I would like to have the members of the panel come up and sit on the platform. I will introduce the members of the panel and then we will talk about the program.

Reading from me on the left, Dr. Laurance Kinsell of San Francisco; Dr. John Mote of Philadelphia; Dr. Smith Freeman of Chicago; Dr. Maurice Segal of Boston; and batting for Dr. Carlisle, who unfortunately was taken ill in Puerto Rico, we have the great good fortune to have Dr. Al Barach.

As you know, ACTH and cortisone have been discussed as much or more in the lay press than in scientific journals. Our patients know more about it than we do, and are sure that it will cure almost everything. Consequently, this subject is something that we are expected to know a great deal about. However, it is much too early to have much exact knowledge. We are finding that some of the concepts of the old clinicians of the last century about the body's reaction to disease are being corroborated on a truly physiologic basis since this work was started.

I am going to start by asking Dr. Smith Freeman to tell us what ACTH and Cortisone are and what may be the relationship of these substances to the functioning of the body in health and in disease.

Dr. Freeman: ACTH is a polypeptide that is liberated by the
anterior lobe of the pituitary gland in response to stimulations which arise in various parts of the body and which presumably may be neurogenic or hormonal in origin. This polypeptide, with a molecular weight that has been given by various authors and workers as between 10,000 and 20,000, passes through the circulation and acts on the cortex of the adrenal gland to cause liberation of steroid hormones. It is a substance which is readily destroyed by proteolytic principals and its fate in the body is not known. For its function there must be an intact adrenal gland to respond to stimulation.

Cortisone is a steroid hormone; a specific substance with a definite chemical configuration which has its origin in the adrenal cortex and which acts on the periphery of the body, on the effector mechanisms to influence their response to metabolic stimuli. It does not require an intact adrenal gland for its function. It cannot be considered in all respects as producing effects synonymous to those produced by ACTH stimulation of the adrenal gland.

Dr. Levine: Dr. Kinsell, will you pick it up from there and tell us something about this stress or alarm reaction that we have heard about and how it relates to the body in health as well as in disease.

Dr. Kinsell: As all of you know, Dr. Selye is responsible for the term, alarm reaction. Over the past decade a great deal has been written and many theories presented concerning the role of the adrenal glands under various conditions, particularly emergency or stress conditions. In extremely brief terms Selye's concept of alarm reactions was that any individual subjected to a stress condition would have a reflex stimulation of the adrenals by way of his anterior pituitary, that is by means of the corticotropic hormone and the compounds poured out by the adrenals the individual would be helped to adjust himself to this difficult environmental situation. The same idea carried further by Dr. Selye, gave rise to his concept of the diseases of adaptation. If one accepts that concept and carries it through, he would place a great many conditions, such as hypertension and various forms of arterial disease in this category.

Dr. Freeman: A good deal of evidence has accumulated which indicates that every disease process probably provokes some sort of hormonal or endocrine readjustment to the disease process. The endocrine balance of the individual may be definitely altered by a disease even though the disease process may not be specifically or directly related to the endocrine system.

Dr. Levine: We now have developed the relationship which exists between stress or disease and the stimulation of the adrenal cortex by the corticotrophic hormones of the anterior pituitary. Since
this may be the basis for the therapeutic usefulness of ACTH, I
would like to ask Dr. Smith Freeman to tell us just what occurs
when ACTH or cortisone is given to experimental animals or to
human beings.

Dr. Freeman: ACTH must be given by injection because of de-
struction by proteolytic principals. It's not active orally. It should
also be pointed out that the effectiveness of ACTH as regards
adrenal stimulation depends upon the mode of administration,
the frequency of administration, as well as the amount of the
hormone administered. The same effect can be accomplished by
much smaller doses given by continuous intravenous drip as by
large injections given intermittently, whether subcutaneous or
intramuscular.

We can't answer the question of how many hormones are lib-
erated when the adrenal gland is stimulated. We can say that no
single hormone has been isolated from the adrenal gland which
in all respects will simulate the effects that can be produced by
adrenal gland stimulation through the administration of ACTH.
However, there are many metabolic effects in common from the
administration of ACTH and cortisone. So what we will say now
applies to both ACTH and cortisone administration.

When ACTH is given, it causes the adrenal gland to secrete.
The response is almost immediate and the manifestations of this
response can be demonstrated by changes in the composition of
the blood. Eosinopenia develops which is maximal at the end
of four hours and which is apparent before that time. Lymphopenia
also tends to develop regularly which may be apparent in two
hours. There is also leucocytosis with a shift to the left. There
are also changes in the hormone content of the blood. Compound
F is considered to be one hormone that is liberated by the adrenal
gland. There may also be another hormone with a stronger effect
on salt and water metabolisms as well as a hormone with andro-
genic activity.

The hormones have their effect peripherally on the tissues.
They may affect the processes occurring in the liver. The tendency
for protein to be converted into carbohydrate is augmented. The
tendency for amino acids to be stored in the form of protein is
suppressed. The mobilization of fat is augmented and the com-
bustion of fat is increased. These are catabolic effects which affect
carbohydrate, fat, and protein metabolism. At the same time there
is a reduction in the peripheral utilization of carbohydrate. There
may be changes in the renal threshold, that is changes in the
tendency for the renal tubule to reabsorb carbohydrate. Changes
in the electrolyte metabolism also occur. There may be more
tendency for sodium to be reabsorbed by the renal tubule and
less tendency for potassium to be reabsorbed by the renal tubule. The androgenic effects become apparent over a period of time. Changes in steroid excretion will also occur. Changes in the electrolyte composition of the blood are usually manifested by increase in the alkali reserve as reflected by the CO₂ content of the blood. The tendency for alkalosis to develop is one of the commonest manifestations of electrolyte imbalance, resulting from over stimulation of the adrenal cortex. There may be hypochloremia associated with this change or there may be an increase in the blood sodium with little or no change in the chloride content of the blood. Concomitantly and usually secondary to the development of the alkalosis there will be a reduction in the potassium content of the blood. This may be associated with weakness on the part of the patient.

The carbohydrate tolerance curve may be shifted towards that characteristic of the diabetic. Glycosuria may also develop in the patient. Hypertension may develop as well. And there may be some storage of water along with the storage of sodium. In addition to these specific effects there are the non-specific effects which Dr. Kinsell referred to. This is probably one of the most fundamental phases by which disease processes are altered, that is to say the body’s response to injury is modified. The response to injury is suppressed and agents which under ordinary circumstances would cause marked cellular reaction with exudation and collagen elaboration no longer provoke that type of response.

Dr. Levine: At this stage of the game I think we ought to bring up the question of infection. We have been talking about reactions. Dr. Mote would you like to talk about the relationship of these substances to infections.

Dr. Mote: There has been a considerable amount of work done with ACTH and cortisone in animals and in human beings. This is one phase of experimental medicine where it would appear that the human being is your best experimental animal because of a number of real discrepancies between the results in animals and in human beings. Now to give an example in the question of infection.

Certainly most of the studies would indicate that the doses of ACTH and cortisone used in animal studies have if anything accelerated the course of the infection. It has spread more rapidly, the mortality rate has increased, and the duration of the experiment has shortened. Now that would indicate that they are both pretty serious hormones to use. Furthermore, in the experimental animal with the doses used of both hormones, there appears to be a suppression of the formation of antibodies.

Now let’s switch to the human being. First I would like to say
that ACTH or cortisone, if the dose is sufficiently high, can and will do away with most or all of the symptoms of a great many illnesses, whether or not the course of the illness is altered. And that is also true of bacterial infections. Now you recall Max Finland treated lobar pneumococcal pneumonia with nothing except ACTH, and in the cases studied they recovered. It is interesting, that although all the symptoms of the disease disappeared in a matter of hours, the bacteria were still present and at least one case had pneumococcus septicemia with no symptoms whatever.

The other area, where it is important with regard to infection, is where patients have been on very large doses of either ACTH or cortisone. Here a bacterial infection can occur and not be detected at all, and the patients may be clinically perfectly well until suddenly they turn over and die. Fortunately that is usually on excessive doses of either hormone.

To give you examples, some patients with terminal carcinoma were treated with large doses of ACTH in Chicago by Taylor and Irons, and most of those patients were clinically well until shortly before death and yet when autopsies were performed they had extensive lesions, abscesses, pneumonic areas scattered throughout their lungs and elsewhere. And then you have McDermott's work in tuberculosis where he was looking primarily at the laryngeal lesions of tuberculosis which receded rapidly under ACTH or cortisone and at the same time the symptoms and essentially most of the signs of the disease improved and some of the major symptoms disappeared entirely. So that I think you have a very real problem here. You have to use these things intelligently, and just because a patient doesn't do well at a given dose of either of them you can't make the assumption that you can go ahead and increase the dose. You may do away with all the symptoms and signs of intercurrent infection, although it is extending, and that's the danger, and that's why we have to be intelligent in their use and not overuse them. On the other hand, used properly, I don't believe the record is too bad for drastic things happening.

Dr. Levine: Talking about infection, let's go on with that. Dr. Segal, what's been your experience with ACTH and cortisone in infections?

Dr. Segal: I would like to talk about the use of ACTH in managing a group of patients with a large variety of pulmonary disease such as I have personally encountered. The danger of infection is really great and particularly runaway infection, once you begin to employ intravenous ACTH in particular. We made a cardinal rule of giving penicillin concomitantly with our use of ACTH in all patients who have any type of underlying pulmonary
pathology. Recently, we were treating a patient with ACTH in continuous intravenous form and he made a spectacular recovery from progressive pulmonary failure, secondary bronchial asthma, and emphysema. And while he was apparently recovering, approximately on the third day after having stopped the intravenous ACTH, he suddenly developed a temperature of 104 degrees F. with frank shaking chills and a great deal of cyanosis. We were unable to determine the cause of this high rise in temperature which persisted for four days. Blood cultures were negative. Widal, agglutinins, were all negative, and he recovered when high doses of penicillin were employed. He didn't respond to aureomycin. We have seen that this sort of thing occurs and in the early days with ACTH, particularly when the antibiotics were not used simultaneously. On the basis of our own observations, we now make a strict rule of giving penicillin along with ACTH.

Dr. Levine: What's been your experience, Dr. Barach?

Dr. Barach: In patients that have bronchial infections as demonstrated by pus cells in the sputum, either due to chronic bronchitis by itself or in association with pulmonary emphysema or bronchial asthma, we have observed increased suppuration in the lungs. These are cases treated for intractable bronchospasm. In one instance a patient discharged a yellow appearing material from the sinuses. It would appear that in those cases in which the choice had been made to use either ACTH or cortisone that an appropriate form of antibiotic therapy accompany the administration.

Dr. Levine: You said an appropriate form of antibiotic therapy. Dr. Segal mentioned penicillin, and he mentioned aureomycin. Would you then, Dr. Barach, use aureomycin and penicillin together or some such combination?

Dr. Barach: I wouldn't use aureomycin or terramycin or chloromycetin with penicillin. There is adequate evidence that these drugs should not be used together, for several reasons. The drug of choice, in my opinion, is penicillin. Certainly more gram positive organisms are found in bronchial infections. One may encounter a resistant staph in which one may use temporarily one of the other antibiotics. As a rule gram negative organisms do not primarily cause infection. They are regularly present after effective penicillin treatment for bronchial infection. Only rarely do they invade the lung. The most common is Friedlander's bacillus. When it is present then chloromycetin or terramycin or streptomycin may be used. There is considerable hazard in the attempt to eliminate both gram positive and gram negative bacteria. I don't think this is the place to discuss that because we are going to discuss that Monday morning. I would agree with Dr. Segal
that penicillin would be the first choice in all gram positive bacteria and only in the event that one has an actual proved case of Friedlander would one use any of the other antibiotics.

Dr. Levine: Dr. Kinsell, is there any reason to use either cortisone or ACTH in infectious processes in chest diseases?

Dr. Kinsell: I think there is a major use for ACTH and cortisone in many severe infections in the chest and elsewhere. Perhaps it would be well to just re-emphasize some of the things that have already been said. First that the adrenal steroids which result from ACTH administrations including cortisone and other things such as compound F do not exert any desirable effect in so far as bacterial growth is concerned. That is bacterial growth goes on at full speed and inhibition of growth is one of the things that they do not do. In the same breath, one can say in a broad and I think in a correct sense that ACTH and cortisone cure nothing. They have a multitude of effects but in terms of clinical thinking do not cure, particularly in regard to conditions which involve the chest.

Perhaps two positive effects deserve considerable emphasis. The one would be, that the adrenal steroids do apparently interpose a barrier between multiple toxins and multiple cells. So that in the case of Dr. Finland's pneumococcus pneumonia with bacteremia, the patient was clinically well despite the fact that he had flourishing bacteria in his blood stream. And one can make sense out of that by assuming this matter of the interposition of a blockade between the toxins elaborated by the bacteria and the body cells which previously had been badly damaged by the toxin. The second effect is that of production of lysis or prevention of formation of fibrous connective tissue. This can be either good or bad. In the case of chest conditions, obviously it can be bad. However, in the case of certain types of chest conditions, this may be desirable. I think that one can say that, if we for the moment leave out tuberculosis and some other granulomatous conditions, if we limit the consideration of ACTH and cortisone to the treatment of the more acute non-tuberculous infections.

In any patient who has a severe infectious process involving the chest which does not respond adequately to chemotherapy, the administration of adequate amounts of ACTH and/or cortisone, depending upon the particular situation, may very well be life saving. If a barrier can be interposed between the toxins and the organism, it will perhaps give the individual an opportunity to rouse and to mobilize his own specific defense machinery and give the chemotherapeutic agent a longer time in which to produce its effect.

Dr. Levine: Do we all agree on that? Dr. Kinsell has suggested
a method of approach in severe infections which would seem to depend on a delicate balance. Dr. Mote, what do you think of it?

Dr. Mote: I am sure there would be considerable difference of opinion on Dr. Kinsell's last point. And I think it will take considerably more work before there will be unanimity of opinion on either side of the fence. We really don't know enough about this barrier that he speaks of, as to how much of it is good and how much of it is bad. And of course this is just one of the minor details. Briefly you might say that this is a new era of medicine and the greatest challenge of modern medicine. And don't be surprised if you see conflicting reports coming out because no one known any of the answers just yet. It will require a considerable amount of experimental work over the next decade before all the answers are clear cut.

Dr. Levine. A question has just come from the floor. It relates to an effect produced by long continued usage of ACTH. In the particular case mentioned, a male of 55, who was on continued ACTH therapy, suffered marked and disturbing loss of libido. Dr. Freeman, does this occur commonly in patients under such treatment?

Dr. Freeman: Loss of libido occurs frequently in the male. Of course you have to qualify this statement because a number of males who have been sick and unable to have many ideas, have gotten rather strenuous ideas, and conversely I quite agree that some of the males certainly lose their libido. Likewise some women have increased libido and some not.

Dr. Segal: The oldest man of our series was 72. And on the other hand he had his first successful erection and emission following a complete remission of status asthma after a successful course of ACTH.

Dr. Levine: We have a question from the floor, which may be related to the same subject. It is in regard to a patient who was receiving ACTH in large doses. One day he offered to buy the doctor's wife a cadillac car and rapidly showed other signs of euphoria and grandiose ideas. What is the relation of euphoria and ACTH treatment? Now who wants to answer that one? Dr. Mote is going to try it.

Dr. Mote: I said I'd try it. As you may know, there have been some studies concerning the electroencephalographic recording of people on ACTH. I'm not an electroencephalographic expert, but there certainly has been an increased amplitude. Some people have thought that what you really are doing is raising the pitch or mental activity and allowing fundamental problems, that you otherwise keep repressed, to come to the top and up to the conscious level. Actually, no one has studied this problem of behavior...
patterns in sufficient detail to know all the answers. It poses an intriguing problem, and it gives some insight into what makes successful businessmen and other people like that. Maybe they have a sensitive adrenal pituitary mechanism. It certainly needs investigation. I'm sorry you didn't get your cadillac.

Dr. Freeman: There are a few other considerations that might have a bearing on the cause of the euphoria. Usually these patients manifest some euphoria which may be physiological in origin. Later on they may have insomnia and then may become frankly psychotic in some instances. Usually at the time when these manifestations become apparent there are frank disturbances in electrolyte and carbohydrate metabolism. Maybe not invariably but frequently this is the case. The combustion of carbohydrate is exclusively the source of energy for the brain, and since the peripheral utilization of carbohydrate is modified by hormonal balance, there is a definite possibility that the utilization of carbohydrate by the brain may likewise be modified or reduced to some extent in relation to the hormone balance brought about by the therapy.

The second possibility is that a redistribution of electrolytes in nervous tissue may be brought about by hyperfunction of the adrenal cortex. An increase in sodium content of the cell, and a reduction of potassium content of the cell takes place in an alkalosis and in response to adrenal hyperfunction. I have also seen psychotic manifestations in patients that have undergone electrolyte depletion when they have been maintained on a low sodium diet or on an acidotic regime for a continued period of time. So I think redistribution of electrolytes might be a factor.

Dr. Levine: Now let's discuss the clinical use of ACTH and cortisone. Dr. Segal, would you like to discuss bronchospastic diseases with particular emphasis to asthma.

Dr. Segal: The patient with serious bronchial asthma, in the status state, presents a difficult and important therapeutic challenge. In this group of patients, ACTH and cortisone offer an effective way, in a good percentage of them, of inducing a remission. These remissions, unfortunately, are brief in duration. They may last varied periods of time, from days or weeks up to several months or perhaps longer in the occasional patient. Repeated courses of therapy may be necessary and six to seven or eight courses of therapy in a period of a year have been given to some of these patients. There is the law of diminishing returns, usually with repeated courses of therapy. The good effects one sees in the first or second administration are not seen again subsequently. We have given approximately 75 courses of therapy and have been rather encouraged at the immediate results fol-
lowing such therapy. Certainly it is an important adjunct along with our physiologically directed therapy. We seldom treat patients with ACTH in severe asthma.

It's generally our custom to set up a continuous intravenous drip of 5 per cent glucose in distilled water, giving three liters in a 24 hour period, accomplishing this by a flow of 30 drops a minute. We add aminophyllin in various concentrations to the intravenous infusions. And then in our very next period we employ ACTH parenterally and to save time we are also employing ACTH in continuous intravenous drip, but more about that later.

We are not able to demonstrate in these cases any reversibility of the antigen antibody mechanism. We don't see any consistent changes in skin tests. We haven't been able to show any changes in passive transference and we have not been able to show in the acute asthmatic patient any block in the effects of histamines or acetylcholine. On the other hand, we have been able to show a protective block against the effect of dog dander or feathers in particular cases involved.

Dr. Levine: Dr. Barach, do you want to pick it up there and tell us how you decide, in the treatment of the asthmatic patient, when to use ACTH or cortisone, and also something about the management of the case under such treatment.

Dr. Barach: My impressions are based on 60 patients who have had either bronchial asthma or bronchospastic type of pulmonary emphysema. These patients have received a total of 120 courses of treatment. In 20 courses, about 16 per cent, ACTH or cortisone appeared to serve a useful purpose. In 12 of these the duration of the improvement was longer than two months.

There are certain groups of people that I think may be benefited by cortisone or ACTH and there are others we have studied who, I think, are not benefited. The ideal patient has bronchial asthma due to ragweed pollen, who is in some general hospital with severe asthma on about the 15th or the 20th of September, where you know that with the first frost the asthma will be over. We have treated several such patients either during the summer or the late summer. That in a sense is a self-limiting disease. The use of ACTH or cortisone under those circumstances gives a period of remission, the average of which is about 19 days, long enough to carry through the ragweed season. There is another group of cases in which the patient with bronchial asthma has not been in bad shape but after a couple of respiratory infections begins to have severe attacks. Some of these cases have done well on ACTH. On the other hand, patients with intractable bronchial asthma, in which there is no obvious precipitating cause, are not
benefitted by ACTH or cortisone except temporarily. In these
cases, our regular experience with ACTH is the swift law of dimin-
ishing returns. The third course, repeated after a week, may be
of little help. Our belief is that in the treatment of any of this
group of cases, if we find a reason and can look forward to elim-
inating the cause, we will get much better results. Such a situation
may be the termination of pollen or the interruption of the in-
tractible cycle due to colds or to prepare the patient for some
other kind of procedure such as pneumoperitoneum or to teach
diaphragmatic breathing, or some other kind of help that will
carry on where the ACTH leaves off. We are on far firmer ground
if we treat patients with intractible bronchospasms of the type
that does not go from one seige into another.

In our early series we had two cases of edema of the lungs on
ACTH. It often is rather difficult to tell if the patient with severe
asthma has circulation insufficiency. But it is desirable in these
cases to give three grams of potassium chloride a day for the
reason that if we do find moist rales developing in the lung we
then give mercuhydrin, preferable on the third or fifth day of
treatment. If you haven’t given potassium chloride and then give
mercuhydrin, you will not only get a loss of sodium but acute
potassium deficit with weakness. Giving potassium is desirable
even though the serum potassium level may be unchanged. Potas-
sium is lost in the urine, and we do not have an adequate method
of measuring this except by the electrocardiogram. So we are in
a better state of protecting the patient from possible complica-
tion if we have given potassium chloride, and then mercuhydrin freely.

I’ve had this experience a number of times that although mod-
erate doses of either cortisone or ACTH would get a good many
people free of symptoms, there are also many more cases of
asthma or bronchospastic emphysema in whom one may give a
160 or 200 mg. of cortisone a day for 10 days without any result.
We have simply wasted the patient’s time. We are better off if
we give a large dosage to almost every patient. I also have the
feeling that the remissions are longer. By a large dose I mean
giving cortisone at 400 mg. a day in divided doses for a period
of three to four days and 300 mg. a day for sometime more. With
ACTH I like to begin with 50 mg. every six hours round the 24
hours. Under those circumstances the remission takes place fast.
On the third day the remission is secure and steady. And if there
is something in this separation of the antigen and the antibody
in asthma, then a longer period of freedom is obtained. One must
watch the weight, maintain a rigid low salt diet, and potassium
chloride must be given. There is no harm in these large doses,
since far larger doses than these have been given. The same
applies to cortisone given intramuscularly. In those cases we realize the problem has been a severe one.

The side effects of the drugs are not so apt to take place with a limited short dosage of four or five days with ACTH and eight days with cortisone as they are naturally with the longer periods of treatment that are used in arthritis. In our cases there have been no serious mental effects. We have observed the usual well being. In only one case a woman was depressed, and this was because she wasn't elated as she had hoped to be.

Dr. Levine: Dr. Barach's discussion of the clinical problem represented by the sodium and potassium levels brings us back to our previous mention of the metabolic effects of these substances. You will remember that among the effects produced are changes in the carbohydrate, fat, and protein metabolism. In addition there are changes in the renal tubule which results in a greater tendency for sodium to be reabsorbed and a decrease in reabsorption of potassium. All of this brings up questions of proper management of the patient under treatment. First of these is what are the laboratory tests essential to the management of the patient receiving one of these drugs. Dr. Kinsell, would you like to give us your opinion?

Dr. Kinsell: I'd be glad to, and I'd like to respectfully disagree to some extent with the management of asthma, from one standpoint only. I agree thoroughly that the initial administration of large amounts of hormones in asthma and in most other chronic conditions represents an optimal procedure. Gradual reduction in the dosage, and in the case of most patients with asthma the following of the eosinophile level, is apt to be a helpful procedure. In the allergic states, particularly, the level of the circulating eosinophiles is apt to coincide precisely with the clinical status and with the degree of therapeutic effectiveness of the hormone. Our experience with asthma is not nearly as broad as that of the previous speaker, but all of the patients whom we have treated or have followed have been known to have severe asthma of many years duration. Asthma which has received every kind of treatment in the book without benefit. And it is our strong feeling that continued treatment without interruption with gradual reduction in dosage will produce a better result in the long pull than will intermittent therapy. That is recurrent courses of therapy. This statement applies only to the severe intractible asthmas with long duration.

Now as to the basic laboratory and physical things that one follows in terms of evaluation of the patient and in terms of keeping him in the best possible clinical condition and in terms of obviating or eliminating completely or nearly completely any
of the untoward effects of ACTH and cortisone. First, every patient under treatment, at least in the early phases and preferably longer, should be weighed every day. If the body weight is increasing rapidly, it may indicate fast fluid accumulation. And by the same token, the dialy checking of the blood pressure in patients who are home should be done. One can perfectly well arrange for a visiting nurse or even a member of the family to do this to save the patient expense and to save the doctor unnecessary trips. Second, an initial base line before any treatment is instituted should be obtained. There should be at least two fasting blood sugars and two eosinophile counts. The vast majority of patients who receive ACTH and cortisone will not get into trouble in so far as their carbohydrate metabolism is concerned. There’s no question that all of us will, in the years ahead, tend to precipitate diabetes in people who are in a rather diabetic state. For that reason, it is most essential that one know what the fasting blood is prior to therapy and that the sugar be followed at intervals of two or three times a week in the first week or two of therapy and then at gradually decreasing intervals. Slight elevation is apt to occur, but if this is increasing one needs to take heed.

The evaluation of the eosinophilic count, preferably by the Randolph technique, is a simple procedure and a valuable one. In the case of ACTH it tells one whether the particular individual has adrenals which are responding to ACTH in adequate degrees. This can be used as a diagnostic procedure of adrenal insufficiency. In terms of therapeutic evaluation, by and large, one tends to keep an eosinophile count at least in the early phases of therapy, below a level of 100 per cubic mm. Many of the asthmatics and patients with other allergic states will have initial counts which are up in the thousands. The normal range varies from 150 to 250 per cubic mm. With adequate therapy in patients with high eosinophile counts, there will be a fall to zero within the first two days of treatment. To obtain this effect one needs to use about 25 mg. of ACTH intramuscularly every six hours, that is 100 mg. a day, or in terms of the continuous intravenous infusion somewhere between 10 to 40 mg. a day, depending upon the patient. With cortisone, the dose may be as much as 600 mgm. in the first day or two, but usually 300 to 400 mgm. will be adequate to produce this desired depression in the circulating eosinophiles.

The matter or routine limitation of sodium and the routine administration of large amounts of protein is most essential. One of the outstanding effects of large amounts of these hormones is the catabolism that breaks down body proteins, so that one wants to supply large amounts of dietary protein, that is in excess
of 120 grams per day of good, biologically adequate, protein and to limit the sodium intake to a low figure. What may be considered a low figure varies among individuals. In some people, particularly those who have any tendency to hypertension or to abnormal fluid accumulation on a cardiac or other basis, it will probably be necessary to limit the sodium intake to less than 300 mgm. daily.

To combine a high protein intake with that low a sodium intake means that one has to use special preparations. A very satisfactory one which we have used and are using to a great degree is one of the reconstituted desalted milk preparations. By using this as a dietary supplement one can increase protein and still keep the sodium low. To administer supplemental potassium, the simplest form is the saturated solution of potassium chloride given in such an amount that the patient receives in the neighborhood of 4 to 6 grams of potassium chloride a day. It is not well to monkey with homeopathic doses. If the patient has any renal insufficiency, then obviously one is careful both about the addition of potassium and the addition of protein. But in the presence of normal renal function, one may safely administer such amounts of potassium.

One other item is the co-administration of testosterone. Reverting to previous discussions, but not with that particular concept in mind, testosterone has the opposite effect of cortisone—like adrenal steroids in that it is a powerful protein anabolic agent. It causes the building up of protein tissues. If one gives a sufficient amount of testosterone, one not only conserves protein and neutralizes the protein catabolic effect of ACTH and cortisone to a large degree or completely, but he also specifically conserves potassium and also tends to put it where it's needed, which is inside the cell. One could go on at great length within terms of intravenous potassium administration under acute conditions, but those are at least some of the essentials relating to the medical management of these patients.

Dr. Levine: That sounds to me as though the use of this material isn't exactly routine office practice. I would like the various members of the panel now, running right down the table, just to take a few minutes and state whether they agree that all this work-up is necessary, or, on the other hand, if something has been left out—and just what are the measures that you think ought to be used in control of the patient under treatment.

Dr. Mote: Dr. Kinsell's outline reflects his training. He happens to be a metabolic man. It's certainly true that in certain situations one may need all of the things which he mentioned. None the less I would say that to try to keep all of those in mind in an office practice would be nearly impossible. My personal view would
be first to check the eosinophils. Second the electrocardiogram periodically every couple of weeks. Third, I would protect the potassium situation of the patient by giving liberal potassium. And fourth, I would restrict sodium intake to no added salt if you are on a regular salt diet.

Again if you are going to work with all high doses of ACTH or cortisone, I agree with him that this business of carbohydrates is something to take into account. But under the ordinary circumstances I'm not at all convinced, on the data I've seen to date, that that is a real threat. I haven't been convinced that one can cause true diabetes by cortisone or ACTH. You can cause glycosuria and hyperglycemia in some cases. In other words, unless one is working with high doses, the management isn't as difficult and does not require as many studies. From a straight clinical point of view, daily weight and blood pressure, in the beginning until the patient is stabilized, is in order.

Dr. Freeman: The initial work-up should be in a hospital. The major items have been indicated by Dr. Kinsell. The tests are really divided into two groups; those that have to do with the evaluation of the therapeutic effectiveness and those that have to do with toxicity.

The initial development of eosinopenia is one of the best laboratory guides as to the adequacy of the dosage of hormone. It indicates that the ACTH is producing a decided stimulation of the adrenal gland or that the amount of cortisone administered is enough to produce this reaction. Then the therapeutic objective becomes to utilize the minimal dose of the hormone which will bring about the desired effect clinically.

As part of this first hospital study we have carbohydrate tolerance and the other things that have already been mentioned. I think the electrocardiographic tracing should also be included in the preliminary study as it may be a valuable aid later on as an indication of the electrolyte imbalance or depletion, and for interpretation of any complication that may arise in the course of therapy. After the patient has had a preliminary study a clinical dosage schedule is initiated and then the dose is tapered to the minimal level for effective therapy. There will have to be routine check-ups after the individual has gone home every week or so until the clinical response is thoroughly established.

What is the minimal dosage that can be used in the management of the chronic patient? The amount is variable and quite unpredictable in a given instance. I remember one patient with pulmonary tuberculosis who developed diabetes so far as carbohydrate tolerance and glycosuria were concerned on 40 mg. of ACTH daily, and this glycosuria and some of the hyperglycemia
persisted for a month after therapy had been discontinued. In other patients I have seen a prediabetic carbohydrate tolerance curve prior to the time of ACTH administration, which was not influenced at all by the administration of fairly large doses of ACTH. So one can make few generalizations about the response of the patient.

We have to realize that the frequency of administration of the hormone is related to the effectiveness of any given dose. And that various nutritional states of the patient may also influence his response to therapy. Debilitated, undernourished individuals give a poor response to ACTH. They usually have a low ketosteroid excretion and other evidences of reduced adrenal function, and they may be slow in their response to treatment as evidenced either by steroid excretion in the urine or by the eosinopenia produced by the hormone. The range of dosage which we have found compatible with chronic therapy has usually been around 20 to 30 mgm. of ACTH daily given in two to three doses. We have seen few patients who could tolerate more than 30 mg. daily for an indefinite period. We have one chronic asthmatic with recurrent episodes of status asthmaticus who has tolerated 40 mg. daily in two doses over a period of six months. We have a few patients that have taken 20 to 30 mg. a day for over two years.

Dr. Segal: It's differences in opinion that has always made horse races popular. We have been disappointed in continuous therapy in bronchospastic disorders. After our preliminary investigations, we have made a rule of treating our patients from three to 19 days with intensive therapy and then carrying on maintainence therapy with rectal aminophyllin and effective bronchodilator drugs and other supportive therapy. We resort to repeated courses of therapy rather than protracted continuous courses. We see a high incidence of refractory asthma that does not improve with continuous daily ACTH therapy. We have studied eight such people. When they came back in severe status asthmaticus we resorted to continuous intravenous therapy. In spite of the inconvenience of administration of this therapy one has a real opportunity of sending an infant on a man's errand. The doses are small. We employ a continuous 24 hour drip technique in contrast to the eight hour technique suggested by Thorne and Gordon and others. We give 10 mg. of ACTH to each liter of solution of 5 per cent glucose in distilled water and use three such liters per day. We have noted that in patients with refractory asthma, the eosinophile count comes down strikingly within a 24 hour period.

Studies of metabolic function are indicated and are of great interest and value in the patient treated for any considerable period of time. We routinely give six or eight ounces of orange
juice every morning to all our patients and that's quite a valuable amount of potassium. In addition, we give potassium iodide in dosages of 15 to 20 minims every four hours, and we feel that takes care of their potassium need. We're not particularly concerned about their potassium need except on the intravenous route of administration. We restrict salt, and should call attention to the danger of the high sodium content in the drinking water of some cities.

Dr. Barach: I think it is good to bear in mind that bronchial asthma can be treated by other means than either ACTH or cortisone. It is a disease in many instances of food or allergic origin in which removal or control of the precipitating factor may be of value or other forms of remissive therapy can be used. I advise against continuous treatment with the substances under discussion over a long period in patients with asthma. Those I have seen on such treatment for two months in bed are unhappy and not well. The longer we give ACTH the more we are apt to run into allergic reactions, diabetes, etc., and must take precautions necessary to prevent hypertension, cardiac insufficiency, and protein loss. Asthma is a disease of a paroxysmal nature, and I would doubt very much that it is necessary to give long courses of ACTH. If we do, then we run into hazards that often make us wish the drug hadn't been used. All of the conditions associated with asthma can be met with or coped with, in brief courses of either ACTH or cortisone.

Dr. Levine: Now a question has been asked from the floor on an entirely different subject. Have cortisone or ACTH any value in the treatment of sarcoidosis? Who wants to answer that? Dr. Mote?

Dr. Mote: There are some studies being reported at one of the meetings this week in which large doses of ACTH have caused marked regression of sarcoid lesions. It was first observed about two years ago in a case of sarcoid of the eye. It wasn't taken too seriously, although the eye lesion cleared up. The work was not followed up for a matter of a year and a half. It certainly requires large doses and it is too early to know how soon and to what extent the disease will recur. With lesser doses it has not been satisfactory and recurrence has been rapid. With larger doses it appears to be most encouraging.

Dr. Levine: The next question. We've heard a lot about the danger of using ACTH or cortisone in the presence of infection, and that of course would include tuberculosis. Is it safe to use ACTH or cortisone in a patient who has fibroid or apparently healed tuberculosis? Dr. Kinsell.

Dr. Kinsell: One has to assume that any patient who has had
tuberculous infection is potentially in line for activation of that infection if he receives long term ACTH and cortisone therapy. And further when one adds to that the ability of ACTH and cortisone to mask even advanced and advancing pathology, it means that he has to constantly be on guard in any patient on long term maintenance therapy. I don’t think there is any question that inactive processes have already been lighted up in quite a number of people. There is no question that many more will be. Precisely what the answer may be to this I don’t believe that anyone knows. Fortunately it is not a usual or a common occurrence, but it can happen and does happen.

Dr. Levine: Having heard so much about the danger of tuberculosis and ACTH, it occurred to me that those who are treating so much arthritis should have gotten into trouble with their patients in the older age group in which we are finding so much evidence of tuberculosis. I spoke to one man who has probably treated as much arthritis as anybody in the country and asked him how many cases of tuberculosis had developed, and he said, “What do you mean cases of tuberculosis, we haven’t had any.” I took occasion to look over a group of his x-ray films, and he had a percentage of nodules that were very obvious in some of the films but apparently none of these people had developed active disease. Has anybody here an opinion of how much activity or potential activity of tuberculosis would seem to be necessary before there is real danger in the use of ACTH or cortisone?

Dr. Mote: I can only tell you what I know, and what I’ve heard. There are cases under treatment who have had recent tuberculosis that have frankly broken down. Two of them with almost disastrous effects because there were no symptoms or signs. A bit of a cough but no fever, nothing in the way of symptoms until an x-ray film was taken and a complete consolidation of one lung found. It turned out to be tuberculous. Now on the other hand, there have been to my knowledge old well healed lesions treated and I don’t recall any of long standing cures that have flared up. I agree with Dr. Kinsell, theoretically, that it’s possible. A patient who has had recent tuberculosis should be watched carefully when using either hormone. If one has to use them one ought to accompany this treatment with adequate doses of antibiotics. Always keep in mind that one can completely mask the flare-up if it should occur. But it doesn’t appear at this time to be a real danger in old, well healed cases.

Dr. Levine: Of course it’s a nice thing to know if the tuberculosis is well healed. How often does coronary thrombosis occur in elderly patients treated with ACTH and associated with that question on the incidence of thrombo-embolic phenomena during
treatment. Dr. Freeman, would you like to answer that question?

Dr. Freeman: Well, we have had one or two arthritic patients who had coronaries while under treatment with ACTH. One man who had been on treatment for about one and a half years had a coronary and there have been several instances of thromboembolic phenomena reported. However, there hasn't been any clear cut evidence that there was a close association between the use of these agents and the development of these changes.

Dr. Mote: Of course one will have to keep in mind that many diseases affected by ACTH and cortisone are rather prominent in the age groups where they have arteriosclerosis and coronary disease. I don't believe there are any statistics that would indicate a direct connection, but there have been some cases of coronary disease develope while patients were on ACTH or cortisone. At the same time with this treatment, we have taken ridden patients and given many of them the chance to live a normal life. I think we have to keep in mind that we are in an age group where these diseases occur. Thromboembolic phenomena have been reported, on the other hand, we have groups supporting the use of the hormones in the treatment of thrombophlebitis. So we have it at both ends. That is an interesting thing about this period in medicine. We can have apparently completely contradictory results which in some cases are perfectly valid observations. It just simply shows how little we know.

Dr. Segal: We know little about these drugs and I am rather curious to see if someone on the floor would ask how these work. They cure nothing, but make a lot of people feel well. The only data we have is that they probably throw up a protective barrier around the cell, protecting it against a wide variety of stress and stimuli. I should like to ask any member of the panel to tell us what is going on inside the cell.

Dr. Mote: I'd love to tackle that one. We talk about this barrier that is set up by the cell. The thing we have to be most careful about is not so much the barrier in that cell but rather an intellectual barrier that this tremendous challenge has thrown up and the terrific amount of imagination that will be required to rationalize any of these problems. Before it is all over we will have a great many new concepts of medicine, a great many new concepts of disease, a great many new concepts of teaching, and I am afraid it will be several decades that we must guard against building up an intellectual barrier at facing what appears to be an insurmountable intellectual challenge.

Dr. Levine: Will insulin control the effect of ACTH on carbohydrate metabolism in a moderate diabetic, especially with reference to brain damage?
Dr. Kinsell: We have, with malice aforethought but under carefully controlled experimental conditions, used ACTH in some mild diabetics under study of the metabolic ward. I think one can answer that question best or most briefly by saying first the diabeticogenic effects of adrenal steroids is associated with insulin resistance. That is if one takes a given diabetic patient who has had an insulin requirement, say of 10 units on a given diet and keeping everything constant, administers increasing amounts of cortisone or increasing amounts of ACTH to that patient, the insulin requirement will go up in a manner which suggests a geometrical progression type of affair. If the dosage of ACTH is sufficiently large, as much as several thousand units of insulin a day, and that is an actual occurrence, may be required to control the diabetic state. When such hormone administration is stopped, in the space of a short time the diabetes tends to go back to its original state. The co-administration of insulin, however, is mandatory if one must give ACTH or cortisone to a diabetic patient because of some condition which endangers his life and in which one has a good reason to believe that the hormones may be of real value.

Dr. Levine: If a patient who is receiving ACTH develops a hemorrhage from a gastric or duodenal ulcer, would you say that this was due to the use of this substance?

Dr. Segal: I think a group of investigators, Dr. Graham in particular, have conclusively shown that there is an increase in lipo enzyme titre with ACTH therapy. Therefore, one should always, before using ACTH or cortisone, get an accurate history to be sure that there is not a peptic ulcer and that one did not exist. There has been an increasing number of blow-outs, perforations, and hemorrhage on this therapy in such cases. I personally have not encountered any.

Dr. Levine: What determines whether to use ACTH or cortisone?

Dr. Barach: That is a difficult question to answer. It depends on several considerations. I don’t know if I am in a position now to state my preference for either ACTH or cortisone. I don’t think I have enough data to make whatever opinion I have valid, and I would just as soon pass it on to someone else. I would like to add one thing however. We have had three allergic reactions to ACTH, two of them very alarming. There was acute anxiety and difficulty in breathing taking place within a very short time after intramuscular injection of ACTH on the second course. In each instance intravenous benadryl seemed to be far more valuable than the previous injection of adrenalin. From the safety point of view as far as I know no such reaction has taken place with cortisone, or have they?
Dr. Mote: I must say it surprised me, but there have been two definite cases of marked allergic reaction to cortisone and I don’t understand it anymore than anyone else does, because it’s certainly not common to have an allergic reaction to steroids. Both of these were where cortisone was injected, not taken by mouth.

Dr. Levine: I think that we can continue with this discussion for quite a little while. There is a great deal to discuss and many questions can be raised, since there is certainly not enough definite information on either substance, how it affects the body or how the body reacts to disease, to stress, to disturbances of many kinds, to permit anyone to make definitive statements.

Since it is necessary to draw the symposium to a close, let us try to summarize what has been discussed this afternoon. First let us accept the fact that with the introduction of these two substances, ACTH and cortisone, we are entering a new stage in the study and treatment of disease. It is the field of attempting to change the reaction of the body to a disease process rather than the attempt to attack the disease itself.

As regards the two new substances in question, it must be remembered that although their effect as measured by end results may be much the same they are different and their mode of action is different.

ACTH is a polypeptide liberated by the anterior lobe of the pituitary gland and which acts on the cortex of the adrenal gland to cause production or liberation of steroid hormones.

Cortisone is a steroid hormone itself which has its origin in the adrenal cortex and acts on the periphery of the body.

ACTH requires an intact adrenal cortex if it is to be effective, whereas cortisone is a substitution product and thus does not require an intact adrenal. Cortisone for all practical purposes produces similar results to those created by stimulation of the adrenal gland by ACTH.

In the use of these drugs there are many and profound changes occurring in the body which must be remembered, measured, and in some cases compensated for, if therapy is to benefit the patient. Consequently, a patient who really needs ACTH or cortisone therapy should always be hospitalized at least in the early part of treatment. During this period the patient should be weighed every day to detect early rapid fluid accumulation. Likewise blood pressure should be checked and a baseline of blood sugar and eosinophil counts should be made. In general, sodium intake should be limited, the protein intake increased, and supplemental potassium should be given.

As regards clinical use, to date it has been found most effective in asthma, Loeffer’s syndrome, and possibly Boecks sarcoid.
Whether there is any application to tuberculosis is yet to be determined. Thus far the evidence points to a deleterious effect on the disease while the patient feels improved. There is some suggestion that methods of its utilization may be found and the substances applied to emphysema, pulmonary fibrosis, and interstitial pneumonitis. In bronchogenic carcinoma, although the disease as such is not involved and its course remains unchanged, the condition of the patient may be sufficiently improved to justify its use.

Certain dangers must be borne in mind. First, the development of severe diabetes in individuals who might be considered pre-diabetic. Second, the chance of infection developing and getting entirely out of hand before it is recognized, and third, that allergic phenomena may be caused by ACTH as well as relieved by it.

The dosage will vary with the individual and the type of case treated, it being a good rule to use the lowest dosage that will produce the adequate results. There is some difference of opinion as to whether long term continuous therapy is more desirable than repeated courses of more intensive treatment.

With these few highlights let us close our discussion by saying the panel today has given us a view of the basic information and experimental background of ACTH and cortisone and some insight into its mode of action, method of using, and possible use for the future. I cannot remember where a subject involving both laboratory investigation and clinical experience has been so well and so clearly discussed. I should like to thank the members of this panel for their discussions and to compliment them on a job well done.