration, irritability and fatigue. He noticed that he was continually making more errors in his work, and complained of making many agonizing mistakes in the late afternoon and sometimes even before lunch. He was also becoming more and more inclined to fits of temper, bad disposition and other manifestations of nervous instability despite conscious efforts to control them. These would be followed by periods of increased apprehension and worry, which had been present, to a lesser degree, most of the time. When the patient returned home after work, he found that he could not relax and was extremely tense and argumentative.

He observed, however, that food had a stabilizing effect and that shortly after dinner he felt like a different person. His preferences in foods were obviously carbohydrates such as potatoes and rich desserts. He was an avid coffee drinker and took two or more teaspoonfuls of sugar in each cup. He also had the acceptable extra-salt habit. Patients with hypoadrenocorticism tend to eat highly salted and otherwise seasoned foods. Libido was decreased markedly for approximately ten years. The patient stated that his response was normal, but he had no desire for sexual activity for several weeks at a time. His weight, which had not varied appreciably in over ten years was well beyond the optimum for him.

Physical findings were normal except for telangiectasia over the chest and abdomen and the other usual features described previously, i.e., absence of chest hair, postural hypotension, and visceroptosis. Blood studies revealed relative lymphocytosis and eosinophilia (48% and 5%, respectively). Blood chemistry values were essentially normal with the exception of those for the glucose tolerance test. The results of the test were characteristic, showing wide variations as follows:

	Blood Sugar (mg/100 ml)
Fasting	99
Glucose given (100 gm)	196
½ hr.	196
1 hr.	199
2 hrs.	57
3 hrs.	63

(followed by severe hypoglycemic reaction)

The patient was given 10 ml of adrenal cortex extract (Eschatin) intravenously, with 50 mg of pyridoxine and 50 mg of testosterone propionate intramuscularly. (Pyridoxine apparently plays a significant role in the enzyme system governing the metabolism of carbohydrates and amino acids.) The importance of a low-carbohydrate, moderate-fat and high-protein diet was impressed upon him at this time. He was instructed to return for further observation and treatment at rather frequent intervals, at which times he received the same injections and counseling. Oral medication consisted of one Bellergal tablet three times daily.

A few visits later, the patient stated that shortly after the institution of treatment he observed that he had no serious craving for sweets and had considerably less nervous tension. His pulse had become more normal compared to a previous reading

of 92, and his blood pressure had dropped from 164/94 to 148/90 mm Hg. He commented that, for the first time, he truly appreciated the full implication of a "spiritual awakening" and felt a new awareness of a purpose in life. His tensions had so far lessened that he was able "to think again."

At the end of one month of complete cooperation on his part, with diet and hormonal therapy as well as psychologic consultations with us, there was a marked improvement in mental alertness and physical energy, and also an significant weight drop.

The patient's eyesight, incidentally, was improved to the point where he needed new glasses with less magnification. His gustatory enjoyment was enhanced to what seemed to be its absolute culmination. As treatment progressed, following a 12-week period, the interval between hormonal administrations was lengthened to two weeks. He was then seen fortnightly for three months, when the schedule was changed to monthly visits.

Along with the endocrine therapy, proper psychologic management is imperative, in order that a broader insight into the unusual psychiatric, physiologic and nutritional aspects of the problem may enlist the patient's entire cooperation. It is important that the physician convey a complete understanding of these aspects of therapy to the patient. The physician, therefore, must have the importance of these several steps clearly fixed in his own mind, and be in a position to outline to the patient the essentials of the hormonal, dietetic, and particularly the emotional ramifications of this type of sick person—the alcoholic (acute stage, chronic stage, or recovered).

Recovered alcoholics are frequently introverted and antisocial. Lack of self-esteem is a common trait emphasized by most psychiatrists. They are dependent persons who must be changed to persons having confidence and a desire for full productivity and usefulness.

Regular consultations of a psychiatric nature must continue indefinitely. There must be a rational explanation in layman's language of the emotional, psychologic and hormonal aspects of the patient's illness in order to effect a lessening of his negativism and a reversal of the personality traits presented at the beginning of treatment. A sympathetic and understanding attitude must be maintained constantly. An alcoholic is an extremely sensitive person who resents lecturing or sermonizing by the physician or members of his family.

Relief of the acute symptoms of alcoholism by means of intensive hormonal therapy has been adopted by many clinicians, but a realization of the necessity of continued treatment of this nature through the many phases of recovery has been overlooked. Most patients are dismissed at this juncture with the admonition that they must not drink again and that the best procedure is to contact A. A. and become active in their program. To these physicians, the attainment of a state of sobriety is paramount without any attempt to understand the new problems which now present themselves.

Within a matter of weeks the pre-treatment excitation of the glandular "symphony" subsides to a state of hypometabolism, so that the manifestations of decreased hormonal function become apparent (particularly regarding the thyroid, adrenals, testes and pancreas).

The patient no longer has the physiologic craving for alcohol but he often

feels that the admonitions heaped upon him during his drinking episodes must be true and that he is verily a psychopathic case, since now he has even more psychosomatic complaints than before. However, a patient with psychosomatic symptoms is seldom psychotic (42). His depression is real, but readily explainable on the basis of a glandular reversal in relation to at least some of the endocrine organs.

This post-treatment syndrome is a different symptom complex, which may even include symptoms of the climacteric, hypothyroidism, and other evidences of decreased metabolism. In our studies, serum protein-bound iodine determinations which were originally in the euthyroid range, dropped to the hypothyroid range after a few weeks of therapy. However, this post-treatment phase can be changed to a "middle of the road" course with a stable metabolism during continued treatment with injections of adrenal cortex extract, testosterone (in males), estrogens (in females), anabolic hormones (nandrolone phenpropionate), and as little as ¼ grain of thyroid in the form of Proloid. We regard with disfavor the current procedure of sobering up acutely intoxicated subjects with large doses of triiodothyronine. The dramatic effects are accomplished through the thyroid-adrenal axis, but disastrous "accidents" are bound to occur if this "technique" is continued.

The adrenocortical failure that occurs in hypopituitarism is manifested by pigmentation, hypotension and hypoglycemic episodes. Sometimes the adrenocortical insufficiency is not detected at first and only becomes evident when the patient is given thyroid for his supposed primary hypothyroidism; by increasing metabolic activity, the thyroid treatment increases the need for sugar and salt, and may thereby precipitate hypoglycemic or hyponatremic crises.

The relationship between adrenocortical and thyroidal function has been recognized for many years. By the mid-thirties considerable evidence had been accumulated to indicate that patients with hypofunction of the adrenal cortex could be thrown into crisis by the administration of thyroid (43), that thyroxine produces an enlargement of the adrenal cortex, and that other and often antagonistic correlations exist between these two glands.

Clinical observations and a study of the histopathologic findings in thyrotoxic patients suggest that their adrenals are deficient compared to those of healthy subjects. On the other hand, the results of laboratory examinations indicate that in the majority of cases the secretory activity of the adrenal cortex is normal. Mikulaj and Németh (44) showed by a series of experiments that long duration of the state of thyrotoxicosis results in marked depletion of the functional reserves of the adrenal cortex, but not to such an extent that insufficiency can be reflected in the values for adrenocortical steroids either in urine or plasma.

A dramatic case in point is that of a 32-year-old man who presented himself in my office shortly after the close of World War II, complaining of severe nervousness, pronounced swelling of the thyroid and bilateral exophthalmos. After discharge from the Army his drinking had become compulsive, and abstinence caused a marked in-

crease of his nervous symptoms. His history revealed that his father was of the same linear, asthenic constitutional type and had been a recovered alcoholic for ten years. The patient had been taken prisoner of war by the Germans and incarcerated for eighteen months. During his internment his diet was by no means one of starvation, but consisted chiefly of potato soup and black bread with protein supplements on two occasions of about 3 ounces of horse meat. The result of his forced high-carbohydrate intake was marked bilateral gynecomastia, which subsided after he was given a balanced diet at an American Army Hospital after liberation. He was eventually discharged in apparently good physical condition. However, slowly and insidiously his intolerance for alcohol became apparent and the signs and symptoms of the hyperthyroidism developed. He had been advised to undergo thyroidectomy by no less than four surgeons, but he steadfastly refused the operation. His basal metabolic rate was +38, his pulse was extremely rapid, and he was practically in a state of collapse. A laboratory work-up (including a glucose tolerance test) revealed a definite hepatic involvement. The blood sugar concentration reached a high plateau during the first two hours, eventually falling to hypoglycemic levels as follows: fasting, 90 mg; half an hour after glucose ingestion, 220 mg; one hour, 208 mg; two hours, 91 mg; and three hours, 60 mg per 100 ml. None of the urine specimens contained sugar. Intensive therapy was started with adrenal cortex extract intravenously. Within a few months the exophthalmos, thyroid enlargement, tachycardia and hepatomegaly dramatically subsided. The patient never consented to surgery but was sustained with 300 mg daily of propylthiouracil and a low-carbohydrate diet for one year, after which time all medication was discontinued. He was in excellent condition when last seen in 1962.

TREATMENT OF THE RECOVERED ALCOHOLIC

In the mid-forties I had a clear field in the treatment of alcoholics since the general medical fraternity considered them either psychopathic or immoral. Alcoholics Anonymous slowly changed the atmosphere, but the medical profession was reticent in accepting the disease concept of alcoholism. I was eventually given the opportunity to treat these patients in a ward in a general hospital, after much persuasion of the medical board. Although they came to be regarded as sick patients, I was later required to treat them in private rooms. The cost of hospitalization was prohibitive to some, and limited my type of practice. However, this hospital is still the only one in Westchester County, New York, which will admit these long-neglected people. Treatment of the acute phase of alcoholism has now been simplified through the use of adrenal cortex extract and the newer and more effective tranquilizing agents, but the problem of keeping these patients sober and correcting their residual complaints has engendered new concepts of treatment and rehabilitation.

The crux of the alcoholic problem is hypoglycemia—whether it occurs in the predisposed person with genetic factors influencing his physical and emotional growth, in the social drinker aggravating his already disturbed carbohydrate function, in the chronic alcoholic in the G.A.S. stage of resistance or fatigue, or in the recovered alcoholic with his psychic and physical complaints. Even in the normal person, a temporary hypoglycemia develops following a debauch. The prolonged hypoglycemia in alcoholics always results in liver involvement. In alcoholics with pronounced hepatic lesions the blood sugar curve is of the diabetic type, falling to hypoglycemic levels.

In the routine examination of any patient, a five-hour glucose tolerance test is as important as the complete blood count, urinalysis and serum protein-bound iodine. Correlation of the clinical symptoms with the level of blood sugar is often revealing to the physician and a lesson to the patient. In this respect, the results of the glucose tolerance test are more valuable when the glucose is given orally rather than intravenously.

The aim of the clinician in treatment of the recovered alcoholic is the integration and normal function of all body organs and of the mind. This can be achieved only through adequate balance by endocrine therapy, proper nutrition, and common-sense psychologic guidance.

Since the pituitary, thyroid and adrenal glands affect the capacity of the organism to respond to ingested glucose, the glucose tolerance test may uncover evidence of dysfunction of these glands. The information so obtained may demonstrate disturbances of hormonal function without resort to complicated steroid analyses or bioassays. However, such tests of carbohydrate function, though offering valuable information, cannot completely replace the usual chemical or bioassay techniques for determination of steroids. These analyses are necessary for precise delineation of gonadal, adrenal, thyroid, or pituitary function. Nevertheless, glucose tolerance tests may serve well to uncover some disturbances in the pituitary-thyroid-adrenal axis. In every case of pathologic drinking we have studied, a low blood sugar has been found a few hours after the initial rise to diabetic levels. There is no rigid rule about the level to which the blood sugar must fall to indicate hypoglycemia. Striker (41) pointed out that a patient with a blood sugar concentration of only 22 mg per 100 ml may sit up in bed and shave, whereas another patient with a blood sugar level of 425 mg per 100 ml may experience definite hypoglycemic symptoms. Striker emphasized that it is the *suddenness* of the fall in blood sugar which produces general reactions, and not the level from which, or to which, it may have fallen. Moreover, the clinical signs of hypoglycemia often are more severe than the blood sugar level warrants.

The treatment, then, of alcoholism centers essentially about the control of the hypoglycemia which is inherent in the potential alcoholic, is aggravated in the active state of alcoholism, and is still present in the recovered alcoholic—but with added endocrinopathies. We are not claiming that we can make social drinkers out of alcoholics. Controlled drinking can be considered only when blood sugar concentration is maintained at normal levels. This is improbable, since definite habit patterns established during the years of abnormal consumption of alcohol are revived with the re-introduction of the intoxicating beverage. Also, there is something to be said for allergy to specific grains or to substances from which the alcohol was fermented (45).

With institution of ACE therapy, the appetite returns and often becomes ravenous for periods as long as three months. Initially, the fat intake should be higher than that which will be sufficient after a few months. Recommended, and also prohibited, foods are listed in Table 1. A high-protein diet is necessary for the reparative processes initiated by the anabolic hormones, testosterone or

TABLE 1
Antihypoglycemic Diet

Foods allowed
All meats, fowl, fish and shell-fish
Dairy products (eggs, milk, butter and cheese; recommended, 1 glass of acidophilus milk daily)
All vegetables and fruits not listed below
Salted nuts (excellent between meals)
Peanut butter, oat and Jerusalem artichoke bread
Gelatin (with whipped cream)
Sanka, weak tea and sugar-free sodas
Soybeans and soybean products
Oatmeal
DeBole's macaroni and spaghetti
Foods to avoid
Potatoes, corn, macaroni, spaghetti, rice, cereals
Pie, cake, pastries, sugar, candies
Dates, raisins and other dried fruits
Cola and other sweet soft-drinks
Coffee and strong tea
Alcohol in all forms

nandrolone. Most important is the absolute restriction of all readily available carbohydrates. Saccharine or Sucaryl is substituted for sugar. No cereals except oatmeal are allowed. Dried fruits and legumes are eliminated. Sanka and tea are substituted for coffee, and no bread or cake is permitted until such time as experience leads to the conclusion that it can be tolerated with no hypoglycemic reaction or gain of weight.

Seldom are tranquilizers necessary when an autonomic-nervous-system stabilizer, such as Bellergal, is used; sleep patterns are usually restored to normal with 1 tablet taken two to three times daily. Chlordiazepoxide (Librium) is of value early in treatment. Diazepam (Valium) never produces ataxia and is an excellent muscle relaxant.

Recovered alcoholics are encouraged to quit smoking, or if not, to at least cut down their cigarette consumption as much as possible. Twenty years ago, primary carcinoma of the lung was a rarity, but I have observed at least 20 cases (including oral carcinoma) in the last fifteen years. Most patients with hypogonadism, male or female, have a chronic cough, but no roentgenologic evidence of pulmonary pathology can be demonstrated. Apparently, however, there are some histologic changes, as shown recently by microphotography of the tissue reactions which take place upon withdrawal of drugs or alcohol. This mitotic activity must be further stimulated by extraneous irritating substances such as the tars and resins found in tobacco smoke. Most alcoholics, through "nervous habit," smoke about two packs of king-sized cigarettes daily. As the patient begins to feel better, he can easily limit smoking to specific periods, such as after dinner, and really enjoy it.

"After a period of abstinence, the alcoholic (unless he has incurred gastritis, cirrhosis or other conditions associated with excessive drinking) usually appears physiologically normal. Yet he relapses" (46). This amazes the psychologists and psychiatrists. If even a perfunctory investigation into the physiologic state of this person were carried out, his "appearance" would be found to cloak a rash of abnormalities.

The question of *why* the alcoholic suffers a relapse seems to bewilder the psychically oriented investigators. On the contrary, it amazes us that there should be any protracted period of sobriety between relapses. The A.A. member with years of sobriety behind him should be more of an enigma. Our feelings of admiration are even greater when it is realized that he must still rely on the tenets of A.A. to resolve each morning that he won't take a drink for twenty-four hours. How discouraging must be the realization that life merely means the maintenance of sobriety for the next twenty-four hours, and that meeting with society's demands means controlling for a limited period this "deep-rooted emotional or psychiatric disorder"!

These investigators admit that there is ample evidence to support our "theories" of endocrine imbalance, but "much more research is needed in this area." I recall their attempt to use cortisone empirically and cortisone alone, and then when their experiment was a failure to condemn the entire endocrine approach.

Psychoanalytic procedures have been utterly unsuccessful since this "deep-rooted emotional factor" is in reality on a physiologic basis. Psychotherapy is of inestimable value if the patient can be made to understand the tangible tenets underlying these factors. Within a matter of weeks there is usually a reversal of some personality defects. Only then may the patient be expected to follow with enthusiasm the dietary and hormonal aspects of treatment. He now awakens in the morning with a purpose and joy in just being alive—not with a feeling that it is another day of struggle. He now has a reserve to withstand emotional stresses and has the satisfaction of being able to master any situation he is likely to encounter.

Various muscular impediments are alleviated as an indirect result of neuromuscular relaxation. Often vision is improved as a result of relieving spasm of the intrinsic ocular muscles. The importance of guidance in the sociologic and psychologic problems of these victims of pathologic inebriety is not to be ignored, but therapeutic physical changes can contribute greatly to restoration of the patient. Correction of physical impediments can aid materially in the process of rehabilitation.

Disulfiram (Antabuse). For the recovered alcoholic of several years' standing, treatment with disulfiram (Antabuse) is not to be considered. For the chronically alcoholic patient, this chemical crutch is rarely required once our combined therapy has been instituted. The patient who has undergone previous slips or relapses may find a great deal of security in his dependence on disulfiram. For this reason, any adjunctive support is welcome, at least temporarily. For

patients who are not receiving endocrine assistance, it is of inestimable value because it is a constant reminder of the consequences of drinking. However, most of my patients returning for their monthly or even quarterly appointments state that the only reminder of their alcoholism is when they check their appointment cards. Consultations at these intervals are never terminated.

A close follow-up of the patient as he emerges from one stage into another is extremely important. Therapy must necessarily be modified at these times. For this reason there should be a close liaison with the physician, who should be constantly aware of the patient's problems.

Like most other major organs, the adrenal gland has several different functions. It is unlikely that only one function may become abnormal, but sometimes deficiency of a single factor may predominate. Therefore, in clinical studies of the adrenal gland, tests must be chosen which will evaluate the numerous functions more or less individually. For example, tests based upon the response of the circulating eosinophils are a measure of the carbohydrate-regulating factors of the adrenal; tests based upon the urinary excretion of the 17-ketosteroids are a measure of adrenocortical androgen production; and tests based upon water excretion are a measure of the electrolyte-regulating factors. The 17-ketosteroids in females are derived from the adrenal steroids, whereas in males they are derived in part (two-thirds) from the adrenal steroids and in part (one-third) from the testicular steroids (47). In this respect, the physiologic constitution has a bearing on the psychologic constitution of the alcoholic.

SUMMARY

The genetically predisposed person who exhibits signs and symptoms of hypoadrenocorticism is considered the potential alcoholic. However, the person who has inherited normally functioning adrenal cortices may, through abuse of alcohol, subject the cortical cells and their enzymes to so much stress that the final outcome is about the same as that in the patient with an inherited insufficiency. By the continued use of alcohol the organism as a whole goes through the stages of alarm reaction, resistance, and eventually exhaustion.

Damaged tissues cannot be restored to normal except by rest and by administration of the secretions elaborated by the malfunctioning glands.

In the alcoholic—whether predisposed, active, or recovered—the prevailing factor is hypoglycemia. All the personality characteristics common to patients with hypoadrenocorticism can be attributed to this hypoglycemia, even before alcoholism becomes a problem. These characteristics become aggravated in the addictive drinker, and persist even in the recovered alcoholic.

The aim of treatment is restoration of homeostasis for all the endocrine factors involved. Therapy consists chiefly of the administration of adrenal cortex extract, adequate nutrition, and psychologic guidance. Diet is of extreme importance. Initially a rather high fat content is allowed, but eventually the diet should be high in protein, moderate in fat, and low in readily available carbohydrates.

REFERENCES

1. Tintera, J. W., and Lovell, H. W.: Endocrine treatment of alcoholism, *Geriatrics 4:* 274, 1949.
2. Lovell, H. W., and Tintera, J. W.: Hypoadrenocorticism in alcoholism and drug addiction, *Geriatrics 6:* 1, 1951.
3. Tintera, J. W.: The hypoadrenocortical state and its management, *New York State J. Med. 55:* 1869, 1955.
4. Tintera, J. W.: Office rehabilitation of the alcoholic, *New York State J. Med. 56:* 3896, 1956.
5. Tintera, J. W.: Alcoholism and genetic influences, *Mod. Med.* 1951.
6. McCandless, E. L., and Dye, J. A.: Effects of alloxan administration in the calf, *Am. J. Physiol. 166:* 355, 1949.
7. Thorn, G. W.: The Diagnosis and Treatment of Adrenal Insufficiency. A monograph in American Lectures in Endocrinology, ed. by W. O. Thompson. Springfield, Illinois, Charles C Thomas, Publisher, 1949.
8. Kuhl, W. J., and Lipton, M. A.: The diagnosis of adrenocortical disorders by laboratory methods, *New England J. Med. 263:* 128, 1960.
9. Long, C. N. H.; Katzin, B., and Fry, E. G.: Adrenal cortex and carbohydrate metabolism, *Endocrinology 26:* 309, 1940.
10. Eisenstein, A. B.; Berg, E.; Goldenberg, D., and Jensen, B.: In vitro effect of adrenal steroids on carbohydrate synthesis in liver, *Endocrinology 74:* 123, 1964.
11. Wilson, R. A., and Wilson, T. A.: The fate of the nontreated postmenopausal woman: a plea for the maintenance of adequate estrogen from puberty to the grave, *J. Am. Geriatrics Soc. 11:* 347, 1963.
12. McGavack, T. H.: Clinical Seminar; "Female Sex Hormones in Practice." Annual Meeting, A.M.A., June 1963.
13. Thorn, G. W., and Engel, L. L.: The effect of sex hormones on the renal excretion of electrolytes, *J. Exper. Med. 68:* 299, 1938.
14. Janes, R. G., and Nelson, W. O.: Effect of stilbestrol on certain phases of carbohydrate metabolism, *Proc. Soc. Exper. Biol. & Med. 43:* 340, 1940.
15. Kitay, J. I.: Amelioration of cortisone-induced pituitary-adrenal suppression by estradiol, *J. Clin. Endocrinol. & Metab. 24:* 231, 1964.
16. Peterson, R. E.: Adrenocortical steroid metabolism and adrenal cortical function in liver disease, *J. Clin. Invest. 39:* 320, 1960.
17. LaLonde, J. B.; Valiathan, S. M., and Ballinger, W. F., II: Hepatic regulation of sodium and water in ascites, *J.A.M.A. 184:* 117, 1964.
18. Dougherty, T. F., and White, A.: Influence of hormones on lymphoid tissue structure and function, *Endocrinology 35:* 1, 1944.
19. Hills, A. G.; Forsham, P. H., and Finch, C. A.: Changes in circulating leucocytes induced by the administration of pituitary adrenocorticotropic hormone (ACTH) in man, *Blood 3:* 755, 1948.
20. Oltman, J. E., and Friedman, S.: Blood eosinophiles in alcoholic states, *A.M.A. Arch. Neurol. & Psychiat. 68:* 530, 1952.
21. Gabrilove, J. L.: The level of the circulating eosinophils following trauma, *J. Clin. Endocrinol. 10:* 637, 1950.
22. Treadwell, B. L. J.; Oswald, J.; Savage, O.; Sever, E. D., and Copeman, W. S. C.: Pituitary function with corticosteroids, *Lancet 1:* 355, 1963.
23. Greenblatt, R. E.: Search the Scriptures. Philadelphia, J. B. Lippincott Co., 1963, p. 13.
24. Harris, S.: Hyperinsulinism and dysinsulinism, *J.A.M.A. 83:* 729, 1924.
25. Buehler, M. S.: Relative hypoglycemia—A clinical review of 350 cases, *Journal-Lancet 82:* 289, 1962.
26. Portis, S. A., and Zitman, I. H.: Mechanism of fatigue in neuropsychiatric patients, *J.A.M.A. 121:* 569, 1943.
27. Portis, S. A.: Life situations, emotions and hyperinsulinism, *J.A.M.A. 142:* 1281, 1950.

28. Cummins, L. H.: Hypoglycemia and convulsions in children following alcohol ingestion, *J. Pediat. 58*: 23, 1961.
29. Isselbacher, K. J., and Greenberger, N. J.: Metabolic effects of alcohol on the liver, *New England J. Med. 270:* 402, 1964.
30. Mindrum, G. M., and Schiff, L.: The use of high-fat diet in cases of fatty liver, *Gastroenterology 29:* 825, 1955.
31. Leevy, C. M., Nutritional factors in liver disease in man, *Am. J. Clin. Nutrit. 7:* 146, 1959.
32. Peters, U. H., and Neumann, H.: Vitamin B_6 deficiency in delirium tremens, *Arch. Psychiat. Nervenkr.* (Berlin) *201:* 165, 1960.
33. Bercovitz, Z. T.: The post-bulbar duodenal spasm syndrome. 14th Annual Meeting, American Geriatics Society, May 1957.
34. Mallov, S.: Effect of chronic ethanol intoxication on liver lipid content of rats, *Proc. Soc. Exper. Biol. & Med. 88:* 246, 1955.
35. Figueroa, R. B., and Klotz, A. P.: Alterations of liver alcohol dehydrogenase and other hepatic enzymes in alcoholic cirrhosis, *Gastroenterology 43:* 10, 1962.
36. Selye, H.: The general adaptation syndrome and the diseases of adaptation, *J. Clin. Endocrinol. 6:* 117, 1946.
37. Fazekas, I. G.; Rengei, B., and Fazekas, A. G.: The effect of adrenal cortex function on the activity of alcohol dehydrogenase in the liver, *Arch. Toxikol. 19:* 229, 1961.
38. Wallace, J. E.: Alcohol dehydrogenase enzyme in barbiturate intoxication, *Med. Tribune* 1964.
39. Leikola, A.: Influence of stress on alcohol intoxication in rats, *Quart. J. Stud. Alc. 23:* 369, 1962.
40. Jellinek, E. M.: The disease concept of alcoholism, New Haven, Conn., College and University Press, 1960.
41. Striker, C.: Diabetes mellitus: an orientation, *Illinois Med. J. 102:* 235, 1952.
42. White, A. A.: Evaluation of psychogenic symptoms in general medicine, *J.A.M.A. 147:* 1521, 1951.
43. Anderson, T. A., and Lyall, A.: Addison's disease due to suprarenal atrophy and death from hypoglycemia, *Lancet 1:* 1039, 1937.
44. Mikulaj, L., and Németh, S.: Contribution to the study of adrenocortical secretory function in thyrotoxicosis, *J. Clin. Endocrinol. & Metab. 18:* 539, 1958.
45. Randolph, T. G.: The descriptive features of food addiction—Addictive eating and drinking, *Quart. J. Stud. Alc. 17:* 198, 1956.
46. Roche Laboratories: Aspects of Alcoholism. Philadelphia, J. B. Lippincott Co., 1963.
47. Callow, N. H.; Callow, R. K., and Emmens, C. W.: 17-Ketosteroid, androgen and oestrogen excretion in the urine of gonadal or adrenal cortical deficiency, *J. Endocrinol. 2:* 88, 1940.

The Hypoadrenocortical State

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To sustain life the human organism must constantly respond and adapt to the stress imposed by the countless ever-changing influences and stimuli exerted by the external environment and arising from the complicated actions and interactions taking place within the organism itself. The body must defend itself against any threat to homeostasis, however small that threat or stressor may be. The degree of well-being depends upon the efficiency of the resistance or defense. The key stone of defense is the adrenal cortex as Selye has pointed out in his masterful exposition of the Adaptation Syndrome in which he identifies three stages - Alarm, Resistance and Exhaustion.[1] Inadequacy at this site leaves the noxious stimulus unopposed and disease process manifests itself in susceptible areas. Since the point or points of susceptibility may be anywhere, it follows that the outward signs of hypoadrenocorticism may compromise almost any system or organ where heredity or other factors may have caused derailment (Selye's word) of the resistance mechanism. The most difficult hurdle for othodox thinkers is the multiplicity of clinical conditions which may be included in the single abstract concept of the hormonal adaptation mechanism. It must have come as a surprise to the medical world when it was demonstrated that such seemingly unrelated conditions as meningitis, peritonitis, Pott's disease, lupus of the skin and miliary tuberculosis were caused by the same "specific" agent (stressor)[2]. It will come as even more of a surprise when the realization dawns that even a more bizarre assortment of diseases can result from non-specific stress and the consequent failure of adaptation. "The apparent cause of illness is often an infection, an intoxication, nervous exhaustion or merely old age, but, actually, a breakdown of the hormonal adaptation mechanism appears to be the most common ultimate cause of death in man."[3] Once the concept is grasped, the details fall into a logical pattern.

Complete inactivity of the adrenal cortex has been well understood for a century as a result of Addison's classical description of the condition. Partial or subtotal function has not fared so well. Recognition has been hampered by the persistence of the "all or none" notion that the adrenal gland reacts in stereotype fashion regardless of the previous stress placed upon it. Climatology is often neglected in considering the significance of steroid values. Diurnal or circadian variations are only

now being carefully studied and we find that each group has its own rhythm — glucocorticoids, mineralocorticoids and 17-ketosteroids.

It is generally taken for granted that every individual is endowed at birth with a normally functioning gland. Little consideration is given to the trauma of "being born" and the implications of the change of the X-Zone into the three layered or differentiated cortex.

The preservation of normal function of the adrenal cortex is a very important consideration for the obstetrician and pediatrician. Evaluation of adrenal function requires investigation into the endocrine development of the fetus; the factors leading to the hypoglycemia so common in the first 24 hours when proper supplementation of electrolytes and carbohydrates could prove invaluable.

The newborn is obliged to adjust to a damaging formula containing much more carbohydrate than human milk. This may give rise to pyloric stenosis colic, cystic fibrosis, eczema or diaper rash, which could be prevented by avoiding this undue stress on the adrenal cortex through proper feeding (at least probationary breast feeding during the first months).

Prenatal and neonatal drains on the adrenal may conceivably account for the absurdly high incidence of mental retardation — calculated by some to be 10% of the children born today.

Genetic factors play a large role. Allergies, for example, a sign of cortical failure, may be expected in 40% of the offspring if one parent has an allergic diathesis, while 75% is expected if both parents fit this category.

The hyperactive or autistic preschool child, the underachiever in school, the negativistic or rebellious early teenager, and finally the adolescent schizophrenic could all be managed if adrenal function were monitored from the very beginning.

An unending line of patients besiege the internist, the general practitioner and the psychiatrist with such vague complaints as dizziness, headaches, insomnia, tinnitus, weakness and fatigue, etc. These, too, could be understood and correctly categorized if there were an efficient test or rule of thumb by which to gauge the overall ability of the adrenal cortex to function under given circumstances. The vagaries of aging could be better understood if the concept of the protected and properly functioning adrenal were kept in mind.

What actually happens when the organism is placed under stress and cortisol pours into the blood stream? What synthesis, synergism and antagonism of the multiplicity of steroids takes place? What happens when the arthritic is given cortisone; when the asthmatic is given prednisone and the natural cortical secretion is blocked and lost because

the patient has been subjected to these individual steroids? The complexity of steroid chemistry and physiology has hidden the exact identification of each change in the action and composition of the metabolic products of cortisol. Definitive research in this area is approaching conclusion under exceedingly competent direction and significant elucidation may be expected in the near future.

Since about 1940 the clinical application of the principles of Selye's General Adaptation Syndrome have proved rewarding in many branches of medicine. There has been very slow erosion of the practice of treating symptoms although the importance of establishing homeostasis is still far from general appreciation. The stress of life itself in all its manifestations implicates the adrenal cortex and its more than thirty steroids. The total organ appears to be involved in every physiological and pathological process. Normal function of the human organism requires the whole balanced output of the adrenal cortex. Homeostasis depends upon the synergism and antagonism of this whole complex of hormones. Deficiency in this area is recognizable as a distinct clinical entity — Hypoadrenocorticism, which may be inherited, or induced by repeated or prolonged stress. Since it is bound to be a recurring theme in any discussion of hypoadrenocorticism, it is important at the outset to realize that hypoglycemia is the most obvious and frequent manifestation of the condition — not merely as a laboratory finding but as a whole complex of often baffling complaints which will be discussed below. This condition is amenable to treatment with the whole natural adrenocortical extract which can be used indefinitely without fear of side effects.

Individual synthetic steroids are still widely used but the early enthusiasm has given way to extreme caution. In rheumatoid arthritis, for instance, cortisone cannot maintain its anti-inflammatory effect for long periods, and the unwanted and often serious side effects of these drugs are too well known to be reviewed here.

The hypoadrenocortic individual inherits poorly functioning adrenals, adequate for ordinary life processes, but, with the occurrence of unusual stress such as worry, grief or fear, the deficiency becomes more marked and consequently more definitive symptoms develop. Thus we find, with a more marked hypoglycemia, aggravation of such symptoms as fatigue, nervousness, irritability, depression, apprehensions, lightheadedness, faintness and fainting spells. An orthostatic hypotension becomes more pronounced and insomnia ensues. If the blood sugar is not supported by a bedtime snack, even though the patient may fall asleep after a variable interval of time, he may awaken at 3:00 a.m. with a cold sweat or nightmare and find it impossible to go back to sleep. We have mentioned the circadian ebb and flow of steroid production. Swift jet

travel through time zones enhances the importance of this. The patient may find himself engaged in important business when his rhythm calls for being in bed asleep.

As we know, the human organism operates for the most part on glucose which must be supplied by the blood at the appropriate concentration. It is understood that the adrenal cortex, through the operation of its glucocorticoids, plays a major role in regulating this concentration but there are many intricate systems involved in carbohydrate metabolism; particularly enzyme systems of the "Kreb's cycle." These operate in all tissues at the cellular level, especially in the muscles and the liver. The enzymes of the liver necessary for glycogenolysis and gluconeogenesis have been identified. Alcohol dehydrogenase and other enzymes implicated in hypoadrenocorticism have been less thoroughly investigated although they play a role in alcoholism and drug addiction.

The other organs participating in carbohydrate metabolism have received too little attention. The prostate, for instance, is responsible for the metabolism of fructose. Chronic benign prostatic hyperplasia is a frequent concommitant of the syndrome under discussion. Roberts has pointed out that the intactness of the testis, the pituitary and the adrenal is necessary for accelerated prostatic growth. Prostaic hyperplasia can be exaggerated by the increased elaboration of growth hormone, adrenocortical steroids and pituitary prolactin or interstitial-cell stimulating hormone under the repeated stimulus of recurrent hypoglycemia. Androgens exert a diabetogenic effect as do these counter-insulin responses. The high zinc, fructose and enzyme content of the prostate favors the production of insulin and thus may induce hypoglycemia.

The kidney contributes perhaps 15 - 20% of the inflow of glucose as calculated from arteriovenous differences and renal blood flow.[5]

In making a diagnosis the history taking is by far the most important part of the consultation. Most often birth weight is low or may even be in the premature range. The account of the mother's inability to nurse the child will usually reveal that many formulae were tried before the child was relieved of his colic and the family could sleep at night. A child born apparently at term, but below the expected weight, is suspect and should be examined for mental development. The early appearance of eczema in the cubital and popliteal fossae or a stubborn diaper rash are clues to an eventual history of hay fever, hives, asthma or generalized eczema or contact dermatitis. This inborn error of metabolism manifests itself in the hyperactive preschool child and the inattentive youngster in the classroom. He is labeled as an underachiever because of his inability to concentrate and his consequent failure in such subjects as mathematics (but with good scores in English). At puberty, because of this

daydreaming and constant admonitions, he becomes rebellious to parents' and teachers' demands. The later negativism, obstinate resentment of discipline and other behavorial peculiarities stigmatize him as a juvenile delinquent. The emotional immaturity and the feeling of inadequacy may lead to experimentation with drugs and eventually to addiction. A glucose tolerance test at any one of these points would indicate a disturbance in metabolism, and proper treatment could avert even so serious a consequence as schizophrenia. We, as well as other groups, have seldom failed to find hypoglycemia in a schizophrenic, drug addict or alcoholic. In the latter instances this is not a consequence but most certainly a contributory cause of these preventable states.

When medical help is finally sought, the seriousness of the complaints will vary according to the patient's level of blood sugar and the rate at which the level decreases. Early symptoms are similar to those seen after the administration of epinephrine, i.e., fainting, tremulousness, an "inward trembling," emotional disturbances, chilliness, circumoral numbness and pallor, mild degrees of mental cloudiness, hunger, apprehension, parasthesia, palpitation, hand tremor, etc. The patient appears to be emotionally upset, has a fixed facial expression; pupils are dilated and the skin is pale.

As the hypoglycemia progresses, a variety of symptoms occur such as headache, difficulty in concentration, disorientation, mental confusion, dizziness, faintness, diplopia, coldness of the extremities, etc. The patient may be unable to walk or may stagger; he may be depressed or restless and maniacal. Unless recognized and treated, severe hypoglycemia can lead to muscle twitching or generalized convulsions followed by retrograde amnesia and unconsciousness — even death.

Family history as to place of origin and ethnic background is of importance. The cold, inclement weather of the northern European states is conducive to adrenal stress and eventual mutation of the genes so that adrenal insufficiency is more often found in the blonde, blue-eyed and fair-skinned. The Swedish girl experiences her menarche at 17 - 18 while the maiden of Mediterranean forbears may start at 9 years of age. This accounts for the small families of the north and the large families in southern Europe where the menopause may occur in the late forties or early fifties instead of the thirties as in the former. Because of the genetic aspect of this condition, it is particularly important to elicit other family data — obesity, unusual stature, allergies, schizophrenia, neurasthenia, alcoholism, diabetes, arthritis.

The hypoadrenocortic is recognizable upon sight as a distinctive individual even though other glandular manifestations may, and usually do, coexist. We have previously described adrenal insufficiency as being

similar in many characteristics to Addisonianism although in this case there is not complete failure of the cortical cells. The classical hypoadrenocortic is a tall, linear, constitutionally inferior individual with a characteristic physiognomy and pathognomonic findings.

Since laboratory tests are only corroborative, clinical perception assumes greater importance. Upon shaking hands with the patient, a cold, clammy palm should arouse the first suspicion since autonomic nervous system instability is almost constant in the hypoadrenocortic. The angular appearance, the sparse beard and full head of fine hair are also indicative. The scalp may reveal seborrhic dermatitis which is usually amenable to I.V. pyridoxine. Pigmentation of the temporal areas is a strong indication. The pupils are dilated and testing for light and accommodation reflexes may reveal extraocular muscle weakness and/or resultant reading difficulties. Anabolic steroids in addition to A.C.E. are usually effective in controlling these difficulties. Vasomotor or allergic rhinitis is almost constant in these people.

Dental formation is a strong clue: the upper teeth are usually well constructed but the lower incisors are crowded and almost every molar will have been filled as a result of caries before the age of twenty. The "twiggy" type female is flat chested with long fingers and the index finger is usually longer than the fourth.

The extremities are long and slender; the span is greater than the height; and the distance from the symphysis pubis to the floor is greater than from the symphysis to the top of the head. In patients in their thirties and older there is an absence of hair on the lower lateral $\frac{2}{3}$ of the legs, generally attributed to wearing off by the trousers. The patellar reflexes are exaggerated and the achilles usually more responsive than normal.

In older individuals flat pigmented moles are common in varying size, and intensity of melanin deposition. The skin is dry and scaly because of a tendency to excrete more than normal amounts of urinary sodium chloride with the result that save for the hands and feet and the axillae there is very little perspiration. Fore the same reason the fluid intake is low through an automatic effort to conserve salt and thus maintain electrolite balance.

The long thin chest with a V-shaped costal angle houses a droplet-shaped heart. The female breasts are small, the areola often pigmented and sourounded by several long hairs. The nipples are not necessarily small or inverted. Tenderness in the left fourth interspace close to the sternum is a sign of concomitant hypoovarianism.

The viscera are ptotic, the colon distended and the stomach tympanitic because of pylorospasm. The indigestion stemming from the

latter may be relieved by belladonna and glutamic acid hydrochloride which relieves the spasm and alleviates the achlorhydria.

Because of the asthenic build, a retroverted uturus is expected in the hypoadrenocortic but it is not the cause of the repeated spontaneous abortions; the inability of the adrenals to supplement the ovarian estrogens predisposes to a small or infantile uterus.

Since the adrenal elaborates 65% of the male hormone in the man, we expect to find compromised development of secondary sex characteristics such as beard, genitalia, and chest and pubic hair.

Of extreme diagnostic importance in this condition is Rogoff's sign — the discomfort elicited by applying firm pressure with the finger tips over the spinatus muscle at the juncture of the lowest rib and the spine. The sensation may vary from discomfort to agonizing pain and reflects correspondingly the turgidity or hyperplasia of the faltering adrenal. The reaction is masked by previous treatment with individual steroids or with adrenocortical extract (A.C.E.).

Before the modern tests for thyroid activity were devised, these patients were thought to be suffering from an atypical hypothyroidism since they usually showed a B.M.R. of minus 14 or lower. In our series, however, the P.B.I., T-3, or T-4 usually falls within normal ranges which rules out hypothyroidism but indicates a condition of hypometabolism. A low P.B.I. in a woman may rise to normal values after a month or two of treatment with A.C.E. and estrogens. A G.I. series often reveals a J-shaped stomach, visceroptosis and, frequently, duodenal spasm. The symptoms of this spasm constitute Bercovitz' Post Duodenal Bulb Syndrome and are amenable to atropine and A.C.E. The differential blood count generally shows a relative lymphocytosis and eosinophilia — both indications of an allergic diathesis. Frequently there is mild albuminuria without other signs of renal involvement.

There is no single reliable laboratory test for adrenocortical function. Even the 17-ketosteroids vary greatly in normal individuals. In hypoadrenocortics who are notably emotionally immature, ordinary stress may put the pituitary-adrenal axis under pressure to increase production and the resulting values appear to be normal. Mere exposure to cold or changes in humidity or atmospheric pressure are known to stimulate production of these hormones. The same is true of the mere hospitalization of a patient. The unfamiliar surroundings produce a certain amount of anxiety and unrealistic readings are obtained. A high carbohydrate diet or even protein foods high in arginine or leucine will stimulate insulin production, and oblige the adrenal to act in opposition. The generally accepted normal 17-ketosteroid values of 8-25 mg./24 hours for the male and 5-15 mg./24 hours for the female do not encompass

the recent findings of Davidovic who reported readings in Yugoslavia for normal males in low-lying districts of 18.52±7.01 mg./24 hours while for health men of the same age from a mountainous area the readings were 48.34±11.46/24 hours — an extreme range of 11.5 to 60.

From this it is clear that specific hormonal assays are misleading since the gland may respond to stress just as a response may be obtained from an exhausted horse by whiplashing. The steroid determination may appear to be normal during the alarm reaction and be sustained during the period of adaptation but be of no clinical significance until, often terminally, exhaustion is manifested by shock and adrenal crisis. At this point adrenal failure is apparent even to the unwary. The degree of adrenal insufficiency must be recognized despite laboratory findings since the gland must respond or else the whole organism collapses. This apparently normal response led some of the early investigators to conclude that the adrenal functioned on an "all or none" basis.

Unless the patient is in extremis and adrenal activity reduced to a fraction of the norm, a definite diagnosis simply cannot be made by steroid assay. The Thorn Test is far from definitive and the water test is actually dangerous in cases of adrenal failure. The most reliable procedure is the five-hour Glucose Tolerance Test but here again the laboratory readings, in association with the symptoms observed during the test, require careful interpretation.[6]

The one common denominator regardless of whether the presenting complaint is some form of allergy, gouty or rheumatoid arthritis, or schizophrenia is hypoglycemia which classically reveals itself by a typical low flat curve currently referred to as idiopathic. When hepatic, renal, prostatic or muscle-mass pathology becomes involved, the reactive or peaked curve appears. As the low flat curve converts into the reactive type, there may be a period of apparent normal glucose tolerance but the diagnostic hypoglycemic symptoms will persist. The hypoglycemia (flat curve) has been demonstrated in the presence of a normal amount of insulin secretion but, as the curve approaches the reactive type with its high initial readings and sudden drop, a condition of hyperinsulinism exists and is often referred to as pre-diabetic. Our contention of the past two decades has recently been confirmed when this was shown to represent failure of the catabolism of the adrenal steroids which leaves the insulin unopposed. With the resulting hypoglycemia, cerebral symptoms appear which are often confused with epilepsy; also certain types of headaches. Concomitant EEGs reveal aberrations at the low-blood sugar levels. A study is in progress on parallel EEG and glucose tolerance findings which promises to clarify some aspects of this neuroendocrine puzzle.

Young individuals particularly exhibit the low flat glucose tolerance curve, generally falling off to a lower level at the fifth hour, which indicates hypoadrenocorticism but not hyperinsulinism as previously thought. Our long-held theory in this regard was recently substantiated when Matsui and Plager[7] demonstrated that a normal amount of insulin may be present, but hypoglycemia occurs because of failure on the part of the glucocorticoids to properly catabolize the insulin. In addition, intestinal malabsorption may be a factor, but it is the delayed destruction of the insulin (evoked by the glucose in the blood) which produces symptoms referrable to the neurovegetative and nutritional systems of the body. Through emotional stress or stresses produced by dietary or alcohol indiscretions, a preliminary rise may be elicited and the subsequent precipitous drop in blood sugar may produce devastating symptoms regardless of the absolute level to which the blood sugar falls. The curve of pituitary-adrenal insufficiency is characterized by an initial rise, often to marked hyperglycemia with a gradual decline to hypoglycemic values.

In summary, let me say that I first described the hypoadrenocortical syndrome in 1949[8] in connection with alcoholism and later in 1955[9] summarized the typical findings in 200 selected cases. The chief complaints were as follows:

1.	Excessive fatigue	94%
2.	Nervousness and irritability	86%
3.	Mental depression	79%
4.	Apprehensions	71%
5.	Excessive weakness	65%
6.	Light headedness	47%
7.	Faintness and fainting spells	42%
8.	Insomnia	40%
9.	Inability to concentrate	100%

Other findings according to organic systems are listed with their frequencies in these papers. It is germane, however, to give here the chief physical and laboratory findings:

PHYSICAL

1.	Postural hypotension	93%
2.	Generalized cervical lymphadenitis	93%
3.	Skin thin and dry	93%
4.	Perspiration scanty	91%
5.	Hair sparse	83%
6.	Crowded lower incisors	80%
7.	Asthenic habitus	78%
8.	Positive Rogoff's sign	71%
9.	Erythema of thenar and hypothenar eminences	28%
10.	Blanching on exposure to cold	21%

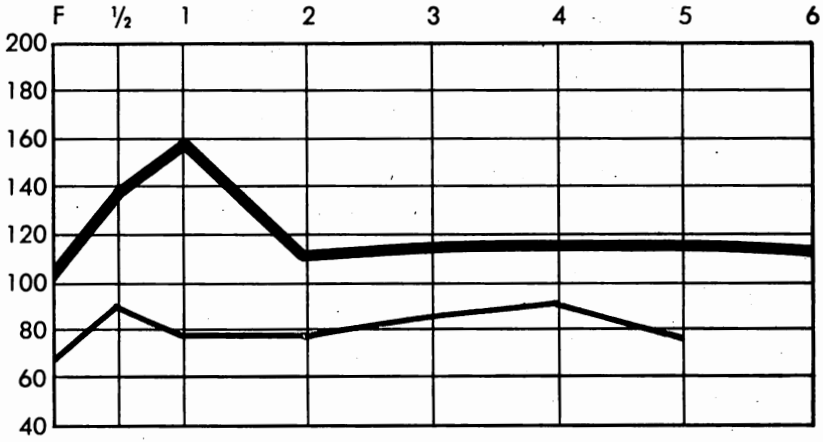
LABORATORY

1. Low basal metabolic rate (avg. - minus 14) 85%
2. X-Ray: J-shaped stomach and visceroptosis 73%
3. Eosinophilia 58%
4. Relative lymphocytosis 51%
5. Low, flat Glucose Tolerance curve (if relative or reactive hypoglycemias are included, the total approaches 100%) 51%
6. 17-Ketosteroids - low
   Male: 2.4 to 29; average 10.9 mg/24 hrs. (N=8-25 mg./24 hrs.)
   Female: 1.2 to 22; average 7.7 mg./24 hrs. (N=5-15 mg./24 hrs.)

The following glucose tolerance graphs illustrate some of the points made above. It will be evident that proper interpretation of the curve is extremely important.[6]

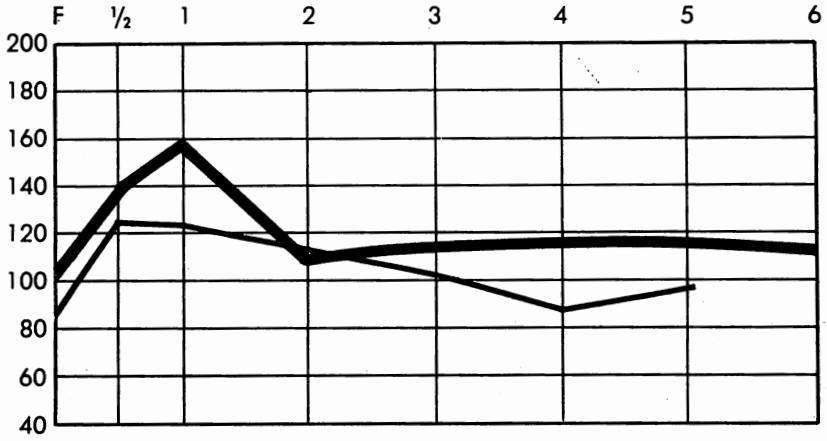
No. 1

This twelve-year-old boy was generally negative to physical examination. He was slow at school. Though he looked well, he was incapable of keeping up physically with his contemporaries. He preferred inactivity and frequently would stay in bed instead of going to school. He shows a classical low flat curve.



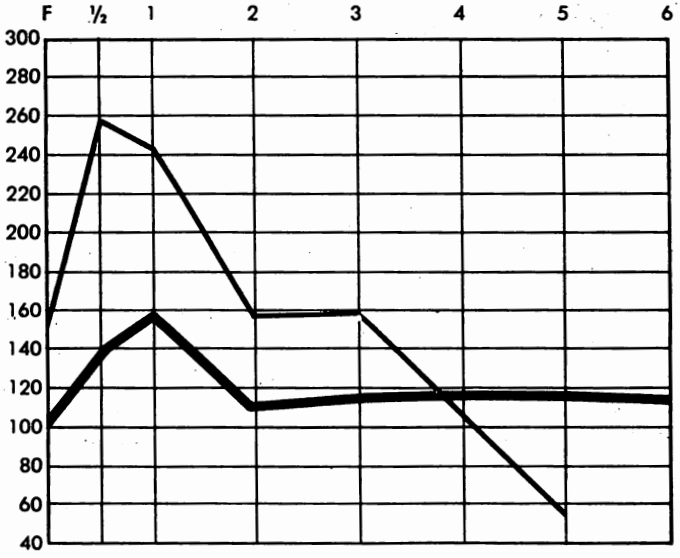
No. 2

This patient, 14 years old, the brother of No. 1, has a slightly less flat curve and shows recovery at the fifth hour. Yet his symptoms were more marked. There was a sudden failure at school plus marked personality changes. He also had no physical stamina.



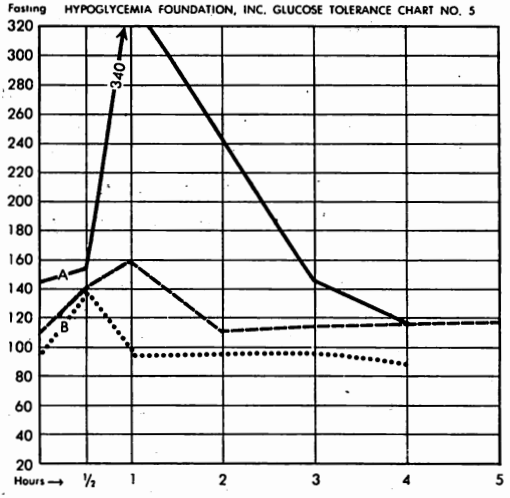
No. 3

This six-year-old girl was never well — infections, allergies, fatigue, dental caries. This case shows the importance of the five-hour test. A four-hour one would have been called diabetes. In view of the drastic terminal drop, one hesitates to contemplate what a dose of insulin would have done to her. This patient is very young to demonstrate the liver involvement indicated by the sustained hyperglycemic phase. Three months later after treatment with A.C.E., a spot one-hour post-parandial blood sugar was 95.



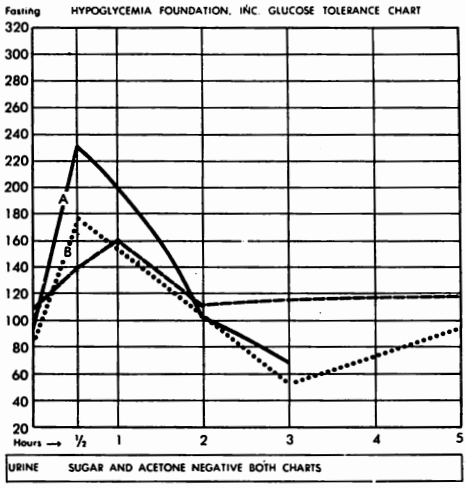
No. 4

CHART No. 4 — Female, aged 3, Graphs A and B are one year apart. Was given the standard 5-hour, 7-sample glucose tolerance test, with quantitative chemical analysis (not micro method). She had been treated for epilepsy, having as many as 30 daily petit mal attacks and occasional grand mal attacks. After examination this child was considered to have an inborn error of metabolism manifested by hypoadrenocorticism with a marked lymphocytosis and eosinophilia. The first curve reveals severe hyperglycemia but after one year Curve "B" is flat with the exception of the ½hr. specimen. Patient had been placed on a strict low-carbohydrate diet with weekly injections of Lipo Adrenal Cortex. Almost immediately the seizures had stopped completely and the anticonvulsive drugs were gradually eliminated. Except for one period, after having received gammaglobulin as a preventive for measles, there has been no return of seizures.



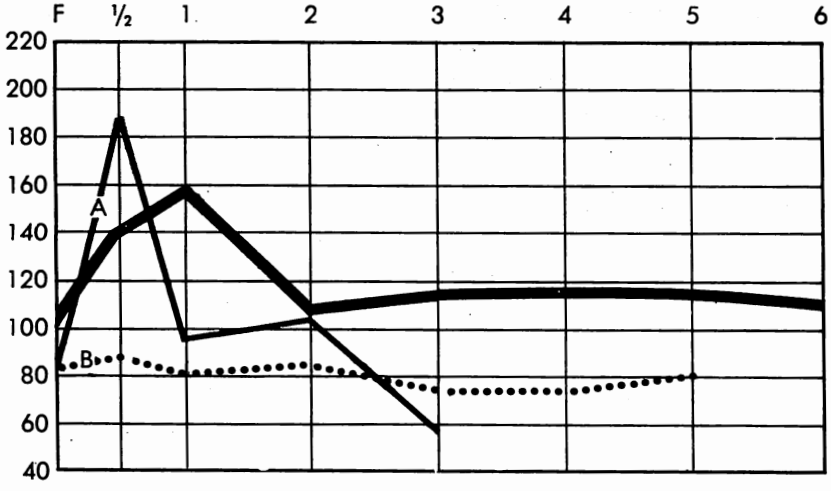
No. 5

CHART No. 5 — Male, aged 23, Graphs A and B are two years apart. Previous history of juvenile delinquency. He was a high school drop out, ran away from home, joined the Navy and was subsequently dishonorably discharged, became an alcoholic and later addicted to drugs; has a family history of alcoholism. He responded well to the usual treatment, obtained his high school diploma and is doing well in college. What was a hepatic-like curve in Graph A now becomes an essentially normal curve for the first two hours, the subsequent fall to hypoglycemic level being due to the stress of maintaining school, married life and working after school.



No. 6

CHART No. 6 — Male, aged 22, Graphs A and B are 6 weeks apart. Through a laboratory error the first test was stopped at the third hour because of severe symptoms of hypoglycemia. The three-hour test of Graph A was taken when the patient was complaining of hay fever, headaches and irritability; the usual desensitization treatment had been of no avail. He had been forced to leave post-graduate school due to severe fatigue and constant frontal and parietal headaches and inability to study. The only treatment between tests A and B was rest and low-carbohydrate diet. In this case the reactive type (A) is converted into the more benign B.



TREATMENT

1. The importance of diet in the treatment of hypoglycemia cannot be overemphasized. There must be strict elimination of all rapidly absorbable carbohydrates. This forestalls the sudden rise and subsequent fall in blood sugar levels. The heightened protein intake is beneficial in its own right since the individual amino acids evoke rises in circulating glucose.[11]

Vitamin intake should be monitored to facilitate proper liver (B6) and adrenal function (B1, 3, 6, 12, and C). Ascorbic acid is particularly important since adrenal requirements for this vitamin are greatly increased by stress.

2. In most instances, if tranquilizing agents have been prescribed, they may be reduced in dosage when agents influencing the autonomic or vegetative nervous system are prescribed. The A.N.S. undoubtedly plays a major part in converting emotional stimuli into symptoms. In order to minimize the role of emotions in the production of functional symptoms in patients with adrenal insufficiency, it has been found advisable to prescribe a combination (Bellergal) of l-hyoscyamine, ergotamine tartrate and phenobarbital. Large doses of this preparation are not required, because of a synergistic action with adrenal cortical extract. Patients are generally started on three tablets a day, one on arising, one at about two o'clock in the afternoon before the expected fall in blood sugar, and then one between dinner and retiring. Portis has demonstrated that paralysis of the right vagus nerve with large doses of atropine will prevent the inevitable afternoon fall in blood sugar.[12, 13] After approximately one to two months the Bellergal may be reduced to two tablets daily. This dosage has been continued for as long as six years. This autonomic system-oriented preparation helps reduce the intensity of emotional stimuli, thus acting to prevent the development of functional disturbances. In my estimation this is one of the most valuable drugs available to the physician.

3. In mild cases at least 10 cc of A.C.E. is given intravenously (or if impractical, intramuscularly) at least once a week for one to two months. In severe, acute cases 10 cc injections may be required as often as every four hours for the first 24 hours; q. 6 hr. for the next 24 hours; then q. 8 hr. until it seems clinically possible to give daily injections which may be continued for 1-2 weeks. After that, weekly injections may be given indefinitely until the interval between treatments may be progressively increased to two weeks, three weeks, etc. Pyridoxine, 1.0 cc (50 mg.) is added to the solution of A.C.E. at least once a week because of the role of this vitamin in the enzyme systems involved in regulating carbohydrate metabolism. Also for its synergistic and antihistaminic

sedative effect, the optional addition of 1 to 5 cc of Benadryl hydrochloride solution to the intravenous infusion is sometimes desirable.

The use of A.C.E., especially if given intravenously, produces a temporary feedback inhibiting the pituitary from whiplashing an already exhausted adrenal and gives a refractory period of about four hours to the cells in the zona fasciculata and zona reticularis. At the same time, the level of circulating glucosteroids is elevated so that restorative processes can take place in the liver. With stabilization of the blood sugar, the overstimulated pancreas is also given a period of respite. However, if cortisone or one of its derivatives is given in place of A.C.E., this steroid would have to be given in divided doses of at least 100 mg. or its equivalent, which would completely inhibit the pituitary and thus the secretion of glucosteroids by the cells of the zona fasciculata and if given over an extended period, atrophy of these cells would occur and further adrenal insufficiency would result. In fact, continued use of individual glucosteroids will invariably increase the level of blood glucose so that diabetic levels develop.

ACTH is also contraindicated in these patients since it would tend to whip the already exhausted adrenal cortex, producing hypertrophy and possibly hyperplasia of the cells of the zona fasciculata, but with little beneficial effect upon the mineralosteroid-producing cells in the zona glomerulosa save for further slight water retention.

4. For males - Testosterone proprionate 20 mg. I.M. once a week initially and methyl testosterone (Oreton) 10 mg. b.i.d. - p.c. daily buccal administration - no more than 2 Gm. over a 3-month period. To help restore nitrogen balance and further reduce demands on the adrenals, Adroyd or Maxibolen may be used. On alternate weeks Durabolin 25 mg. I.M. instead of testosterone may be used. When intervals have been increased to one month, 1 cc Decadurabolin may suffice to maintain a positive nitrogen balance.

5. For females - After negative Pap smear and culpocytology - Theelin or conjugated estrogens 5 mg. (50,000 i.u.) weekly injections, and natural estrogens (Menagen or Premarin) orally daily (during childbearing years from the 3rd through the 26th day of the menstrual cycle.) If there is a history of fibroids or dysmenorrhea, pregesterone may be beneficial in addition to the estrogen (from the 12th through the 26th day of the menstrual cycle).

6. Some comment is indicated on the various medicaments mentioned above. There seems to be some misunderstanding as to the use of the whole natural adrenal cortical extract (A.C.E.). It is uniquely valuable and safe.[14] In addition, it is effective for long-term use and in many cases should replace the corticosteroids. To our personal knowl-

edge more than 50,000 individual doses (10 cc or more) have been administered over 20 years with no report of undesired side effects and with consistent reports of beneficial results, often dramatic. In extreme cases or in conjunction with surgery, dosage may range as high as 200 cc so long as salt intake is maintained. Lipo Adrenal Cortex (Upjohn) is also available for intramuscular use. One cc of this preparation is equal to 10 cc of the aqueous extract.

Bellergal has been dealt with elsewhere at some length. Other drugs are of special interest mainly because of possible unwanted or toxic side effects. Large doses of chlorpromazine, for instance, over a long period will substantially reduce the secretion of ACTH.[15]

Since hypoadrenocorticism is characterized by hyponatremia and hypokalemia, these side effects must be kept in mind. Hyponatremia, a factor in the "Inappropriate Antidiuretic Hormone Syndrome," causes headache, disorientation, somnolence and other cerebral symptoms. Severe headaches often accompany the alkalosis associated with hypokalemia. Pending electrolite adjustment these can be relieved by glutamic acid-hydrochloride in doses large enough to acidify the urine. As we have seen, the kidney in man contributes perhaps 15-20% of the inflow of glucose. Any agent which would depress renal glucogenesis could theoretically result in symptomatic hypoglycemia within an hour.[4] It is well therefore when prescribing any of these drugs to be alert to possible toxicity for the liver, kidney and cerebrum.

Diazoxide[16] has been effective in the hypoglycemia associated with inoperable islet cell carcinoma[17] and in a few other cases of organic hypoglycemia but it cannot be recommended as a routine anti-hypoglycemic. Its use is still experimental and the molecular configuration may have to be altered to reduce side effects. These include hyperglycemia, hirsutism, hyprtension, edema, palpitation, leukopenia, thrombocytopenia, and hypogammaglobulinemia. It was necessary to discontinue diazoxide in five out of nine cases in one reported series.[18]

SUMMARY

Our clinical experience and Selye's fundamental research lead us to the conclusion that a very large number of pathological conditions become apparent only when bodily defense is "derailed" because the adrenal cortex is exhausted by excessive stress or the adrenal cortex is inherently deficient. These conditions can be forestalled or alleviated through supporting and resting the cortex and reducing internal and external stress. This can be accomplished with diet and A.C.E. and by stabilizing the automatic nervous system and controlling any associated endocrine dyscrasia.

REFERENCES

1. Selye, H.: Stress, Acta, Inc., Med. Publishers, Montreal, Canada, (1950)
2. Selye, H.: The Story of the Adaptation Syndrome, Acta, Inc., Med. Publishers, Montreal, Canada, (1952) page 105.
3. Selye, H.: Textbook of Endocrinology, Acta, Inc., Med. Publishers, Montreal, Canada, (1947).
4. Roberts, H.: Journal of the American Geriatrics Society, 14: 795 (August 1966).
5. Cahill: Advances in Enzyme Regulation, Vol. 2, George Webber, ed., Macmillan Co., N.Y. (1964).
6. Tintera: Journal of the American Geriactric Society, 14: 126 (1966)
7. Matusi and Plager: Journal of Endocrinology, 78: 1154 (June 1966)
8. Tintera and Lovell: Geriatrics, 4: 274 (1949)
9. Tintera: New York State Journal of Medicine, 55: 1869 (1955)
10. Physician's Guidelines to Diagnosis and Treatment of Hypoglycemia or the Hypoadrenocortical State; The Hypoglycemia Foundation,* New York (1966).
11. Fajans: Unpublished Lecture.
12. Portis and Zitman: Journal of the American Medical Association, 121: 569 (1943).
13. Portis: Journal of the American Medical Association, 121: 569 (1943).
14. Modern Drug Encyclopedia and Therapeutic Index (1965).
15. Bass: Postgraduate Medicine, 37: 82 (1965).
16. Graber, A. L., Porte, D., Jr., and Williams, R. H.: Mechanism diazoxide hypoglycemia. Program American Diabetic Association, p. 45, (1965).
17. Marks, V., Rose, F. C., and Samols, E.: Hyperinsulinism due to metastasizing insulinomi: Treatment with diazoxide. Proceedings of the Royal Society of Medicine, 58: 577, (1965).
18. Medical Tribune and Medical News, 25 Jan. 1967.

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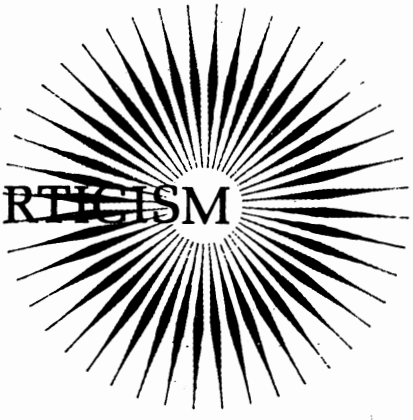
HYPOADRENOCORTICISM



ENDOCRINOLOGIC APPROACH TO
THE ETIOLOGY AND TREATMENT
OF FUNCTIONAL HYPOGLYCEMIA

NON-SURGICAL TREATMENT OF
HYPOGLYCEMIA STATES INCLUDING
THOSE OF ALCOHOLISM AND
DRUG ADDICTION

TABLE OF CONTENTS

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THE ENDOCRINE APPROACH TO THE ETIOLOGY AND EFFECTIVE CONTROL OF FUNCTIONAL HYPOGLYCEMIA

Functional hypoglycemia with its subtle and varied clinical manifestations has always been considered a difficult symptom to control medically. In fact, because of the presumed nonprogressive nature of this disorder, most physicians tend to discount and treat the accompanying psychologic and neurologic complaints as psychosomatic. Few, if any, attempts are made to determine the degree and severity of the hypometabolic disorder or to recognize that anxiety states or so-called neurocirculatory asthenia are the most common manifestations of hypoglycemic tendencies.

Continuing clinical investigations in this type of patient over the past 25 years have shown that undetected or untreated hypoglycemia is implicated in the development of diabetes, chronic alcoholism, drug addiction, Meniere's Disease, intractable allergies particularly asthma, homosexuality, and many of the behavioral or scholastic problems leading to delinquency in children and adolescents. In many of these patients, psychotherapy has not benefited the patient until the basic hypoglycemic state was corrected.

The following brief review of the regulatory mechanisms involved in maintaining normal glucose homeostasis may promote a better understanding of the etiology of hypoglycemia.

Normal Glucose Homeostasis—The transient hyperglycemia normally following the ingestion of carbohydrate foods stimulates the pancreas to secrete insulin. About 90 per cent of the newly formed glucose is stored as fat which cannot readily be reconverted to glucose but which can be used to provide energy to a large number of tissues. The brain however, cannot utilize energy from any source other than carbohydrate, chiefly glucose. Unfortunately, the liver can only store about 5 grams of glycogen for rapid conversion to glucose. When supplies of exogenous and endogenous glucose are exhausted, the liver must supply new glucose from amino acids and other sources. The extent to which demands for necessary glucose are met depends upon: (a) normal liver cell integrity; (b) supplies of appropriate nutrients; particularly amino acids; (c) glucosteroid promotion of glycogenesis; (d) growth hormone; (e) the secretion of stimulators of glycogenolysis such as glucogon, epinephrine, thyroid hormone, sympathetic nervous system activity, etc.; (f) autoregulatory mechanisms depending upon blood glucose concentration.

As blood glucose levels begin to decrease, growth hormone, epinephrine and glucosteroids stimulate gluconeogenesis in an attempt to reverse the downward trend. Epinephrine antagonizes the action of insulin in certain tissues by stimulating an increase in the enzyme, glucose-6-phosphatase, which blocks glucose uptake. Glucosteroids not only make certain tissues refractory to insulin stimulation but also increase those factors that antagonize insulin. As long as hormonal secretions are in balance glucogon, epinephrine and glucosteroids combined with increased activity of the sympathetic nervous system antagonize the effects of insulin so that diminished blood sugar levels are reversed within 15 to 20 minutes.

Factors Interfering with Glucose Homeostasis—A slight deficiency in enzyme systems or adrenal secretions disturbs the glucose regulatory mechanisms and interferes with attainment of normal glucose homeostasis. In addition to epinephrine and norepinephrine produced by the medulla, the adrenal cortex secretes no less than 32 hormones. In general, these may be classified as (a) glucocorticoids; (b) mineralocorticoids (aldosterone); and (c) the 17-ketosteroids which include androgens, estrogens and progesteroids. Deficient adrenal cortical hormone is characterized by a depletion of carbohydrate in blood and tissues. Factors governing the disturbance in carbohydrate metabolism include: (1) intake of food or alcohol; (2) rate of absorption from the intestine; (3) rate of deposition in the tissues; (4) rate of glycogenolysis; (5) gluconeogenesis from protein; (6) deamination from amino acids; (7) conversion of deaminized acids to glucose; (8) rate of insulin catabolism; (9) inhibitory effect on peripheral utilization of carbohydrate; and (10) direct effect on oxidation of fat and protein.

In the typical low flat curve generally encountered in uncomplicated adrenal insufficiency and pituitary-adrenal insufficiency, there is no hyperglycemia to cause undue stimulation of the islet cells. As stated by Duncan[8], "there is no proof that insulin is produced in excess of normal." It would seem more likely, therefore, in view of the absence of a stimulative hyperglycemia and the mildness of the degrees of hypoglycemia, that a mild variant from normal in the homeostatic control of blood sugar levels is at fault. Since these patients exhibit disturbances in the vegetative (autonomic) nervous system, suspicion is cast on the sympathico-adrenal component of this regulatory mechanism. Of course, it is not unreasonable to suspect that disturbances in the vegetative nervous system may play a role in producing the hypoglycemia or may have a retarding effect on the glycogenolysis via the sympathico-adrenal system.

More recently Tintera[9] reported that functional hypoglycemia is not a true hyperinsulinism, except in rare cases of pancreatic adenoma, but is due to the failure of certain glucosteroids to antagonize or catabolize insulin. This premise is based on reports showing that the adrenal, and specifically the pituitary-adrenal, function is necessary to counteract insulin-induced hypoglycemia. Since the adrenal cortex secretes the 11-oxygenated glucosteroids which oppose the action of insulin, the adrenal gland can be said to maintain glucose homeostasis by antagonizing the hypoglycemic action of insulin.

The adrenocortical hormones also increase body stores of carbohydrate; the rise in liver glycogen and blood sugar being attributed to gluconeogenesis. On the other hand, glucosteroids inhibit the utilization of carbohydrates and this factor may be even more important than gluconeogenesis in elevating carbohydrate levels. Therefore, in any stress situation which alters or interferes with the normal concentration of any of the cortical steroids, definite changes in levels of hepatic and blood sugar are to be expected. The degree of involvement will depend upon which, and to what extent, each of the adrenocortical hormones is involved.

Thus, an imbalance of adrenal cortical secretions or a hypoadrenocortical state is responsible for the low blood sugar levels in patients subject to hypoglycemic tendencies. This hypoadrenocortic state has been termed "Tintera's Syndrome" to avoid confusion with the hypoadrenocorticism or adrenal insufficiency observed in Addison's disease. Recent estimates show that between 16 and 20 per cent of the population have low blood sugar levels, 98 per cent of which are associated with Tintera's Syndrome. This syndrome must be considered as much an 'inborn error of metabolism' as diabetes and as such is inherited, but also may be acquired.

GUIDELINES TO THE DIAGNOSIS AND TREATMENT OF TINTERA'S SYNDROME

The following guidelines are intended to assist physicians in routinely screening patients for hypoglycemia associated with the hypoadrenocortical state and to facilitate diagnosis and treatment.

Symptomatology—The degree and severity of complaints varies with the level of blood sugar and the rate at which these levels decrease. Early symptoms are similar to those seen after the administration of epinephrine, i.e., fainting, tremulousness, an "inward trembling," emotional disturbances, excessive perspiration, chilliness, circumoral numbness and pallor, mild degrees of mental cloudiness, hunger, apprehension, parasthesia, palpitation, hand tremor, etc. Objectively, the patient appears to be emotionally upset, has a fixed facial expression, complains of tachycardia with a bounding pulse, pupils are dilated and the skin is pale and wet with perspiration.

As the hypoglycemia progresses, a variety and combination of symptoms occur such as headache, difficulty in concentration, disorientation, mental confusion, dizziness, faintness, diplopia, coldness of the extremities, etc. The patient may be unable to walk or may stagger; he may be depressed or restless and maniacal. Unless recognized and treated, severe hypoglycemia can cause muscle twitching, generalized convulsions followed by a retrograde amnesia and unconsciousness.

Diagnosis—The typical hypoadrenocortic patient is hypotensive with an accompanying orthostatic hypotension, an above average intelligence, a positive Rogoff's sign, a low basal metabolic rate (Ave. −14) but normal PBI, and a low flat glucose tolerance curve falling off to hypoglycemic levels. 17-ketosteroid determinations in patients not subject to stress are low or low normal. Patients are extremely sensitive to alcohol.

Prolonged hypoglycemic states are characterized by a high initial curve falling off to marked hypoglycemic levels at about the third hour. Physiologic responses during the oral glucose tolerance test may be extreme, indicating a very erratic blood sugar regulation. Fatigue, nervousness, apprehension, irritability, fainting, mental confusion, cold sweats, stupor, and in most cases, a need for physiologic support are observed.

When first seen, the patient's hands will be cold, moist and clammy. The fingers are usually long and nontapering and the index finger is usually longer than the fourth. Close questioning usually reveals the patient's com-

plaints of fatigue, tiredness, weakness, and lack of powers of concentration, have been attributed to psychoneurosis by each of the many physicians previously consulted. It is not unusual to learn the patient had seen at least a dozen or more physicians previously. A careful history in the majority of cases will reveal a family or personal history of allergy or chronic alcoholism.

A complete blood count often shows relative lymphocytosis indicative of a generalized lymphadenopathy. Eosinophilia is also present but is most marked in patients with allergies.

On physical examination vasomotor changes and generally a hyperreflexia are found, so that a concomitant diagnosis of autonomic nervous system instability can be made. In fact, the typical hypoadrenocortic patient does not know the meaning of the word relaxation. He responds well to Bellergal but not to the usual tranquilizers, sedatives, psychic energizers, anti-depressants or combinations of these.

Briefly summarized, physical findings in the male may include: a heavy head of hair, often a spotty beard, absent or sparse chest hair, asthenic habitus, absence of hair on the lower lateral two-thirds of the legs, tendency to inguinal herniation, and a positive Rogoff's sign. In the female: hirsuitism of the upper lip; flat chest; hairs around the areolae; asthenic habitus; diamond-shaped escutcheon; retroverted uterus; dry skin, especially of the legs; sensitivity in the left fourth intercostal space at the border of the sternum, particularly marked in the presence of an estrogenic deficiency; and a positive Rogoff's sign are characteristic.

Diagnosis is based on the foregoing and laboratory diagnostic aids. The latter must include a complete blood count, PBI or T-3, urinalysis, and a Folin-Wu Quantitative analysis of an oral 5-hour, 7-sample glucose tolerance test (including the first half hour). The patient should have been in a fasting state and under normal basal conditions for at least twelve hours before and during the test, and preferably all medications withheld for at least 5 days. Tolerance test curves diagnostic of hypoglycemia are appended on pages 11-14.

Treatment—The primary objective in the treatment of Tintera's Syndrome is to achieve a state of homeostasis between the endocrine glands, their dependent systems and the organism as a whole. Homeostasis in this syndrome is the establishment of a balanced relationship between the nutritional, hormonal and nervous functions (systems) of the body. The purpose, therefore, is to strive primarily to achieve a state of endocrine balance and secondly to maintain this balance by a state of mutual reciprocity. To attain these goals, there is no objection to the immediate relief of disturbing presenting symptoms through the parenteral use of such modern agents as Librium, Valium or Thorazine but only as an adjunct to treatment that will restore the normal physiologic state.

Extensive clinical trials have shown that the therapeutic approach developed by Tintera has proved markedly effective in a great majority of patients. Numerous reports from other physicians who have applied this approach confirm its effectiveness.

RECOMMENDED DIETARY AND ENDOCRINOLOGIC APPROACH TO TREATMENT

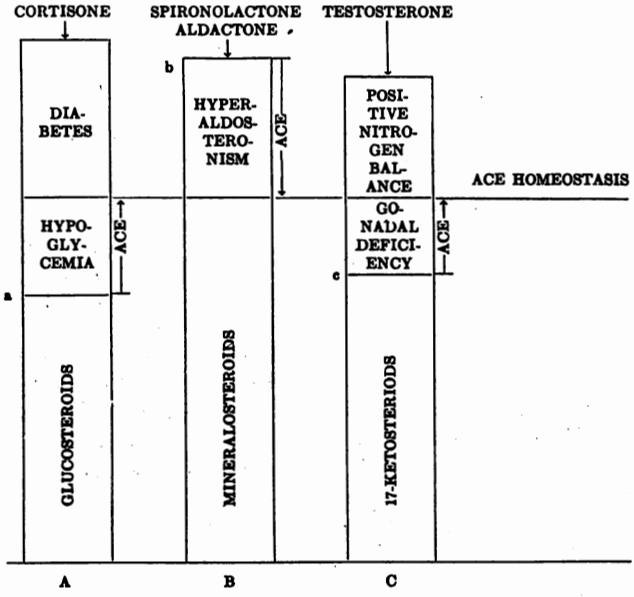
1. *Readily* available carbohydrates must be *completely* restricted and sufficient protein supplied to reverse the catabolic process. The prescribed diet is included in the appendix and provides for a low carbohydrate—moderate fat—high protein intake with sufficient vitamin content to maintain normal liver and adrenal function. A high ascorbic acid intake is particularly important since adrenal stores of this vitamin are known to become depleted during stress.
2. At least 10 cc of Adrenal Cortex Extract are given intravenously (or if impractical intramuscularly) at least once a week for one to two months. The interval between injections can then be progressively increased to two weeks, three weeks, etc. Pyridoxine, 1.0 cc (50 mg.) is added to the solution of Adrenal Cortical Extract. The rationale for the addition of pyridoxine is based on the role of this vitamin in the enzyme systems involved in regulating carbohydrate metabolism. Also for its synergistic and antihistaminic sedative effect, the optional use of 1 to 5 cc of Benadryl hydrochloride solution added to the intravenous infusion is sometimes desirable.

   "The use of Adrenal Cortical Extract, especially if given intravenously, produces a temporary feedback inhibiting the pituitary from whiplashing an already exhausted adrenal and gives a refractory period to the cells in the zona fasciculata and zona reticularis for about 4 hours. At the same time, the level of circulating glucosteroids is elevated so that corrective processes proceed in the liver. With stabilization of the blood sugar, the over-stimulated pancreas is also given a period of respite. However, if cortisone or one of its derivatives was given in place of Adrenal Cortical Extract, this steroid would have to be given in a divided dose of at least 100 mg. or its equivalent. This dose would completely inhibit the secretion of glucosteroids by the cells of the zona fasciculata. If given over an extended period, atrophy of these cells would occur and further adrenal insufficiency would result. In fact, continued use of glucosteroids will invariably increase the level of blood glucose so that diabetic levels develop."

   ACTH is also contraindicated in these patients since it would tend to whip the already exhausted adrenal cortex, producing hypertrophy and possibly hyperplasia of the cells of the zona fasciculata, but with little beneficial effect upon the mineralosteroid-producing cells in the zona glomerulosa save for further slight water retention.
3. Bellergal usual dose 1 t.i.d. but may be increased to 1 q.i.d. However there may be a preference for the convenient Bellergal Spacetabs 1 b.i.d. or ½ spacetab in the A.M. and 1 h.s.
4. For males—Testosterone proprionate 50 mg. I.M. once a week initially and methyl testosterone (Oreton) 10 mg. b.i.d.—p.c. daily buccal administration for no more than 2 Gm. over a 3 month period. To help restore nitrogen balance and further reduce demand on adrenals —

Adroyd may be used. On alternate weeks Durabolin 25 mg. I.M. instead of testosterone may be used. When intervals have been increased to one month 1 cc Decadurabolin may be all that is required to maintain a positive Nitrogen balance.

5. For females after negative Pap smear and cytology—Estrogen 5 mg. (50,000 i.u.) weekly injections and natural estrogens (Menagen or Premarin) orally daily (during child-bearing years from the 3rd through the 26th day of the menstrual cycle). If there is a history of fibroids or dysmenorrhea Progesterone may be beneficial in addition to the Estrogen (from the 12th through the 26th day of the menstrual cycle).



HOMEOSTASIS CHART — ALCOHOLISM

The mechanism for achieving and maintaining homeostasis for the hypoglycemia of alcoholism or drug addiction is well illustrated in fig. A which we reproduce from Tintera [9] on Alcoholism and Drug Addiction.

Figure A represents the state of the adrenal cortex in most chronic alcoholics, i.e., a rather severe deficiency of glucosteroids, a moderate overproduction of aldosterone, and a mild decrease in the production of 17-ketosteroids. Under basal conditions it may be assumed that the normal adrenal produces the equivalent of about 15 mg of cortisone-like activity in twenty-four hours. A 10-ml dose of adrenal cortical extract (ACE) contains 1 mg of cortisone-like activity. Normal level of glucosteroids (A), mineralosteroids (B) and 17-ketosteroids (C)—Homeostasis. In chronic alcoholism, glucosteroid activity is reduced to (a) through pre-existing relative adrenal insufficiency, enzyme interference, unresponsiveness of the pituitary, and exhaustion of the zona fasciculata cells; mineralosteroid levels (b) rise above normal; and 17-ketosteroids (c) fall—Estrogenic "neutralization" and failure of the zona reticularis. Cortisone raises the concentration of glucosteroids from hypoglycemic to diabetic levels. Adrenal cortex extract (ACE) is usually sufficient to counteract hyperaldosterone levels, by its feedback mechanism in relation to the pineal gland and anterior pituitary, but spironolactone will counteract the aldosterone directly in the presence of cirrhosis. Supplemental testosterone, in the presence of gonadal deficincy, will raise the negative nitrogen balance to a positive one.

GLUCOSE TOLERANCE CHARTS

The values used in the accompanying charts are based on the oral glucose test—Folin-Wu method and the quantitative chemical analysis of the venous sample is considered generally more reliable than the micro analysis used with the more convenient arterial finger prick samples. The micro method of course usually must be used for young children and in situations when the larger venous sampling is not practical. We have selected only six recent charts out of the thousands available in Dr. Tintera's records. It is interesting to note that the great majority of G.T.T. charts, whether of Diabetics or Hypoglycemics, usually show a fasting blood sugar in the "normal" range, thus reminding us of the utter uselessness of a simple fasting test alone.

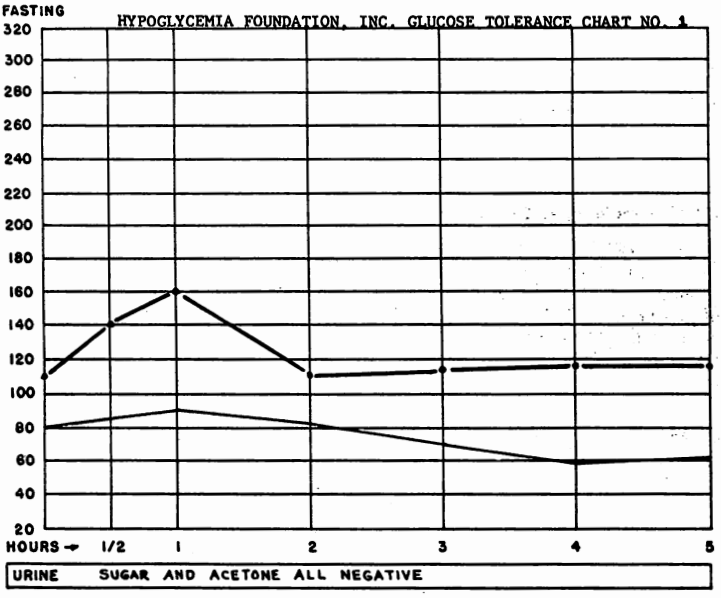


Chart #1 — female, aged 53

This graph is typical of hypoadrenocorticism even though the patient was postmenopausal. The symptoms of fatigue, irritability, flushing, etc. were promptly relieved with estrogens, adrenal cortex extract and a low carbohydrate diet.

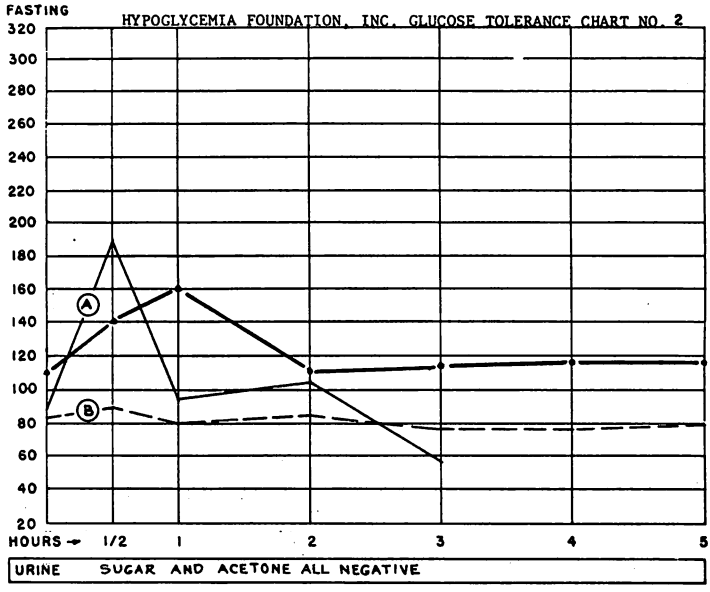


Chart #2 — male, aged 22 — Graphs A and B are 6 weeks apart

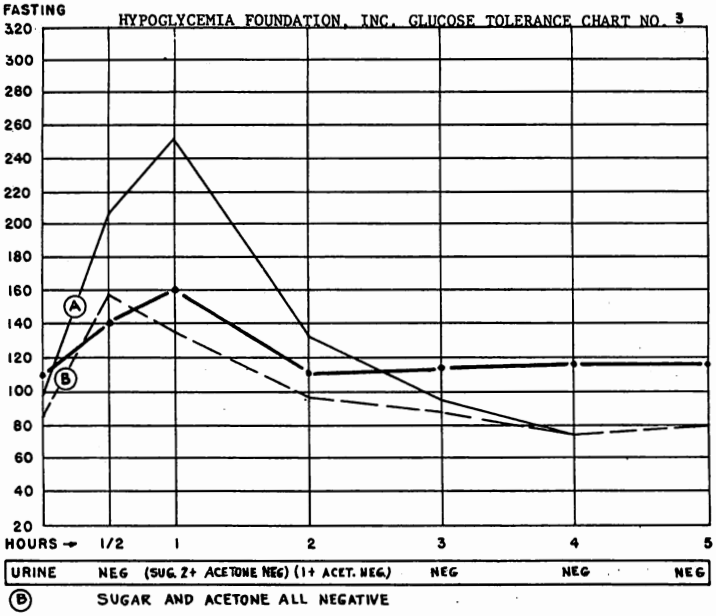
Through a laboratory error the first test was stopped at the third hour because of severe symptoms of hypoglycemia. The three hour test of Graph A was taken when the patient was complaining of hay fever, headaches and irritability; the usual desensitization treatment had been of no avail. He had been forced to leave post-graduate school due to severe fatigue and constant frontal and parietal headaches and inability to study. The only treatment which occurred between tests A and B were rest and low carbohydrate diet.

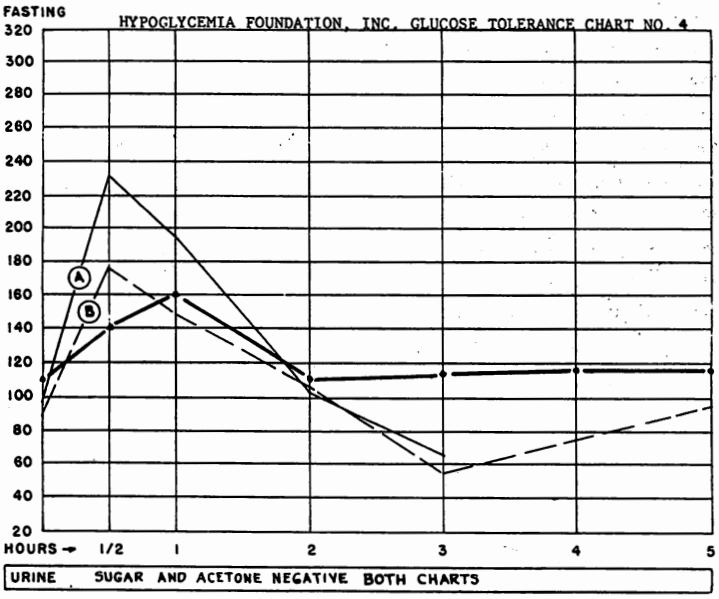
Chart #3 — male, aged 37 — Graphs A and B are 6½ months apart

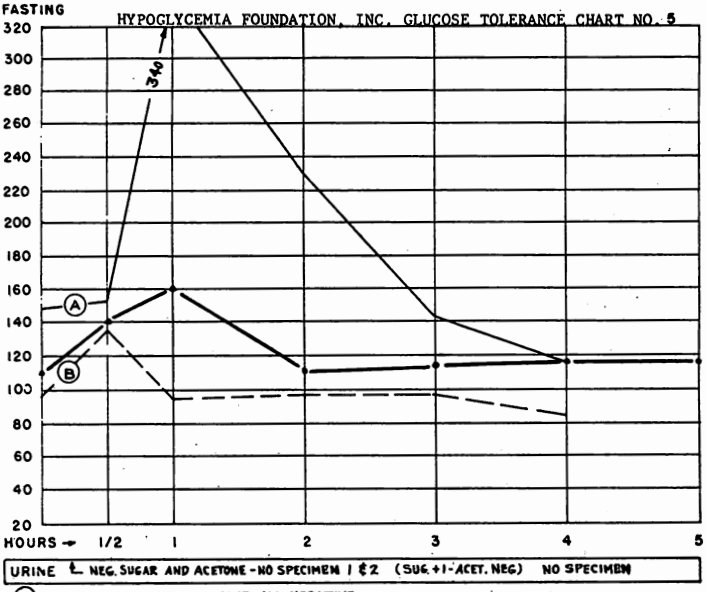
Treatment during this period was in accordance with these "Guidelines." Patient was seen weekly for one month, every two weeks for two months, then monthly. In addition to achieving a normal curve in B as shown, the obesity was corrected, vasomotor rhinitis improved, and all vital signs normal. This patient was referred for treatment by a local diabetic association because of odd findings of both hypoglycemia and hyperglycemia.

Chart #4 — male, aged 23 — Graphs A and B are 2 years apart

Previous history of juvenile delinquency, high school drop out, ran away from home, joined the Navy and subsequently dishonorably discharged, became an alcoholic and later addicted to drugs; has a family history of alcoholism. He responded well to the usual treatment, obtained his high school diploma and is doing well in college. What was a hepatic like curve in graph A now becomes an essentially normal curve for the first two hours, the subsequent fall to hypoglycemic level being due to the considerable stress of maintaining school, married life, and working after school.


FASTING
HYPOGLYCEMIA FOUNDATION, INC. GLUCOSE TOLERANCE CHART NO. 3
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
A
B
HOURS → 1/2 1 2 3 4 5
URINE NEG (SUG. 2+ ACETONE NEG) (1+ ACET. NEG.) NEG NEG NEG
(B) SUGAR AND ACETONE ALL NEGATIVE


FASTING
HYPOGLYCEMIA FOUNDATION, INC. GLUCOSE TOLERANCE CHART NO. 4
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
A
B
HOURS → 1/2 1 2 3 4 5
URINE SUGAR AND ACETONE NEGATIVE BOTH CHARTS


FASTING
HYPOGLYCEMIA FOUNDATION, INC. GLUCOSE TOLERANCE CHART NO. 5
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
340
A
B
HOURS → 1/2 1 2 3 4 5
URINE ℄ NEG. SUGAR AND ACETONE - NO SPECIMEN ℄2 (SUG. +1 - ACET. NEG) NO SPECIMEN
(B) SUGAR AND ACETONE ALL NEGATIVE

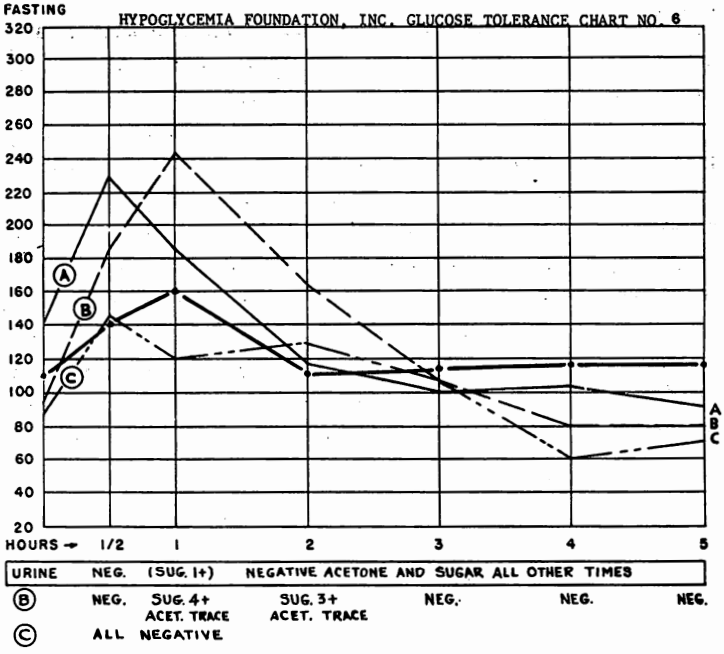

FASTING
HYPOGLYCEMIA FOUNDATION, INC. GLUCOSE TOLERANCE CHART NO. 6
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
A
B
C
A
B
C
HOURS → 1/2 1 2 3 4 5
URINE NEG. (SUG. 1+) NEGATIVE ACETONE AND SUGAR ALL OTHER TIMES
(B) NEG. SUG. 4+ ACET. TRACE SUG. 3+ ACET. TRACE NEG. NEG. NEG.
(C) ALL NEGATIVE

Chart #5 — female, aged 3 — Graphs A and B are one year apart

Was given the standard 5-hour, 7-sample glucose tolerance test, with quantitative chemical analysis (not micro method). She had been treated for epilepsy, having as many as 30 daily petit mal attacks and occasional grand mal attacks. After examination this child was considered to have an inborn error of metabolism manifest by hypoadrenocorticism with a marked lymphocytosis and eosinophilia. The first curve reveals a very severe hyperglycemia but within one year assumed a flat curve with the exception of the ½ hour specimen. Patient had been placed on a strict low carbohydrate diet and weekly injections of Lipo Adrenal Cortex. Almost immediately the seizures were reduced to nil and the anticonvulsive drugs gradually eliminated. Except for one period after having received gammaglobulin as a preventitive for measles there has been no return of seizures.

Chart #6 — female, aged 14 — Graphs A, B and C are each 6 months apart

Patient was seen for routine physical and was requested to have the usual 5 hour Glucose Tolerance Test. The only positive history was mild hayfever during preceding two years. Family history of diabetes both maternal and paternal. Since physical findings were minimal the patient was only placed on a low carbohydrate diet and was seen at monthly intervals at which time she received the Adrenal Cortical Extract intramuscularly (Lipo). Six months later a rerun of the glucose tolerance test indicated no improvement and in fact showed higher elevations of the first hour with increased glycosuria and fell to slightly lower hypoglycemic levels at the 4th hour. Treatment was intensified through intravenous injections of the Adrenal Cortical Extract (Eschatin) at more frequent intervals, q. two weeks. Finally, six months later the glucose tolerance curve was essentially within a normal range with moderate hypoglycemic reactions at the 4th hour but no glycosuria. General condition markedly improved.

REFERENCES IN DATE ORDER

1. Tintera, John W. and Lovell, Harold W., Endocrine Treatment of Alcoholism, Geriatrics, Vol. 4, No. 5, Sept.-Oct., 1949.
2. Lovell, Harold W. and Tintera, John W., Hypoadrenocorticism in Alcoholism and Drug Addiction, Geriatrics, Vol. 6, No. 1, Jan.-Feb., 1951.
3. Tintera, John W. Hypoadrenocortical State and its Management, N.Y.S. Jour. Med., Vol. 55, No. 13, pages 1869-1876, July 1, 1955.
4. Goldman, Herbert B. and Tintera, John W. Hypoadrenocorticism in Otolaryngology, A.M.A. Archives of Otolaryngology, Vol. 64, pp. 381-389, November, 1956.
5. Tintera, John W. Office Rehabilitation of the Alcoholic. N.Y.S. Jour. Med., Vol. 56, No. 24, December 15, 1956.
6. Goldman, Herbert B. and Tintera, John W., Stress and Hypoadrenocorticism, Annals of Otology, Rhinology and Laryngology, Vol. 67, No. 1, Page 185, March, 1958.
7. Goldman, Herbert B. Hypoadrenocorticism and Endocrinologic Treatment of Meniere's Disease, N.Y.S. Jour. Med., Vol. 62 No. 3, pages 377-382, Feb. 1, 1962.
8. Duncan, Garfield G., Spontaneous Hypoglycemia, p. 888, Diseases of Metabolism, W. B. Saunders Co., Philadelphia, Pa., 1964.
9. Tintera, John W. Stabilizing Homeostasis in the Recovered Alcoholic through Endocrine Therapy: Evaluation of the Hypoglycemia Factor. Journal of the American Geriatrics Society, Vol. XIV, No. 2, Page 126, Feb., 1966.

APPENDIX

ANTI-HYPOGLYCEMIA DIET

The diet is designed to be high in complete proteins, moderate to high in total fat (roughly balanced between saturated and unsaturated fats) and very low in simple or readily assimilated carbohydrates.

Foods Allowed

All meats, fish, and shell fish.
Dairy products (eggs, milk, butter, and cheese. Also recommended—1 large glass of acidophilus milk daily). Milk between meals; milk, cheese before retiring.
Salted nuts (excellent between meals).
Peanut butter.
Sanka, weak tea, and sugar-free sodas.
Soybeans and soybean products.
Low carbohydrate bread in moderation, preferably made chiefly of combined oat, soya, gluten and Jerusalem artichoke flours.
All vegetables and fruits not listed below.

Foods to Avoid

All sugars and honey.
Potatoes, corn, macaroni, spaghetti, rice.
Regular bread, pie, cake, pastries, candies.
Dates and raisins and other dried fruits.
Cola and other sweet soft drinks.
Coffee and strong tea.
All hot and cold cereals (except occasionally oatmeal).
All alcoholic beverages (narcotics, and drugs which act as stimulant or depressant, are to be avoided).

We cannot overemphasize the importance of a proper diet. The diet essentially consists of strict elimination of *rapidly absorbed carbohydrates* in order to obviate the sudden rise in blood sugar with its subsequent fall.

A hearty breakfast and between meal and bedtime feedings of milk or fruit are advised to prevent any slackening off of blood sugar levels, which are prone to occur two to three hours after eating. Salt is allowed in unrestricted amounts because of the tendency to sodium depletion. During hot weather we advise supplementary salt in the form of tablets to replace the loss caused by perspiration.

Since failure to follow the diet can negate the rest of the treatment the physician should be careful to question the patient about diet on each visit, and should provide some written diet sheet to assist the patient. The laymen's primer "Hypoglycemia and Me?" is ideal for this and related purposes, and is available from the Hypoglycemia Foundation.

Since persons on the anti-hypoglycemia diet usually lower their cholesterol levels, it may be helpful in some cases to include a cholesterol test in the initial laboratory tests so that the patient can be made aware of the improvement.

MISCELLANEOUS COMMENTS AND HELPFUL REMINDERS

1. Throughout these "Guidelines" consideration of those under 7 years of age have generally not been included. The adrenal cortical extract is safe and effective from the Pediatrician to the Geriatrician, but dosage must of course be modified to suit age and general conditions. Many other phases of the "usual" or "Guidelines" treatment do not apply, or are only partially suited to young patients, all of which will be obvious to the physician. These "Guidelines" do not specifically consider those situations of severe hypoglycemia or adrenal crisis that may result primarily from major surgery, steroid withdrawal, severe accidents and other forms of sudden and extreme stress, although obviously the administration of adrenal cortical extract in large doses is indicated in such situations.

2. Most hypoglycemics show a low B.M.R. without having hypothyroidism and over-medication with thyroid hormone could result in an adrenal crisis.

3. There is a definite preference for the **intravenous** administration of adrenal cortical extract in 10 c.c. doses (Eschatin) as having proven most beneficial. If the Lipo form (Upjohn) is used, one c.c. should be injected deep into gluteal muscles. This form is more slowly assimilated and may be used instead of or alternately with the aqueous form, 1 c.c. of the Lipo being equivalent to 10 c.c. of the aqueous—the intravenous Eschatin being generally preferred, especially at initiation of treatment. (Consider possible allergic reaction to cottonseed oil base Lipo—see note at top of page 19.)

4. During pregnancy hypoglycemics should continue to receive the usual dosages of adrenal cortical extract. For the prevention of post-partum psychoses extra injections are recommended as especially valuable just before and during labor and after delivery, for the increased general well being of mother and child, and to prevent any endocrinopathics in the newborn.

5. For alcoholics and drug addicts we point out that the treatment in general as outlined is of inestimable value. For the acute phases of alcoholism and drug addiction initial treatment would be much the same, except that the adrenal cortical extract would be given in 10 c.c. intravenous doses every four hours for the first twenty-four hours and every six hours for the next twenty-four hours and every eight hours for the next two or three days, or longer if needed, along with other supportive treatment, including psychological. For a complete coverage of this subject see references 5 and 9 on page 15.

6. Often hypoglycemics will have been seen previously by many other physicians. They may have been subject to a variety of treatments, including electric shock therapy and deep psychoanalysis, or have been incorrectly dismissed as simply psychoneurotic. Since there indeed may be a confusing psychological overlay to their extremely varied symptoms and complaints, a consideration and understanding of the whole person is paramount, and will tax the phsician's listening patience and ingenuity. For a discussion of the psychosomatic and somatopsychic dilemma frequently facing the diagnostician we refer you to an excellent article by Felix Wróblewski, M.D., which appeared in the Ames Company, Inc. "Pictoclinic," Volume 12, Number 7, 1965. More than ordinary attention should be paid to personal and family history, marital or business problems and all of the day-to-day stress situations with a view toward helping the patient avoid these, or change or control his attitudes and reactions. It is also important to relate his diet and the timing or frequency of his eating to daily stress situations. With many hypoglycemics, especially those with addictions, the need to establish the Will to be helped is very important.

SAFE AND DANGEROUS

We have learned through extensive correspondence with physicians and "patients" that there is a great deal of misunderstanding surrounding the use of cortisone and other corticosteroid hormones on the one hand, and the use of whole natural adrenal cortical extract on the other.

The purpose of this section therefore is primarily to provide information in support of the safety and effectiveness of treatment with the whole natural adrenal cortical extract as provided by several of the leading ethical pharmaceutical houses. We feel that these extracts are uniquely valuable in many instances where other medication is ineffective or dangerous or both. We feel that in addition to being safe and effective for long-term use, they can and should be also used as safe and effective substitutes for the corticosteroids in many instances. We conservatively estimate that the clinical experience of physicians whom we have contacted regarding the use of this extract covers a concurrent span of considerably more than 15 years, and the administration of well over 50,000 individual doses (10 cc or its equivalent or greater) with no report of any undesirable effects and with consistent reports of beneficial results, frequently dramati.

Cortisone or its derivatives are indeed widely used for their rapid empirical results despite the fact that medical literature is replete with warnings of the dangers of prolonged use with serious side effects, both known and unknown. Therapy with cortisone is "replacement therapy," and if used regularly creates a lifetime dependency upon the drug, with ever increasing certainty of damaging and irreversible side effects. We believe these facts are so well known to the medical profession and not disputed that we see no point in mentioning them further here.

WHOLE NATURAL ADRENAL CORTICAL EXTRACT

In addition to the vast and very favorable clinical experience with the whole adrenal cortical extract covering many thousands of people of both sexes and all ages, including infants and pregnant women, we cite the following references. We quote from the Physicians Manual prepared by the Joint Committee of the New York State Medical Society and the New York State Pharmaceutical Society: "Adrenal cortex injection U.S.P., dose, usual I.M. & I.V. 10 ml. repeated as necessary, range 10 to 100 ml." Also reference N.Y.S. Jour. Med. Vol. 62 No. 3-Feb. 1962—Goldman, Herbert B. "Hypoadrenocorticism and Endocrinologic Treatment of Meniere's Disease — 'There are no contraindications to the use of the whole physiologically balanced adrenal cortical extract in doses ranging anywhere from 1 to 100 cc. Electrolytic disturbances are never encountered provided the patient eats a sufficient amount of salt'." Also from the above (referring to ACTH and cortisone)—"their therapeutic application is not without danger as I have pointed out in previous reports, whereas whole adrenal cortical extracts aid in the recovery of the endocrine system."

We refer you to the package brochures of Parke, Davis'—"Eschatin" and Upjohn's—"Lipo-Adrenal Cortex" (which statements are of necessity FDA approved and which indicate no untoward or dangerous side effects). You will find that average daily maintenance dosages of 1 to 5 cc. of Eschatin are suggested and that large doses of 10 to 20 cc. or more every 6 to 8 hours may be required for acute adrenal insufficiency. Also that 1 cc. of Eschatin has a biological activity equivalent to that of 100 micrograms U.S.P. hydrocortisone standard, or in other words, 10 cc. of Eschatin has 1,000 micrograms or 1 milligram of hydrocortisone like activity. It will be seen that 1 cc. of Upjohn Lipo is also equal to 1 milligram of hydrocortisone like activity and further that the Upjohn literature indicates that in the presence of infection or other complications the dose should be increased to 2 to 5 cc. or more daily, which would obviously be the equivalent of 50 cc. of Eschatin. NOTE—because Lipo has a cottonseed oil vehicle, possible allergic reaction to this oil should be considered before administration. Upjohn also provides an aqueous form for intravenous or intramuscular injection, which, however, contains alcohol and is usually painful.

Wilson Laboratories provide a product labeled Adrenal Cortex Injection N.F. and their package brochure advises that the usual dose is 10 cc. repeated as necessary, intramuscularly or intravenously with no known toxicity or side effects and no known contraindications within the suggested dosages. (One cc. contains biological activity equivalent to 100 micrograms of U.S.P. hydrocortisone standard.) NOTE: The aqueous forms of Parke, Davis and Upjohn are bovine while Wilson Laboratories' aqueous and Upjohn's Lipo are porcine.

Also from the New York State Journal of Medicine, Vol. 55 No. 13, July 1, 1955. "The Hypoadrenocortical State and its Management"—John W. Tintera, M.D. "Depending upon the severity of the condition 10 cc of adrenal cortical extract are administered intravenously at varying intervals ranging from every four hours initially to as long as once a week." Also from a Harvard University Press textbook, "Functional Endocrinology—From Birth Through Adolescence" (authored by four physicians, 1952) page 205, "Aqueous adrenocortical extract is safe to use, and when given in adequate amounts, it covers all the hormonal needs of a hypoadrenocortical organism. It is practically impossible to give a toxic overdose. For these reasons it provides a very good means of treating patients who are suffering from hypoadrenocortical crisis."

We also cite from the American Medical Association Archives of Otolaryngology, Nov. 1956, Vol. 64—Goldman & Tintera—"Adrenocortical extract may be required prior to, during, or following surgery, or at all of these times. There is no need for concern over the electrolyte and water balance of the body. If indicated, however, dextrose or saline may be given as desired, with doses of adrenocortical extract ranging from 5 to 200 cc."

From the February 1966 Journal of the American Geriatrics Society we present five pertinent quotations from an article entitled "Stabilizing Homeostasis in The Recovered Alcoholic Through Endocrine Therapy—Evaluation of The Hypoglycemic Factor"—"Treatment embraces restoration of a state of homeostasis of all endocrine factors involved, principally

by the administration of adrenal cortical extract, adequate nutrition and guidance of a psychological nature."—"Every recovered alcoholic requires at least 10 c.c. adrenal cortical extract intravenously once a week for one to two months, after which time the intervals may be gradually increased to two weeks, three weeks, etc."—"In the patients who have received adequate treatment with adrenal cortical extract, the blood sugar curve has approached that of the normal, and in practically every instance the glycosuria was eliminated. In contradistinction, cortisone has a tendency to produce a curve similar to that of the diabetic, and also to induce glycosuria." —"The use of adrenal cortical extract, especially if given intravenously, will produce a temporary feedback action to inhibit the pituitary from whiplashing an already exhausted adrenal and give a refractory period to the cells in the zona reticularis and zona fasciculata for about four hours."— "So far as we have been able to ascertain, only one course of treatment can correct this vicious hyperglycemic-hypoglycemic reaction from occurring, and that is through the use of the whole adrenal cortical extract plus any other adjunctive preparations which might be indicated by a careful history and physical examination, including a minimum of laboratory procedures."

A goodly portion of the clinical experience, with its first-hand long term knowledge of the use of the whole natural adrenal cortical extract, stems from more than twenty years of use by J. W. Tintera, M.D., who is familiar with all of the references cited here, and concurs in the opinions we have expressed with regard to the safety and efficiency of adrenal cortical extract therapy, having witnessed it in his own long practice and in the hands of many physicians who have consulted him on this subject over the years.

In view of the above and the vast totally favorable clinical experience which exists, we are thoroughly confident that the whole natural adrenal cortical extract is uniquely valuable. Balanced in nature's own proportions, it provides a synergistic combination of 32 or more hormones which no man-made compound can duplicate. It is certainly not at all related *therapeutically* to cortisone or cortisol, or to any synthetic or extracted steroid-hormone fraction. Adrenal cortical extract provides the basis for a "no risk" therapeutic regimen that is at once ataractic in its effect as well as therapeutic, being the only agent we know about which provides a *"rest and recovery"* period for the adrenal-pituitary-thyroid-axis system instead of the life long dependency inherent in cortisone and other "replacement" therapy.

The following additional references with regard to the safety, efficacy, and dosages of the whole natural adrenal cortical extract were not included originally under the assumption that these basic references were well known and readily available to the physician. However, it now seems that these too should have been supplied for the convenience of our readers. (The original texts are so extensive that our references here are necessarily brief and selected.):

THE DISPENSATORY OF THE UNITED STATES OF AMERICA – 25TH EDITION: "The usual *dose* of adrenal cortex injection is 10 ml. intramuscularly or intravenously, with a range of 10 to 100 ml. The dose is repeated as often as necessary (see above for details). The maximum safe dose is limited by the trace of epinephrine (up to 0.2 mg. per 100 ml.) remaining in the injection."

THE NATIONAL FORMULARY–TWELVTH EDITION–OFFICIAL FROM SEPTEMBER 1, 1965: "Category – Mixed natural adrenocortical hormones. Usual dose – Intramuscular and intravenous, 10 ml., repeated as necessary."

MODERN DRUG ENCYCLOPEDIA AND THERAPEUTIC INDEX 1965: "Generic Name: Adrenal cortex extract. Description: An extract of natural adrenocortical hormones obtained from the adrenal glands of domestic food animals. Each cc contains the biological activity equivalent to 100 mcg. of hydrocortisone, as assayed by the U.S.P. method; 9 mg. sodium chloride and alcohol 10%.

"Action and Uses: *For use* in the maintenance of patients with chronic adrenal insufficiency. More intense hormonal therapy is recommended for prevention of temporary adrenal insufficiency induced by adrenal surgery, overwhelming systemic infections (Waterhouse-Friedrichsen syndrome) and for Addison's disease in crisis.

"Administration: *Subcutaneously, intramuscularly,* or *intravenously.* The therapeutic dose varies widely, depending upon the degree of adrenocortical insufficiency, the condition of the patient, and the presence of infection and other complications. In general, dosage should be governed by the clinical response. Maintenance in Addison's disease–total daily dose is 1 to 10 cc. The administration of supplementary sodium salts is indicated adjuvant therapy. In the presence of infection or other complications as much as 50 cc to 100 cc, given within a few hours, may be required. One plan of treatment combines intermittent, intramuscular or intravenous injection (10 to 20 cc hourly until response is established) and continuous infusion (30 to 50 cc per 500 cc of infusion solution)."

NEW AND NONOFFICIAL DRUGS 1964: "The cortex of the adrenal gland is essential for life. Adrenalectomized animals die in a few days. Effects of acute adrenal insufficiency, in disease or after experimental procedures in animals, include blood concentration, low blood pressure, gastrointestinal disturbances, asthenia, subnormal temperature and low basal metabolic rate. There also may be loss of sodium and retention of potassium in most species, loss of carbohydrate reserves with hypoglycemia and retention of nitrogenous products in the blood. Injections of suitable ex-

tracts of adrenal cortex that contain little or no epinephrine may restore even moribund animals to apparently vigorous health for as long as the injections are continued, especially if sodium chloride and water are administered concurrently.

"*Adrenal Cortical Extracts*—Extracts of the adrenal cortex contain several potent substances that influence electrolyte, water or carbohydrate metabolism to various degrees. These substances tend to regulate the number of circulating eosinophils and the activity of thymus and lymphoid tissue. They also exert influence over skin pigmentation in human beings. However, as demonstrated on small animals, no one of these substances, and no synthetic substance possesses all of the facets of a potent cortical extract. "Adrenal cortex extracts have been assayed in many ways. There are advantages to each method, but the maintenance of life in the adrenalectomized animal is the most significant measure of activity for such extracts. The Council has recognized the assay method devised by Pfiffner, Swingle and Vars."

This publication has been compiled to provide in collected form the major papers of John W. Tintera, M.D. This collection does not include all Doctor Tintera's papers..it provides those which represent his concept by classification of pertinence, allergy, alcoholism, schizophrenia, and the hypoadrenocortical state.

"Stabilizing Homeostasis in the Recovered Alcoholic Through Endocrine Therapy: Evaluation of the Hypoglycemic Factor" in Doctor Tintera's opinion best illustrated his basic concept of the hypoadrenocortic syndrome and was used as the vehicle for the exposition of his concepts.

Doctor Tintera's work represents a milestone in the application of endocrine evaluation and treatment of a number of subtle "stress induced syndromes". He viewed the patient as a unified "whole" and his concept should be properly classified as psychoneuroendocrinologic.

The purpose of treatment is to achieve HOMEOSTASIS and the continuation of HOMEOSTASIS, thereby permitting the patient to achieve and retain physical and emotional stability.

There is considerable confusion concerning the hypoglycemia factor. In Doctor Tintera's view, hypoglycemia is a finding, a common finding, in a number of stress syndromes, and correction of the hypoglycemic factor, through appropriate therapy, in the majority of instances, effects homeostasis.

The Adrenal Metabolic Research Society of the Hypoglycemia Foundation, which incorporates in its structure the John W. Tintera, M.D. Memorial Fund, is devoted to the investigation of the hypoglycemias, their etiology and significance. The Foundation will be pleased to provide additional data and cooperate with physicians and laymen in the pursuit of answers to the widespread hypoglycemic syndrome.

Marilyn Hamilton Light
Executive Director

March 30, 1972