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Cortisone in Allergic Asthma

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I. CORTISONE IN ALLERGIC ASTHMA

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"All is not asthma that wheezes."[1] Tho pert, this is not true. By definition all is asthma that wheezes but all asthma is not allergy. We are here discussing allergic asthma. The mechanism of asthma is dependent upon bronchial obstruction. It is a functional condition of the bronchi "in which periodic or spasmodic attacks of dyspnea with a prolonged expiratory phase are associated with wheezing, cough and expectoration of tenacious sputum."[2] Allergic asthma must, therefore, be differentiated from all other conditions causing wheezing and cough---bronchitis, cardiac asthma of left heart failure, inflammatory lung lesions, and wheezing due to pressure of an enlarged thymus, enlarged glands, bronchogenic tumors, aneurism, and foreign bodies. This differentiation is extremely important most especially in conditions where Cortisone and ACTH would be, in fact, contraindicated.

The history of asthma is a long one. As far back as the 5th Century B.C.,[3] there are references in Greek writings to conditions resembling asthma but no real differentiation is made between this condition and dyspnea. Helmont[4] and Willis[5] in the 17th Century clearly emphasized the spasmodic nature of asthma and in the last of the same Century, Sir John Floyer[6] was the first to note that the cause was "contracture of the muscular fibers of the bronchi." Shakespeare[7] knew the condition we call asthma. He refers to "wheezing lungs" in Troilus and Cressida (Vi) and in the same work uses the term "tisick" when Pondarus says "a whoreson tisick, a whoreson rascally tisick so troubles me---that I shall leave you one of these days". (V,iii) As noted from the text, he must have believed the condition to be due to syphilis. To this day the laity in the Appalachian mountains still speak of asthma as phthisic. Again Samuel Johnson says "my diseases are an asthma and what is less curable, seventy-five".

It was not until 1811 that Robert Bree in "Disordered Respiration"[8] indicated that hypersensitivity was the true etiologic factor in allergic asthma. He himself was an asthmatic which, as usual, made him the more aware of the symptoms and signs of the disease. He writes "hair powder has been observed in many instances to bring on, first sneezing, then by association of muscles, more powers are put in action to expell irritating matter, which may possibly have only touched some points of the trachea uncovered by mucus". He further notes "an itching of the skin, of the breast and neck, is frequently a symptom in the asthmatic paroxysm, sometimes preceding the violence of the fit and generally declining as the agony of respiration increases". That there is nothing really new under the sun that some one else has not observed and probably recorded is pointed out by Feinberg[2] for 120 years later a medical journal records the "new" sign of allergic asthma "itching of the chin, neck and chest". It was Salter[9], however, in 1859 who placed this conception of sensitiveness on a firm clinical foundation. He also stated that attacks of asthma are caused by contraction of circular muscles around small bronchi; that heredity is an important factor; that attacks may be provoked by many of the allergens we speak of today---foods, animal emanations, drugs. He well described the consequences and complications of asthma---thickening of bronchial musculature, bronchiectases, pulmonary stasis, atelectasis, passive congestion, right heart hypertrophy and dilataion, cor pulmonale, emphysema and the typical asthmatic physique.

The treatment of asthma dates to the era B.C. It would be hard to find any condition in which more drugs and procedures have been tried. The very multiplicity of drugs throughout the centuries speaks for itself but real progress is linked with the development of the concept of and research in anaphylaxis and allergy.

In 1910 Barger and Dale[10] isolated histamine beta imidozolethylamine from ergot and in 1911[11] found histamine in the intestinal mucosa. Its precursor, histidine, is a common cell constituent.

Best and McHenry[12] reported it is found most often in barrier tissue such as skin and intestinal mucosa. Histidine may be converted to histamine by the removal of a carboxyl group not only by antigen antibody reaction but also by bacterial action.[13]

Dalton[14] in a recent paper on the role of the eosinophile in allergy, suggests that it is not the antigenic protein itself that calls for the eosinophilia but the antibody. He theorizes that antibodies being chemotactic for eosinophiles produce a localized eosinophilia at the site of the shock tissue, and as eosinophile production is increased a circulating eosinophilia usually develops. At the local site of antigen-antibody reaction, eosinophiles are broken down which releases histamine.

Histamine tends to act on cells that are ennervated by the autonomic nervous system and is known to produce constriction of smooth muscle, dilation and increased permeability of capillaries and to act as a secretagogue on the glands of exocrine secretion. It appears in the blood immediately after administration of an antigen, and in the guinea pig the phenomenon of anaphylaxis and the administration of histamine seem to be identical.[15]

While, as pointed out by Dragstedt[16] histamine release is at least a major factor in the causation of allergic symptoms, it is probably not the only factor. It is because of this that Sir Thomas Lewis[17] called the factor "H substance", and said, "I shall speak of an H substance, and in using it shall mean any substance or substances liberated by the tissue cells which exerts on the minute vessels and nerve endings an influence culminating in the "Triple Response". The relationship between the amount of histamine activity in the blood and the symptoms is not as direct as one would desire. The identification of histamine in the blood is always difficult, as Dragstedt has repeatedly pointed out. As Katz[18] has shown, there is always the problem of differentiation between histamine bound to cells and histamine in the free state. He[19] added horse serum in vitro to the blood of a rabbit sensitized with that serum and noted that the cell-free plasma showed a great increase of histamine. Rose and Brown[20] got essentially the same results and repeated the experiment with use of egg sensitive rabbits with the same effect. While we thus have evidence from these experiments as well as others[21,22] that there is a transfer from the bound to the free states, we as yet do not have definite evidence that the reverse is also true. There are indications that it is.[21] This change in the state of histamine makes it hard to assay its exact role in allergy. In the main, however, the histamine theory is plausible, though the antihistamines have proven of very little practical help in the treatment of asthma.

In discussing the treatment of allergic asthma, it would be well to review here again a concept of what takes place in the patient. As in all patients with allergic symptoms, we first must have a so-called asthmatic state---a state defined by Rockemann[1] as an inherited one in which a patient is more likely to develop these symptoms than do others in exactly the same environment. It is the soil in which allergy in the usual sense can flourish. We have further the capacity in these individuals to develop sensitiveness and to produce or react to an H substance so as to cause a variety of symptoms of vasomotor origin. In asthmatics, allergens---be they ingestants, contactants, inhalants, bacteria or injectants---acting on such a person whose bronchi are sensitized causes the production of antibodies. The reaction, we may assume, of the antibody and antigen causes the release of an H substance or toxic product which in turn causes the symptoms of asthma.

In the treatment of asthma as in all diseases the ideal approach would be to attack the fundamental basis, that is, the X, Y or Z factor that makes a person develop, say, coronary disease, or ulcer, or mental diseases or asthma. Unfortunately, we know as little about that factor as does the cardiologist, the gastro-enterologist or the psychiatrist.

The next mode of attack would be to avoid the allergen---the most specific method at present available. Here again, even if we can identify the allergen, the economic and social factors often make avoidance impossible or impractical. In our present complicated society, it is very difficult to do what on the surface seems very simple. How easy is it, for instance, to avoid tobacco, or wheat, or corn or even dust---unless one is a hermit. I well recall a patient, Mrs. Nelson, who had come to me with a long history of asthmatic attacks. She had avoided all foods but coffee and cookies, and still had her attacks. The procedure seemed self evident from the food angle. I told her to eat all elase and avoid coffee and cookies. Lo and behold---no asthma! I was very proud but unfortunately at the next office visit she had her old trouble---a recurrence of wheezing and coughing. Mrs. Nelson could not stay away from her coffee klatches. "One lives not by bread alone." Fred Allen, describing a rice diet to reduce his high blood pressure said, "I ate so much rice that in three weeks I was doing my own laundry." Beyond that, the allergic cannot get away from himself and changes of environment all too frequently result in changed allergens and changed sensitivity.

The next specific mode of attack would be specific desensitization with increasing quantities of the offending allergen. In this connection, it should be noted that a member of our own staff, Dr. Henry Ulrich,[23] was a pioneer in the use of specific desensitization---a fact that is here too little recognized. This is, of course, the method most frequently and successfully used now if the avoidance is not practical or possible. The difficulty is that too frequently patients have serious reactions or respond incompletely to treatment. It is in this group of asthmatics that we use non-specific or palliative methods too numerous to mention--all too often of very little help---the antihistamines, the iodides, the sympathetic stimulants, the parasympathetic depressants, the antibariums, etc., etc. It is this group of patients that is referred to psychiatrists, sloughed to other doctors and climates. These are the unfortunatis who wander from state to state, doctor to doctor, hospital to hospital. It is this group---the miserable, pathetic, semi-invalid, perennial asthmatics that need more help---the allergic group which the allergist has been unable to do much for with the usually successful allergic management---and who go on to the serious asthmatic complications.

As asthma must be regarded as primarily a disease of adaptation, Selye's[24] concept of the general adaptation syndrome would be of benefit. The antigen stimulates the reticulo-endothelial system, especially plasma cells, to produce antibodies. The reaction of the allergen and antibody results in toxic products which directly or indirectly stimulate the hypophysis to produce ACTH. It is interesting to note that treatment with desensitization gets results at least in part by stimulation of increased production of ACTH.[24] Abelson and Moyes[25] in a recent article in the Lancet give evidence pointing to the possibility that the therapeutic action of ephedrine in allergic conditions is partly due to the release of pituitary adrenocorticotropic hormone. The secretion of ACTH can be increased also by a wide variety of stimuli,[24] inanition, anoxia, heat, cold, trauma, bacterial toxins, foreign proteins. It can also be increased by histamine, thyroxin and estrogens. Normally both mineralo-corticotrophic and gluco-corticotrophic stimuli affect the adrenals proportionately. If the response is too violent or the gluco-corticotrophic production is inadequate, allergic reactions result. As gluco-corticoids mitigate the response of shock organs to allergic stimuli and mineralo-corticoids increase the responsiveness the degree of sensitivity would depend on the balance between gluco and mineralo hormones. How the gluco corticoids diminish sensitivity in cells is not understood.

Immediately after the announcement that Cortisone relieved the symptoms of rheumatoid arthritis it was natural as indicated by Selye's concept to assume at once that all the so-called Collagen

diseases and hypersensitive states would be similarly affected---notably the allergic diseases and in particular asthma. White[26] has shown that animals that have had an adrenolectomy show extreme susceptibility to anaphylactic shock. Pretreatment of these animals with Cortisone or ACTH gives them protection.[27] Rose and his associates[28] had demonstrated on rats the direct relationship between adrenal cortex and the metabolism of histamine and its specific enzyme histaminase. The tissue and blood histamine was markedly increased and the mechanism for the destruction of histamine impaired following adrenalectomy.[29] They also demonstrated that the ability of histamine aerosols to produce dyspnea was blocked in four patients by ACTH therapy.[30,31] Segal[32] noted that the abnormal sensitivity of the asthmatic patient to injected histamine was lessened or abolished by treatment with ACTH on repeated injections; but Curry[33] noted no such protection against histamine or methacholine by single doses of 50 to 100 mg. of ACTH---an observation also made by Herschfus.[34] These studies would indicate that ACTH probably does not relieve bronchial spasm through an antihistaminic or anticholinergic action. Cortisone and ACTH as reported by Kendall[35] are powerful tools with which it is possible to study problems related to the etiology and treatment of a large group of diseases. Though Cortisone and ACTH can produce profound changes in the person with these conditions, the mechanism of action is still very imperfectly understood. It is certainly not a deficiency as no such deficiency of Cortisone has been noted in asthma, or other conditions in which it is of such dramatic though temporary benefit. Sayers[36] suggests that Cortisone acts by (1) interference with the release of or toxic action of anaphylactagenic substances produced in antigen---antibody reactions, (2) alteration in cell permeability through its action on hyaluronidase, or (3) suppression of responses in mesenchymal tissues. It is easy to see that these types of action would definitely influence allergic manifestations.

When Cortisone is given to rabbits, Hogan[37,38] noted a delay in the development of all elements of connective tissue response. This effect would, of course, interfere with the connective tissue reactions seen not only in hypersensitivity but also in disease activity and wound healing. Taubenhaus and Amromin[39] also noted an inhibition effect of cortisone on collagen formation and fibroblasts--the opposite effect from that of desoxycorticosterone.

White[26] believes that Cortisone acts in the hypersensitive state by (1) alteration in the relative concentration of antigen and antibody in the tissues, (2) alteration in the tissue factors which influence the combination, or (3) alteration in the tissue response to antigen antibody reaction.

Be all this as it may, it is sufficient to state that there is early in the course of treatment with ACTH or Cortisone physiological changes due to induced hyperactivity of the adrenal cortex; a fall in the eosinophile count; leukocytosis; sodium and chloride retention and associated water retention or excretion; elevated serum carbon dioxide---combining powers; decreased sodium and chloride in the sweat; increase in urinary histamine; corticoides and seventeen keto steroids; increased gluconeogenesis with hyperglycemia; a diabetic-type of dextrose tolerance curve and increased deposition of liver glycogen; decreased inorganic serum phosphorous; increased uric acid excretion; increased serum cholesteral; increased calcium excretion; a negative nitrogen balance.[40,41,42,43] In considering the effect of ACTH in allergic persons, in particular,[44,45] we must also consider the euphoria induced, and the increased appetite and neuropsychiatric changes. Interference with the acetyl choline cycle as reported by Torda and Wolff[46,47] with at times deficiency and at other times enhancement of in vitro synthesis is another important factor. Large doses of steroids have also been reported, by Selye[48], as hypnotic in effect while Archer[49] in a recent letter in the A.M.A. Journal stresses the relationship of the pituitary adrenal axis to fat metabolism and to fatty infiltration of the liver---

changes also associated with pregnancy and jaundice--conditions which at times benefit arthritis as well as asthma.

While the conditions treated with ACTH and Cortisone have included almost all serious ones the body is heir to, some of the most dramatic results have been reported in the field of allergy with nearly 100% encouraging though temporary results. Rose treated six patients with severe asthma.[30] The first two patients received 150 mg. of ACTH daily for two days and 100 mg. daily for two more days. The next four received 100 mg. daily for three days, 75 mg. daily for two days, and 25 mg. the sixth day. He reports complete success in relief of asthma in four patients within 48 hours. The other two patients while not completely free of symptoms were decidedly improved. Tho apparently only remissions, the results were certainly striking for the type of patients reported. Bordley[44] treated five patients with severe asthma with daily doses of 30 to 100 mg. of ACTH given at six hour intervals. Here also marked relief was obtained in four to 48 hours. Total ACTH given varied from 360 to 775 mg. Not only was the asthma relieved but in two patients nasal polyps disappeared tho they recurred in 23 days and one month respectively. Randolph[50] reports thirteen cases of very serious asthma, two seasonal ragweed asthma and eleven perennial advanced cases of this disease. The majority would certainly be included in that terribly discouraging class of asthmatics referred to by Rockeman as "intrinsic"; and were further complicated by nasal polyps and aspirin sensitivity. As he points out these cases were chosen because of their difficulty as diagnostic and therapeutic problems. Ten of these eleven severe asthmatics obtained marked relief of symptoms and remissions from one week to five months following treatment with ACTH. Total dosage was 125 to 325 mg. One patient could not be treated with the usual method and dosage due to fluid retention. The degree of relief varied from 50% to complete relief---the more satisfactory results being in patients with no clinical or x-ray evidence of emphysema, empyema or scarring. Even in those having recurrence of bronchial asthma after treatment, symptoms were "readily relieved following the inhalation of small amounts of epinephrine spray"---in decided though temporary contrast to the pre-treatment condition. Their general status improved markedly--a condition not due to suggestion as placebos did not work in the same manner. Haddon Carryer[51] treated three patients with hay fever and asthma caused by ragweed pollen. Each patient experienced relief on the day Cortisone was started and two remained free of symptoms until three or four days after it was discontinued. The third had no recurrence while under observation. The hay fever symptoms were also relieved but not as markedly or quickly as the asthmatic. The relief was accompanied by a decrease in nasal secretion and decrease of nasal mucosa pallor. No undesirable side effects were noted. Howard[52] reports on his experience in 19 asthma patients with ACTH and in five with Cortisone. In 15 of the 19 patients treated with ACTH there was complete remission of symptoms within a few hours to 11 days. The duration of remission varied from 3 to 263 days. The four that did not respond completely included one in the 6th month of pregnancy, one that had asthma in humid days only, and two in whom inadequate doses were given in error. In their experience, cortisone compared unfavorably with ACTH in alleviating signs and symptoms of asthma. Only one patient of these five had complete relief while the other four had only 25 to 50% improvement.

Because of these reports, it is to be understood that the privilege of being able to use ACTH through the help and courtesy of Dr. E. Flink, was greeted with great enthusiasm and anticipation. The first patients, I decided, would be really "tough ones"--whom I had followed, and used up my total therapeutic armamentarium as well as that of other men in the field. Since the material was given every six hours the patients were hospitalized. This made it possible to follow the response to treatment, especially the eosinophile count (to be certain that the adrenals did respond). This was done in spite of the fact that, as is well known, hospitalization and rest are often great

therapeutic agents, in themselves, and could very easily confuse the response. In these people, however, because of the length of previous observation, I believed I could easily detect real improvement.

ILLUSTRATIVE CASE: This patient, female, married, age 49, a former nurse and present hotel proprietor, gives a history of asthma since 1943. She has also had a perennial stuffy nose in 1947 and 1948 but no asthma at that time. The condition is aggravated by hard work, dust, colds and cold air. Partial relief is at times obtained by aminophyllin, ephedrin, and adrenalin. The past history is not remarkable but for irrigation of the sinuses in 1949. The physical examination, X-ray, and electrocardiograms were negative. Routine blood and urine were not helpful. This patient has been under my care since January, 1950 and the usual procedures including elimination diets, sedation, desensitization with dust, fungi, vaccine, histamine, antihistamine, antibarium, and antiboditic drugs were tried but in May, 1950, she became very seriously incapacitated by her condition and a trial of ACTH was advised. ACTH was given for 96 hours in a total dose of 360 mg. with no marked effect. The total eosinophile count showed the adrenal response by a marked drop from 1609 to 680 to 90 to 0. As a matter of fact, she required repeated administrations of adrenalin and aminophyllin while being given ACTH as well as after treatment. The drug was given every six hours.

As I reported[53] it was difficult for me to understand the effect of ACTH in this and two other cases of asthma treated in this manner. The dosage was given as reported; the response of the adrenals was definitely indicated by the eosinophile count. It also seemed that if relief was to be obtained it should occur fairly soon just as had been reported. Furthermore these cases did not have emphysema or other pulmonary pathology. At any rate here were three cases of severe asthma that did not respond to ACTH---a rarity at least at that time in the literature of this remarkable drug. Perhaps more prolonged or more intensive treatment was indicated. Perhaps Cortisone would be of greater benefit.

As would be deduced from the effects of the hormone and confirmed by the literature,[54] absolute contraindications to the use of Cortisone are few but should be used with caution in diabetes mellitus, psychotic disorders, cardiac failure, during major surgery, severe infections, myocardial infarction, pulmonary embolus, cerebral accidents and probably because of its effect on connective tissue, in tuberculosis, syphilis and peptic ulcers. Equally important is the question of the effects of long continued administration and large dosage. As pointed out by Kendall and others, the answer is not a simple one. In general, however, the response is neither rapid nor long continued. The effects are reversible when the hormone is discontinued. Beyond that, it is neither necessary nor desirable to give large doses for a prolonged period of time.[55] The immediate undesirable effects reported are fluid retention, moon face, acne, hirsuitism,[56] irregular menses, changes in mood or psyche, nervousness, fatigue, transient parasthesias, weakness, hypercoagulability, minor changes in carbohydrate metabolism and nitrogen balance.[54] These are usually not marked and are easily controlled by a reduction in dosage compatible with comfort. While the weakness noted at times has no constant relation to low serum potassium, it is at times desirable to give potassium chloride when the level is below normal. Low sodium diets will usually control fluid retention though very infrequently diuretics may be indicated. Estrone or progesterone will frequently prevent the most annoying of the symptomatic side effects in menopausal women. Above all, suboptimal dosage will minimize these undesirable features as well as the danger of poor healing, missing new clinical symptoms such as active infections, pain, fever, peritoneal irritation from perforated ulcers[57,58,59] as well as the changes of hyperadrenocorticism.[60]

As Cortisone became more available and less expensive, the opportunity pre-

sented itself to give this hormone to ambulatory patients. This avoided the expense of the hospitalization necessary with ACTH and eliminated the effect of hospitalization alone on these patients, thus simplifying the evaluation of therapy. Cortisone was given to these severe, chronic perennial asthmatics. All the usual specific and non-specific allergic therapeutic measures had been tried with little or no or very temporary effect. The initial dose was 200 mg. (100 mg. intramuscularly in each buttock). Thereafter the dosage was 100 mg. daily for six days. In the second and third week the dosage was reduced to 100 mg. three times a week. Here we discontinued the treatment to see if we could get a remission. If none was obtained or if symptoms recurred gradually, treatment was again started. The dosage depended upon the response of the individual patient. No attempt was made to have the patient completely free of symptoms as long as he was comfortable. In this type of patient a little relief for a prolonged period was a great accomplishment. The weight, blood pressure and urine and cholesterol levels were followed. For a time the eosinophile counts and vital capacity were taken but we soon found, as have others, no correlation to the symptoms. After obtaining a satisfactory effect, Cortisone was given by mouth in equivalent doses and with apparently equivalent results in all but two patients. In these two the dosage was increased by 20%. The Cortisone acetate in the same form supplied for injection was mixed in milk or fruit juices to hide the extremely bitter taste. The overall therapeutic and hormonal effects of Cortisone when given orally do not differ from those produced when given parenterally. Subjective relief is often noted in six to eight hours after injection. As the duration of action of the orally given hormone is partially dissipated within 12 to 14 hours, it was given in two divided doses--in the morning and at bedtime. When the hormone was available in tablet form of 25 mg., it was so given.[61] At the end of a six week period, an attempt was again made to stop therapy to see if a remission could be obtained.

Table I

Number of patients	30
Ages	15 to 62
Males	22
Females	8
Duration of asthma	3 to 32 years
Diabetics	2

In this series, 30 patients with allergic asthma--chosen for their extreme severity, chronicity, and failure on the usual allergic regimes for years--Cortisone acetate was given in the manner described. I wish to stress that patients with marked emphysema, bronchiectasis, cor pulmonale or psychoses were not included. Two asthmatic patients with diabetes mellitus were treated. The ages varied from 15 to 62. Twenty two were men and eight were women. The duration of the disease varied from 3 to 32 years. The apparent causation of the allergy ran the gamut of allergens. Psychic factors were present, as in all asthmatics, to a greater or lesser degree.

The initial results in these 30 cases were to me, at times, startling---and to the patient often under the euphoria of the hormone, almost miraculous. Expressions, especially at the first response to the treatment, were such as "I never felt better in my life"---"I feel great". Within a few days to a week there was a marked diminution in the wheezing with a feeling of well being and increased energy. Within the second to third week, the cough lessened and almost completely disappeared. Many with nasal polyps noted a clear nose for the first time in many years with regression of the polyps. Several remarked on the fact that "I can smell things now". The maximal initial improvement developed by the end of the second or third week and as the dosage was reduced, the euphoria decreased, and the enthusiasm was not so great but still satisfactory. Minor flareups of wheezing or coughing did occur in some patients.

Table II

RESULTS	
Good	22
Fair	8
Poor	0

Results were evaluated according to the patient's own description and judgment and the overall picture including objective findings. Those who experienced 50% relief or more were considered to have fair results. Patients who had mild to practically no symptoms were considered to have had good results.

By this criteria the results of treatment were good in 22 and fair in 8. In the eight that had only fair results, there was a more or less persistent cough though no frank asthmatic attacks.

CASE REPORTS

Case 1. This patient is a male, professor of art, age 48, with a history of severe asthma since the age of 18 and hay fever since the age of 9. Asthma occurred only during the hay fever season for four weeks starting August 15th. He received pollen desensitization in 1935, 1936 and 1937 with excellent results. He then went to New York and had no difficulty. He returned to Minnesota in March, 1947 and had no hay fever or asthma until the spring of 1948. At that time he contracted a "bad cold" and a few days later had severe asthmatic attacks which lasted until the warm weather. Since that time he has had asthma of a very severe nature associated with a persistent cough only in cold weather but aggravated by tobacco, coffee, tea, coal dust, grain dust, and emotional upsets (mostly humorous!) He has been so incapacitated that he could not step outside of a warm room without difficulty. To get to his classes he had to be taken in a previously warmed car and immediately go to a warm room. The only relief he obtained was from heat and rest. Drugs of all types including aminophyllin and adrenalin were of no help. He had had desensitization and nasal surgery with no benefit and refused to have skin tests as he had them so many times before. In other words, he had the "whole works" as far as allergic regime and therapy in the usual sense was concerned. He was really desperate and could think only of the idea of moving to a warm climate---an idea which was very difficult to accept even if it would be of permanent benefit as the status of his work made that almost impossible. Physical examination revealed a very intelligent, cooperative male and was negative except for wheezing rales in the chest. Routine laboratory tests were negative including x-ray of the chest and electrocardiogram. The eosinophile count was 990/cu. mm. Cortisone was started with an initial dose of 200 mg. intramuscularly. The dose was reduced then to 100 mg. daily. Three days later he had very little wheezing but still retained the cough. He complained of a mild weakness but felt energetic and had a feeling of well being. The cough had almost entirely disappeared at the end of the second week during which the dose had been reduced to 100 mg. of Cortisone three times a week. At this time he felt perfectly normal. His weight, urine and routine laboratory work were unchanged. Because of his feeling of well being and energy, he had to be cautioned against over exertion as he had shoveled snow for the first time in years and took long walks. At the end of three weeks, I attempted to stop Cortisone but within six days he began to cough again and had a few wheezing spells. He was then given 50 mg. of Cortisone orally and has remained practically symptom free except when he exerts himself in cold weather. As soon as it gets warmer, I intend to stop medication again when I believe he will get along well.

Case II. This patient is a female, secretary, age 23 when first seen in consultation on June 8, 1949. At that time she had had asthma for one and one half years, so severe as to require hospitalization at frequent intervals and ephedrin more or less constantly. She had also had severe asthma as a child from the age of 10 through 14 but this

had subsided for no apparent reason. There were no known aggravating factors of any kind except that "colds" seem to start the attacks though she had a persistent cough at all times throughout the whole year. She seemed worse when in damp or long closed places. Family history was negative. Physical examination revealed a well developed female with no significant physical findings except wheezing rales in both lungs. X-ray of the lungs was negative as was the electrocardiogram. Routine laboratory work revealed nothing of note except an eosinophile count of 12%. Routine skin tests--intradermal--revealed significant findings especially as to foods and fungi. On elimination of positive factors and desensitization to alternaria and penicillium, the patient markedly improved and had no symptoms for the first time in many years until October 1, 1950 when she had a severe upper respiratory infection with a high fever. At this time she began to have severe asthma necessitating hospitalization. Under usual management of oxygen, antibiotics, aminophyllin, fluids, she recovered sufficiently to leave the hospital. She continued to have almost continuous episodes of asthma and coughing in spite of all I could do by the usual methods previously found successful. Because of this failure, Cortisone was started in the usual way. Within three days she felt much better---had no asthma but a very slight cough. She developed a marked euphoria---all was well with the world including especially her doctor! She had unlimited energy. In the second and third week the euphoria lessened but the feeling of well being persisted. Cortisone was discontinued at the end of three weeks but the usual allergic regime used previously including fungi desensitization was continued. There were no side effects, no change of consequence in the usual laboratory tests or weight. She has had no asthma, no cough and feels good.

The side effects in this series of patients followed for two to eight months were not many and certainly not serious and at times very desirable. Increased appetite was noted in 24 though this had a tendency to decrease with decrease in dosage. Euphoria--mild and quite pleasant---was noted in 18. This also decreased after the first three weeks, though the feeling of well being remained. Severe acne was noted in one. Transient edema was mild to moderate in three and here no medication was required except a reduction in sodium intake with a later reduction in dosage of Cortisone. The only cases of glycosuria were in our two diabetics in whom the insulin requirements were more than doubled during the first three weeks. When the dosage was reduced the insulin requirement returned to the pretreatment level. One case of furunculosis developed but subsided with the use of penicillin. One case of asthma had a change of shock tissue and developed a severe urticaria which also responded to Cortisone therapy. Certainly in the doses used here in asthmatics, we had no difficulty, no side effects severe enough to warrant discontinuing therapy although dosage had to be reduced below the optimal level.

Table III

SIDE EFFECTS	
increased appetite	24
Euphoria	18
Acne	1
Edema (transient)	3
Glycosurea	2
Furunculosis	1
Change of shock tissue	1

Table IV

REMISSIONS:	
2 months to 6 months (after 3 wks. treatment)	3
2 months to 4 months (after 6 wks. treatment)	2
6 weeks (after 9 wks. treatment	1
4 to 5 weeks	2
2 to 4 weeks	6
less than 2 weeks	16

On the dose schedule used all our cases responded satisfactorily. An at-

tempt was made at the end of three weeks to stop treatment to see if a remission could be attained. Three asthmatics did not require further Cortisone up to the present. The rest noted increasing cough at first and later recurring wheezing within a few days. Two patients have remained comfortable when Cortisone was stopped at the end of six weeks treatment. The others have had to resume treatment. One, after nine weeks treatment, resumed Cortisone after six weeks remission and sixteen after less than two weeks. The great majority gradually were getting worse after three to four days lapse.

While the psychic factor is very important in all asthmatics, and interviews with the doctor very often have a marked effect on their symptoms even with placebos, I believe I followed those patients long enough to evaluate the effect of the hormone itself. This is especially true now that oral medication is used, but we must always remember that many asthmatics have prolonged remissions for often no apparent reason.

Table V

SUBSEQUENT DOSAGE	
25 mg. daily	2
50 mg. daily	22
75 mg. daily	1

Five are in remission and are getting no Cortisone. Two were maintained on 25 mg. daily; twenty two on 50 mg. daily and one on 75 mg. daily. Occasionally in exacerbations, the dosage was increased for a few days to as much as 100 mg. daily and then again reduced. On these doses we noted no apparent deleterious effects.

An interesting problem was the effect of treatment with Cortisone on direct skin tests. Contrary to expectation and some reports[44] but in agreement with the results of others,[32] no apparent consistent effect was noted. It is to be noted that Stoerk[60] found that while Cortisone failed to prevent the anaphylactic type of hypersensitivity in guinea pigs, the animals vaccinated with dead tubercle bacilli failed to give a positive tuberculin skin reaction when Cortisone was given before injection of tuberculin. Massell et al[61] gave ACTH to 11 patients with acute rheumatic fever with favorable results in all but one yet ACTH had no effect on skin reactivity to streptococcic products. Vital capacity measurements also did not correlate with effects of treatment. Cholesterol levels were taken but contrary to reports[62], I found no consistent elevation.

COMMENT

As in rheumatoid arthritis and other conditions in which ACTH and Cortisone have been used the full therapeutic possibilities in asthma will have to await time and experience. The beneficial effects are usually contingent upon continuing therapy as in rheumatoid disease but in a condition as fluctuating in its cycle as asthma, it would seem that a large number of even perennial asthmatics should have prolonged remissions without any hormone. While there are no apparent serious effects from short periods of treatment with comparatively small doses used in allergic patients, we must have a great deal more knowledge as to the consequences of prolonged or repeated use. So far all adverse effects have been temporary---disappearing on hormone withdrawal or on lowering dosage. In this connection it has long been observed that in cases of Cushing's Syndrome resulting from unilateral tumor of adrenal cortex the other adrenal cortex may undergo atrophy but its function returns even years later after the tumor is removed.

I have attempted to keep dosage at as low a level as was compatible with comfort and have attempted to stop treatment at intervals. If recurrence takes place, a new course of treatment can be started with results equal to the original. As pointed out by Hench in arthritis the interrupted course method might provide a more physiologic response. This should be even more

applicable in a condition such as asthma where there are repeated natural remissions and relapses or seasonal exacerbations when treatment might be started or dosage increased. None of these patients to date have had asthma of greater severity than before taking Cortisone.

SUMMARY

1. Thirty patients with severe, perennial asthma were treated with Cortisone both parenterally and orally in gradually decreasing doses.

2. The response to treatment was good in 22 and fair in 8.

3. There was a prolonged remission in 5 cases but 25 had to be maintained on doses of the hormone varying from 25 to 75 mg. daily--orally.

4. The side effects noted were mild and did not necessitate stopping therapy.

5. From this study of severe asthmatics it would seem that some of these patients may get an induced remission on initial large doses with a gradual reduction of dose later.

6. It would appear that some severe asthmatics require relatively small maintenance doses of Cortisone to keep them under adequate control for long periods with relative safety.

7. It must be emphasized that treatment with Cortisone is still very expensive.

8. In seasonal or periodic allergic conditions, it appears that courses of Cortisone therapy should be very satisfactory. It must be realized, however, that Cortisone is a very potent agent and should be used in our present state of knowledge only in those conditions that do not respond to usual simple, time tested and non-harmful measures which usually are of great help. Cortisone offers a method of getting a remission in some cases of asthma more consistently than any other regime.

9. A very definite disadvantage with Cortisone therapy is the need of prolonged administration in some cases. Again I wish to emphasize that there are grave potential dangers in the use of Cortisone and as pointed out here and emphasized in a recent Bulletin[64] on the Shwartzman Phenomenon, it would be advisable to give the hormone in the smallest possible dose over the shortest period of time consistent with good results. Again it should at present be used in major and not minor disabilities.

10. The best method of treatment in the usual asthmatic patient as in most allergic diseases, is still the avoidance of the allergen or specific desensitization. Cortisone often provides the opportunity to employ more specific therapy while the patient is in a better nutritional and psychiatric state.

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II. MEDICAL SCHOOL NEWS

Coming Events

March 26-28 -- Continuation Course in Pediatrics for General Physicians
April 2-6 -- Continuation Course in Urology for General Physicians and Surgeons
April 5 -- Phi Delta Epsilon Lecture; "The Concept of Collagen Disease," Dr. Paul Klemperer. Museum of Natural History, 8:15 p.m.
April 5-6 -- Symposium on Lupus Erythematosus
April 9-11 -- Continuation Course in Gynecology for General Physicians
April 16-18 -- Diseases of the Blood in Infancy and Childhood

* * *

Dr. Ralph V. Platou, Professor and Head of the Department of Pediatrics at Tulane University Medical School, will return to the University of Minnesota campus to participate in a continuation course in Pediatrics to be presented at the Center for Continuation Study March 26-28. Dr. Platou was formerly a member of the faculty of the Department of Pediatrics at the University. He will speak on the following subjects in the continuation course: "Subdural Collections in Meningitides," "Diphtheria - Diagnosis and Treatment," and "Spirochetal Diseases." Dr. William L. Bradford, Professor of Pediatrics at the University of Rochester, will be the other visiting physician for the course. Dr. Bradford will discuss "The Meningitides - Diagnosis and Treatment," "Respiratory Infections in Infants and Children," and "Pertussis." Two days will be devoted to consideration of infectious diseases in childhood. The final morning of the course is concerned with common orthopedic problems in pediatric practice. Clinical and full-time members of the Departments of Pediatrics and Orthopedic Surgery will participate along with the two visiting faculty members.

A Symposium on Lupus Erythematosus, to be presented at the Center for Continuation Study April 5 and 6, will bring Dr. Paul Klemperer, Pathologist, Mount Sinai Hospital, New York City, to our campus. Dr. Klemperer is well known for his many contributions regarding the pathology of this disorder. During his visit to our campus, Dr. Klemperer will also deliver the annual Phi Delta Epsilon Lecture on Thursday, April 5. His subject will be, "The Concept of Collagen Disease." The visiting faculty members for the course include Dr. Louis J. Soffer, New York City, and Dr. John R. Haserick, Cleveland, Ohio. Dr. Haserick was formerly a member of the faculty of the University of Minnesota Medical School. Dr. Henry E. Michelson, under whose direction the course will be given, will be joined by members of the staff of the Medical School and the Mayo Foundation.

A continuation course in Urology will be presented April 2-6 under the direction of Dr. C. D Creevy with the Division of Urology. The course is sponsored by the North Central Section of the American Urological Association and will bring to our campus as visiting faculty members Dr. Hugh J. Jewett, Baltimore, Dr. Lloyd G. Lewis, Georgetown University Medical School, Washington, D.C., Dr. Reed M. Nesbit, University of Michigan Medical School, Ann Arbor, and Dr. Parke G. Smith, University of Cincinnati Medical School. Many clinical and full-time members of the staff of the Medical School and the Mayo Foundation will participate as faculty members for the course.

Foundation News

The Membership Committee of the Minnesota Medical Foundation, headed by Dr. Vernon D. E. Smith, is presenting programs at county medical society meetings during the months of March and April. The programs will include one or two brief scientific presentations, exhibition of color motion pictures on outdoor sports filmed and edited by Dr. Smith, and a brief presentation on the purposes and activities of the Foundation. It is hoped that the series of programs will be effective in increasing the participation of the medical profession of our state in such Foundation activities as medical research, support of scholarships, and increased activities of the Minnesota Medical Alumni Association.

III. UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
WEEKLY CALENDAR OF EVENTS

Visitors Welcome

March 18 - 24, 1951

Sunday, March 18

University Hospitals

9:00 - 10:00 Surgery Grand Rounds; Station 22.

10:30 - Surgical Conference; Todd Amphitheater.

Monday, March 19

Medical School and University Hospitals

9:00 - 9:50 Roentgenology-Medicine Conference; L. G. Rigler, C. J. Watson and Staff; Todd Amphitheater, U. H.

9:00 - 10:50 Obstetrics and Gynecology Conference; J. L. McKelvey and Staff; M-109, U. H.

10:00 - 12:00 Neurology Rounds; A. B. Baker and Staff; Station 50, U. H.

11:00 - 11:50 Physical Medicine Seminar; Emotional Problems in Traumatic Cord Injuries; Winifred Phelps; E-101, U. H.

11:00 - 12:00 Cancer Clinic; K. Stenstrom and A. Kremen; Eustis Amphitheater, U. H.

12:15 - 1:20 Obstetrics and Gynecology Journal Club; Staff Dining Room, U. H.

1:30 - 2:30 Pediatric-Neurological Rounds; R. Jensen, A. B. Baker and Staff; U. H.

4:00 - Public Health Seminar; 113 Medical Sciences.

4:00 - Pediatric Seminar; Dr. Hauser; Sixth Floor West, U. H.

4:30 - 5:30 Dermatological Seminar; M-436, U. H.

5:00 - 5:50 Clinical Medical Pathologic Conference; Todd Amphitheater, U. H.

5:00 - 6:00 Urology-Roentgenology Conference; C. D. Creevy, O. J. Baggenstoss, and Staffs; Powell Hall Amphitheater.

Minneapolis General Hospital

9:00 - 10:00 Pediatric Rounds; Dr. Tobin; 5th Floor Annex.

10:00 - 11:00 Pediatric Rounds; Franklin Top; 7th Floor Annex.

1:00 - 2:00 Staff Meeting; Classroom, 4th Floor.

2:00 - 3:00 Journal Club; Classroom, Station I.

Monday, March 19 (Cont.)

Veterans Administration Hospital

9:00 - G. I. Rounds; R. V. Ebert, J. A. Wilson, Norman Shrifter; Bldg. I.

11:30 - X-ray Conference; Conference Room; Bldg. I.

1:00 - Metabolic Disease Rounds; N. E. Jacobson and G. V. Loomis; Bldg. I.

4:00 - Medical-Surgical Conference; Conference Room, Bldg. I.

Tuesday, March 20

Medical School and University Hospitals

9:00 - 9:50 Roentgenology-Pediatric Conference; L. G. Rigler, I. McQuarrie and Staffs; Eustis Amphitheater, U. H.

9:00 - 12:00 Cardiovascular Rounds; Station 30, U. H.

12:30 - 1:20 Pathology Conference; Autopsies; J. R. Dawson and Staff; 102 I. A.

1:00 - 2:00 Physiology Seminar on Cardiac Metabolism; 129 Millard Hall.

3:15 - 4:20 Gynecology Chart Conference; J. L. McKelvey and Staff; Station 54, U.H

4:00 - 5:00 Physiology-Surgery Conference; The Pneumotachygram; Leonard Peltier; Todd Amphitheater, U. H.

4:00 - 5:00 Pediatric Rounds on Wards; I. McQuarrie and Staff; U. H.

5:00 - 6:00 X-ray Conference; Eustis Amphitheater, U. H.

*8:00 p.m. Minnesota Pathological Society Meeting; The Pathology of Rheumatic Disease; Dr. Murray Angevine; Medical Science Amphitheater.

Ancker Hospital

8:00 - 9:00 Fracture Conference; Auditorium.

1:00 - 2:30 X-ray Surgery Conference. Auditorium.

Minneapolis General Hospital

8:00 - 9:00 Pediatric Rounds; Forrest Adams; 4th Floor Annex.

8:30 - Pediatric Allergy Rounds; Dr. Nelson; 4th Floor Annex.

Veterans Administration Hospital

8:45 - Surgery Journal Club; Conference Room, Bldg. I.

8:30 - 10:20 Surgery Conference; Seminar Conference Room, Bldg. I.

*Indicates special meeting. All other meetings occur regularly each week at the same time on the same day. Meeting place may vary from week to week for some conferences.

Tuesday, March 20 (Cont.)

Veterans Administration Hospital (Cont.)

9:30 - Surgery-Pathology Conference; Conference Room, Bldg. I.

10:30 - 11:50 Surgical-Pathological Conference; Lyle Hay and E. T. Bell

10:30 - Surgery Tumor Conference; Conference Room, Bldg. I.

1:00 - Chest Surgery Conference; J. Kinsella and Wm. Tucker; Conference Room, Bldg. I.

1:30 - Liver Rounds; Samuel Nesbitt.

2:00 - 2:50 Dermatology and Syphilology Conference; H. E. Michelson and Staff; Bldg. III.

3:30 - 4:20 Autopsy Conference; E. T. Bell and Donald Gleason; Conference Room, Bldg. I.

Wednesday, March 21

Medical School and University Hospitals

8:00 - 8:50 Surgery Journal Club; O. H. Wangensteen and Staff; M-109, U. H.

8:00 - 9:00 Roentgenology-Surgical-Pathological Conference; Allen Judd and L. G. Rigler; Todd Amphitheater, U. H.

11:00 - 12:00 Pathology-Medicine-Surgery Conference; Surgery Case; O. H. Wangensteen, C. J. Watson and Staffs; Todd Amphitheater, U. H.

12:00 - 1:00 Radio-Isotope Seminar; 113 Medical Sciences.

5:00 - 5:50 Urology-Pathological Conference; C. D. Creevy and Staff; Eustis Amphitheater.

5:00 - 7:00 Dermatology Clinical Seminar; Dining Room, U. H.

8:00 p.m. Dermatological Pathology Conference; Todd Amphitheater, U. H.

Ancker Hospital

8:30 - 9:30 Clinico-Pathological Conference; Auditorium.

3:30 - 4:30 Journal Club; Surgery Office.

Minneapolis General Hospital

9:00 - 10:00 Pediatric Rounds; J. D. Tobin; 5th Floor Annex.

11:00 - 12:00 Pediatric Rounds; Franklin Top; 7th Floor Annex.

12:15 - Staff Meeting; Case Presentation; Dr. Haddy; 4th Floor Annex.

1:30 - Pediatric Rounds; E. J. Huenekens; 4th Floor Annex.

Wednesday, March 21 (Cont.)

Veterans Administration Hospital

8:30 - 10:00 Orthopedic-Roentgenologic Conference; Edward T. Evans and Bernard O'Loughlin; Conference Room, Bldg. I.

8:30 - 12:00 Neurology Rehabilitation and Case Conference; A. B. Baker.

2:00 - 4:00 Infectious Disease Rounds; Main Conference Room, Bldg. I.

4:00 - 5:00 Infectious Disease Conference; W. Spink; Conference Room, Bldg. I.

7:00 p.m. Lectures in Bacis Science of Orthopedics; Conference Room, Bldg. I.

Thursday, March 22

Medical School and University Hospitals

9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; M-109, U. H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

11:00 - 12:00 Cancer Clinic; K. Stenstrom and A. Kremen; Todd Amphitheater, U. H.

4:30 - 5:20 Ophthalmology Ward Rounds; Erling W. Hansen and Staff; E-534, U. H.

5:00 - Bacteriology Seminar; Studies on the Synthesis and Turnover of Nucleoproteins; C. P. Barnum; 214 Millard Hall.

5:00 - 6:00 X-ray Seminar; Eustis Amphitheater, U. H.

5:00 - 6:00 Radiology Seminar; Thoracic Surgery Conference; Dr. Varco, et al., Eustis Amphitheater, U. H.

7:30 - 9:30 Pediatrics Cardiology Conference and Journal Club; Review of Current Literature 1st hour and Review of Patients 2nd hours; 206 Temporary West Hospital.

Minneapolis General Hospital

8:00 - 9:00 Pediatric Rounds; Forrest Adams, 4th Floor Annex.

11:30 - Pathology Conference; Main Classroom.

1:00 - 2:00 EKG and X-ray Conference; Classroom, 4th Floor Annex.

Veterans Administration Hospital

8:00 - Surgery Ward Rounds; Lyle Hay and Staff.

9:15 - Surgery Grand Rounds; Conference Room, Bldg. I.

11:00 - Surgery-Roentgen Conference; Conference Room, Bldg. I.

1:00 - Chest Rounds; William Stead.

Friday, March 23 - HOLIDAY

Saturday, March 24

Medical School and University Hospitals

7:45 - 8:50 Orthopedic X-ray Conference; Wallace H. Cole and Staff; M-109, U. H.

9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; E-221, U. H.

9:00 - 10:30 Pediatric Grand Rounds; I. McQuarrie and Staff; Eustis Amphitheater, U. H.

9:15 - 10:00 Surgery-Roentgenology Conference; J. Friedman, O. H. Wangensteen and Staff; Todd Amphitheater, U. H.

10:00 - 11:30 Surgery Conference; O. H. Wangensteen and Staff; Todd Amphitheater, U. H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

10:00 - 12:50 Obstetrics and Gynecology Grand Rounds; J. L. McKelvey and Staff; Station 44, U. H.

Ancker Hospital

8:30 - 9:30 Surgery Conference; Auditorium.

Minneapolis General Hospital

8:00 - 9:00 Pediatric Rounds; Forrest Adams; 4th Floor Annex.

11:00 - 12:00 Pediatric Clinic; Charles May; Classroom, 4th Floor Annex.

Veterans Administration Hospital

8:00 - Proctology Rounds; W. C. Bernstein and Staff; Bldg. III.

8:30 - Hematology Rounds; P. Hagen and E. F. Englund.