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THE TREATMENT OF ASTHMA*
WITH SPECIAL REFERENCE TO THE ORAL USE
OF THE ADRENAL HORMONES AND
SODIUM CHLORID

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STUDIES in protein sensitization in allergy have been of great value in identifying that group of individuals who suffer from allergic manifestations, but they have contributed little to our knowledge of the underlying pathologic physiology of the condition. It would seem more reasonable to pursue the study of the state of hypersensitivity rather than that which plays upon this hypersensitivity.

ASTHMA A VEGETATIVE IMBALANCE

It is necessary to consider the cells of the tissues which manifest the allergic paroxysm, the nature of their response and the physiologic state responsible for it, and also the individual and his constitutional physiologic imbalances which predispose to sensitization. The discovery of how the various precipitating factors—physical, chemical,

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and biological—act upon the physiologic imbalance of the individual and precipitate the allergic reaction in the cell should lead to effective preventive and therapeutic measures.

We must broaden our conception and get away from the idea that precipitating factors are always chemical substances, usually protein, brought in contact with the cells, directly, or through the body fluids. It has been the experience of all that meteorologic conditions influence the occurrence and severity of asthmatic paroxysms. In other than pollen types, asthma is generally more severe in winter and spring than in the summer. Approaching cyclonic disturbances have a definite aggravating effect. Asthmatic paroxysms are usually more common at night than during the day. W. F. Petersen¹ shows these phenomena are accompanied by a relative tissue alkalosis. Severe nervous strain and infections with the accompanying exhaustion of the sympathetico-adrenal system frequently initiate allergic phenomena.

The allergic constitution is characterized on the part of the nervous system by an excess of parasympathetic nerve action; and on the part of the electrolytic system as a low calcium-potassium balance (Pottenger)^{2,3,4,5,6} on the part of the endocrine system by a hypofunction of the sympathicotrophic hormones; on the part of the body fluids by an increase in potassium and an instability of the water balance (Peyton)⁷; and on the part of the tissues by a tendency to alkalosis. The sensitized cells show increased permeability and hyperactivity.

When we consider the numerous and diverse factors which may apparently produce the same type of response in the cells, and that allergy is localized as to tissues and not general (although it may be multiple), we can hardly expect that a

single mechanism could be involved in its production; nor is it likely that a single therapeutic measure would be the most effective in all instances. However, in a physiologic balance, a deficiency in one factor, if not too great, may be adequately compensated by an overabundance of a similarly acting different factor. Hence in therapeutics a certain measure may be of value, even though the condition which it attempts to correct may not be primarily at fault. Measures of this type are those which attempt to increase the acidity of the tissues, to change the concentration of the mineral elements of the body fluids, to change the activity of the autonomic nervous system and to change the endocrine balance.

PHYSIOLOGIC BASIS FOR TREATMENT OF
ASTHMA WITH ADRENAL HORMONES

In this paper we are reporting the initial clinical effects of the use, by mouth, of the hormones of both the medulla and cortex of the adrenal gland and sodium chlorid.

Adrenal extracts have long been used in the treatment of allergic manifestations. Crude fresh extracts were employed in the treatment of hay fever before Takamine⁸ published his work on adrenalin in November, 1901. Since that time epinephrin has been one of the most widely used of all drugs in the treatment of asthma. The work of Hartman,⁹ Swingle and Piffner,^{10,11} and Kendall¹² on the active principle of the cortical portion of the adrenal has made further inquiry into the relation of the adrenal gland to allergy advisable. Chance observation led us to pursue this subject, and our investigation has yielded encouraging results.

Inasmuch as we started this work as a clinical study a short review of the first stages would be instructive. In August, 1932, we began feeding

whole beef adrenal glands to a group of patients suffering from asthenia. These were administered within a few hours from the time they were removed from the animals. Our reason for this was because of the various reports connecting this condition with adrenal deficiency. The improvement in their energy and sense of well-being was very definite. In September, 1932, a child whom we were treating had been suffering from continuous asthma for several months and was completely exhausted. With the idea that we might at least relieve his exhaustion we gave him seven grams of whole raw beef adrenal gland, which was first ground and then mixed with peanut butter. That night the child became free from asthma and remained so for three days.

This gave the impetus to the studies leading up to the present report. Later, one of us (F. M. Pottenger, Jr.) began extracting the cortical hormone, as described below. A large amount of crystalline epinephrin was obtained as a by-product, the cortical extract being practically free. Therapeutic tests were made with both by mouth, because the whole gland was effective by mouth. We found both fractions to be effective, and when given together they were more efficacious than when given alone.

The full physiologic action of the adrenal gland is not yet understood. The question arises whether or not there is more than one hormone in the cortex. In the raw gland-feeding experiments, adult patients rather generally noticed an increased libido, which effect is not produced by the extract. Further, one gram of raw gland is therapeutically equivalent to about 100 gram equivalent of extract. The extract contains the active principle isolated by Swingle and Pfiffner, since the first three steps of their original technique is followed in making our product; and it has been shown to

be active by prolonging the life of completely adrenalectomized cats.

Our knowledge of the physiology of the active principle of the cortex is based on studies of adrenalectomized animals and their response to the hormone. The most striking feature is the rapid loss of weight of the animals after removal of the adrenals. This has been shown to be due to loss of sodium (Rubin and Kirck),¹³ with corresponding loss of its chlorid salt. Accompanying the loss of body fluid and base is an increasing acidosis and rise in the nonprotein nitrogen of the blood (Harrop).¹⁴ At the same time, fluid is drawn out of the tissue cells to replace the ebbing body fluids. As the cells contain a high concentration of potassium, the blood potassium rises and at death reaches a height found in acute potassium poisoning. There is no change in the blood calcium. All these changes could be largely, if not entirely, explained on the basis of loss of sodium. Thus, as the thyroid regulates iodine metabolism, the parathyroid calcium metabolism, it seems that the adrenal cortex regulates sodium metabolism. Accordingly it was proposed by Loeb¹⁵ to use sodium chlorid in Addison's disease. By giving a sufficient amount of salt without the cortical hormone the symptoms of Addison's disease can be alleviated in all but extreme cases.

The anaphylactic action of the adrenal hormones has been studied by Wolfram and Zwemer.¹⁶ They found that either epinephrin or the cortical hormone would protect against anaphylactic shock. The action of epinephrin was more prompt; that of the cortical extract more prolonged. If the epinephrin was given after the cortical hormone, its effect was enhanced.

We have had one patient on extract for two years, but have noticed none of the antihormonal

effects which Collip¹⁷ has observed in case of the thyrotropic hormone of the pituitary.

COMMENTS ON THE CLINICAL EFFECTS

It is proper at this point to attempt to explain the observed clinical effects which we are reporting, on a physiologic basis. All physiologic balances or imbalances—nervous, endocrine or humoral—manifest themselves primarily through their action on the tissue cells. The type of activity of the various body cells is more or less specialized, depending on the function of the organ to which they belong; but the cells can only respond by a change in their state of activity, which in turn is dependent on their permeability. There is considerable evidence to indicate that the cellular membrane is composed chiefly of phospholipins and cholesterol in definite proportions, the former favoring permeability and the latter inhibiting it. The permeability of the whole membrane is again influenced by the electrolytes in the surrounding fluid. The most important of these electrolytes are potassium and calcium. Changes in the ratio of potassium to calcium ions changes the permeability and activity of the cell. A relative increase in potassium ions increases permeability, a relative decrease decreases the permeability. Stimulation of the parasympathetic nerves and an alkalosis increases the potassium/calcium ratio. Stimulation of the sympathetics, epinephrin and an acidosis decrease the potassium/calcium ratio. In the experiments quoted above, it was shown that the deficiency of sodium developing in adrenal insufficiency was partially compensated by replacement from the base of the cells, largely by potassium. This suggests that there is a balance between the potassium of the cells and the sodium of the body fluids.

There is an increase in the blood potassium (Kylin)¹⁸ in asthmatics. The action of the cortical hormone may be to decrease the potassium by raising the blood sodium. This is also the theoretical basis for giving salt by mouth. (One action of adrenalin has long been shown to be through increasing the effect of calcium on the cell membrane.) We attempted to get indirect evidence of this action of sodium through study of the blood chlorids. We found in a group of asthmatics that all the blood chlorids were within the lower half of the accepted normal limit, or subnormal. The chlorids of thirty-three of the fifty patients reported on at this time averaged 454 milligrams per 100 cubic centimeters of whole blood, the lowest being 357; the highest, 496. In spite of the low balance, heavy salt intake, together with cortical hormone, failed to give a significant rise such as is seen in Addison's disease.

Disturbance in the water balance of the body has been observed to accompany allergic manifestations. We have noted a regular loss of weight in patients on elimination diets when a food to which the patient is sensitive is added. This may amount to from three to four pounds. Foldes¹⁹ describes a water retention in migraine, the attacks sometimes occurring while the retention is developing; at other times, during its excretion. We do not know just what is taking place in the sensitized tissues during these changes in the water balance of the body. The disturbance in the water balance may be a link in the chain of physiologic reactions precipitating the allergic paroxysm or it may be a side effect. In any event the hormone of the adrenal cortex has been shown to play a vital rôle in the maintenance of the water balance of the body; and in allergy its administration, either in supplementing a deficient supply

from the patient's own adrenals, or by compensating for a deficiency in some other gland may serve to stabilize the water balance.

We have mentioned the rôle played by the nervous system and endocrine systems in regulating physiologic balances, and also that meteorologic conditions have profound effects. However, we must not forget the great but as yet poorly understood potentialities of diet, or rather nutrition. Few physicians have the courage, and fewer the knowledge, to improve on the definition that a normal diet for a normal person is the food he likes cooked the way he likes it, and we can rest in comfort with the knowledge that nature provides an overabundance of the necessary factors and the normal body has a tremendous power of selection and economy of consumption. However, in patients where a physiologic imbalance exists we must include diet in our study of cause and effect. This study should not only include calories, fats, carbohydrates and proteins, but also mineral content, vitamin content and the reaction of the ash of the diet and the physicochemical state of the food; and not so much the oral intake of these substances as their absorption and utilization in the body. We hope to report certain dietetic studies at a future date. However, in this connection it is interesting that a careful dietetic study of a group of our asthmatics showed a very low sodium chlorid intake in all cases.

Another observation for which we have no explanation but which we feel supports our hypothesis that there are numerous and diverse factors, various combinations of which may allow the development of sensitization and may determine the tissue in which sensitization develops is that, in our experience, hydrochloric acid in large doses very often effectively controls pollen hay fever, while our results with the adrenal hormones and

salt have been much less satisfactory. On the other hand, we have seen less benefit, as a rule, to asthmatics from hydrochloric acid, while the adrenal hormones and salt have given gratifying results.

We have employed epinephrin in doses of one-sixteenth grain three times a day. The cortical hormone is prepared as follows: The fat is removed and the glands are subjected to the first three steps of the Swingle and Pfiffner technique. Then the residue is dissolved in alcohol, the alcohol is removed under vacuum, and the residue is redissolved in alcohol, after which the less soluble fractions are precipitated by chilling. The extract is then standardized, so that one cubic centimeter equals ten grams of whole raw gland. One-half to one cubic centimeter is given in orange juice two or three times a day after meals. The sodium chlorid is given as table salt in doses of from three to six grams in eight ounces of water one-half hour before meals. If the morning dose causes loose stools, the salt should be given after breakfast. Our patients are given as much rest as possible. Those institutionalized are put to bed until the asthma is controlled. Sedatives and hypnotics are given when indicated. Although these patients were on a special diet it is in no sense an elimination diet.

BOTH EPINEPHRIN AND THE CORTICAL HORMONES
ARE PROVED TO BE ACTIVE WHEN
GIVEN ORALLY

We are limiting this report to the results observed in the first few weeks of treatment. Clinical experience has shown that the other factors in the regimen do not produce the results described. We do not know how long the adrenal hormones must be kept up. We have evidence that desensitization has been accomplished by long-

continued use of the extract, but our cases are too few to permit us to make a definite statement on this particular point at this time. How big a factor the nutritional measures which we use in these cases is has not yet been worked out.

The sodium chlorid by mouth produces the following effects: (1) Improvement in the feeling of well-being; (2) improved bowel function, the stools containing a larger amount of moisture though formed; (3) some lessening of the frequency of asthmatic attacks, and (4) fortification of the effect of the cortical extract. In no case has salt alone, in our experience, controlled asthma, but the combined use of salt and hormones has lessened the amount of hormones necessary to relieve the patient.

In nineteen children treated in the clinic, and in nine adults institutionalized, we have not failed in a single instance to relieve the asthma. The children have almost universally been the type who have considerable bronchitis with bronchiectatic change. However, the asthma has been precipitated again in some cases by colds or other acute infections or overexertion. In no case has the recurrence proved refractory to subsequent treatment. However, the discussion of the prolonged treatment of asthma is outside the scope of this paper, as we are limiting ourselves to the value of these measures in freeing the asthmatic patient from his attacks.

Our experience with the adrenal hormones and salt has been much more limited in other allergic conditions. It seems to be of value in migraine. The cortical hormone combined with epinephrin ointment has been quite effective in controlling eczema. As we mentioned above, it has not been as satisfactory in hay fever as in asthma.

THE EFFECTS OF EPINEPHRIN AND THE CORTICAL
HORMONE SHOWN IN FIFTY CASES

The accompanying chart (Table 1) summarizes the results of our therapy. The patients are segregated as to the type of therapy used, and whether or not the patient was treated institutionally or in the out-patient clinic. In all cases the daily consumption of a large quantity of sodium chlorid was insisted upon.

Of the fifty cases reported, the results of all but two have been satisfactory. Neither of these patients was able to submit to a program of rest, which is so essential to the relief of their condition, but both patients experienced considerable increase in energy and a feeling of increased well-being, although neither was completely freed of the attacks.

Although we have discussed the result of treatment only from the standpoint of relief from the paroxysm, in summarizing our results we have divided the relief obtained into "moderate improvement" and "marked improvement." Both groups obtained satisfactory relief from the immediate attack, but this classification is determined by our knowledge of their subsequent course. Relief in these instances was obtained in from a few minutes to five days. In speaking of relief we do not mean temporary relief, such as is obtained from a single injection of epinephrin, but a more permanent relief which leaves the patient free from symptoms. In those patients classified under "moderate improvement," recurrence of symptoms has been noted, with colds and exhaustion states, while those showing "marked improvement" have been free for from three months to two years.

TABLE 1.—Results of Treatment by the Use of Adrenal Hormones Administered Orally

Type of Patient	Type of Therapy	Improvement			Total Number Patients
		Slight	Moderate	Marked	
In-patients	Epinephrin only	0	1	1	2
In-patients	Epinephrin only	0	2	3	5
In-patients	Cortical extract only	0	0	1	1
Out-patients (children)	Cortical extract only	0	0	12	12
Out-patients (adults)	Epinephrin and cortical extract	2	7	19	19
In-patients	Epinephrin and cortical extract	0	2	4	10
	Epinephrin and cortical extract	0	0	2	2
	Miscellaneous therapy ²	2	18	30	50

¹ Three of adult in-patients treated less than two weeks. In each instance, relief of symptoms was obtained.

² Use of epinephrin ointment and eschatin in conjunction with oral epinephrin.

The following is typical of the type of children that we have been treating:

CASE No. C-10434.—Male, aged eight years. Suffering from severe asthma. Treated with cortical extract and epinephrin orally, and a diet giving acid ash.

At the age of three years the patient suddenly developed asthma. He was given potassium iodid, ephedrin, lactose, Maltine, and cod-liver oil, with no appreciable effect. In the spring of 1932 he was found sensitive to 57 of 300 antigens. He was given treatment without relief. In 1933 his asthma became worse, and in December was extremely distressing. His attacks were usually preceded by colds and were accompanied by severe coughing and wheezing. The attacks were milder during the summer and more severe during the winter. He gave a history of having little energy and always complained of being tired.

Examination revealed a red-haired, pale-skinned child of the angiospastic pseudo-anemic type. He had hypertrophied tonsils and enlargement of the cervical lymph glands. His chest showed many rhonchi and râles throughout, and was markedly emphysematous. The x-ray showed increased linear markings radiating from the hilum, suggestive of chronic bronchitis. Calcified nodes were present within the hilum on both sides.

A diagnosis of chronic asthma, with bronchitis, was made.

Although the patient had several colds, after treatment was begun they were less intense. After treatment began, February 10, 1934, he did not have a single paroxysm of asthma. During the first half of the school year, 1933-1934, he had missed school nearly half of the time, on account of colds and asthma. During the second half he lost only two weeks, and during the year of 1934-1935, he did not lose a single day of schooling. Previously he was unable to play with other children; but now he is interested in athletics and is a leader in sports, and it is with the greatest difficulty that he is kept from playing too hard. Severe physical exertion brings on coughing spells. During the eighteen months under treatment he has gained fourteen pounds, and his physical condition is excellent.

SUMMARY

1. Asthma (allergy) is a condition in which all systems of vegetative control of cellular activity—nervous, endocrine, and electrolytic—may be in imbalance.
2. The accidental discovery of the usefulness of cortical extract in the treatment of asthma.
3. Both epinephrin and the cortical hormone are proved to be active when given orally.
4. The effects of epinephrin and cortical hormone in the control of the asthmatic state is illustrated in the treatment of fifty patients.

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