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John G. Mateer
Richmond W. Smith Jr.
Dwight C. Ensign
Raymond W. Monto
J. W. Keyes

See next page for additional authors

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Problems In Adrenal Steroid Therapy: Medical Staff Conference

Authors
John G. Mateer, Richmond W. Smith Jr., Dwight C. Ensign, Raymond W. Monto, J. W. Keyes, J. H. Shaffer, Clarence S. Livingood, and Raymond C. Mellinger
PROBLEMS IN ADRENAL STEROID THERAPY
Medical Staff Conference

J. G. MATEER, M.D., Physician-in-Chief

Panel

R. W. SMITH, JR., M.D. 1 J. W. KEYES, M.D. 4
D. C. ENSIGN, M.D. 2 J. H. SHAFFER, M.D. 5
R. W. MONTO, M.D. 3 C. S. LIVINGOOD, M.D. 6
R. C. MELLINGER, M.D. 1

Dr. Smith: The rapid development in basic steroid chemistry and in the commercial preparation of various therapeutic derivatives, with the inevitable flood of proprietaries, has led to considerable confusion for the practicing physician. It is apparent that we cannot discuss, in the short time at our disposal this morning, the indications for steroid therapy in the many areas of internal medicine and surgery. Accordingly, we will limit the discussion to the comparative properties of the various steroids, certain adjuvants of therapy and the ways in which the various specialties of the Hospital are presently using these materials.

It is logical to begin by commenting on the comparative properties of the corticosteroids which now are being used widely in clinical practice. These are listed in Table I. In order to compare their respective properties, hydrocortisone has been selected as the reference point, inasmuch as it is now recognized as the naturally occurring corticosteroid of greatest physiological significance. This is not to overlook the potential clinical importance of aldosterone but since this mineralocorticoid has no immediate therapeutic role it will be referred to only in passing. Hydrocortisone has been arbitrarily assigned a potency rating of 10 in each of the 4 physiological properties compared. The various steroids have been rated according to their effects on electrolyte excretion, carbohydrate metabolism, inflammation and ACTH suppression. The latter, as most of you know, refers to the property of a steroid to inhibit the synthesis or the release of corticotropin by the pituitary, which inhibition in turn results in the arrest of adrenocortical activity and leads ultimately to cortical involution. One point of importance is that with all the steroids listed, the anti-inflammatory or therapeutic effects and the ACTH-suppression effects run essentially parallel. So far, the organic chemists have been unable to divorce the anti-inflammatory action from the antianabolic or carbohydrate regulating action. This is a point often not appreciated by many practicing physicians. The tendency is to say, “Well, inasmuch as a steroid has less sodium-retaining action, it is safer.” Its other properties are overlooked. If we are to use the newer derivatives in practice we must realize that

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This is an edited report of a current conference of the Department of Medicine of the Henry Ford Hospital.

1 Division of Endocrinology
2 Division of Arthritis
3 Division of Hematology
4 Division of Cardiology
5 Division of Allergy
6 Division of Dermatology
there will be more potent effects on carbohydrate metabolism and on adrenal involution.

Dr. Ensign will say a few words about the many aliases that surround the delta derivatives, prednisone and prednisolone. The double bond in ring A, which distinguishes these steroids from their parent compounds, has not altered the relative potencies of the two. Since the overall potency enhancement of both has been so great, in the order of from 3 to 5-fold, the dosage difference for the two is, milligram-wise, quite small and possibly will not be heeded as clinically significant. This is one of the inherent dangers of enhancing potencies. The physician who once was impressed by the 50 mg. dose difference between 200 mg. of cortisone and 150 mg. of hydrocortisone, these being pharmacologically comparable, might not readily appreciate the differences between 40 and 30 mg. of prednisone and prednisolone, respectively.

The potencies of the halogenated steroids are well recognized. However, they have not been used widely for parenteral therapy due to the striking enhancement of the sodium-retaining action. Fluorohydrocortisone, for example, is also potent in respect to the other properties listed and the chief clinical value, apart from its topical use, is its ability to inhibit the adrenal cortex without yielding significant amounts of urinary 17-ketosteroids to confuse the measure of endogenous ketosteroid production. This applies even more to the fluoro derivative of prednisone. Perhaps the real significance of fluorohydrocortisone is the fact that it heralds a promising man-made chemical phenomenon, for there is early evidence that halogenation of other, non-adrenal steroids may potentiate their respective physiological properties.

Only early observations have been made on the biological potencies of the halogenated derivatives of prednisone and prednisolone. I have question marks in the table because this slide (Table 1) was made some eight months ago. The potencies may be a little nearer to that of fluorohydrocortisone than the 50 times hydrocortisone as listed. They are probably nearer 25 or 30 times hydrocortisone but I have had no extensive experience with the compounds.

**TABLE I**

**COMPARATIVE ACTIVITIES OF THE ADRENAL STEROIDS**

<table>
<thead>
<tr>
<th></th>
<th>Sodium Retention</th>
<th>Anti-inflammatory</th>
<th>CHO Effect</th>
<th>ACTH Suppression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldosterone</td>
<td>1500</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>F-Hydrocortisone</td>
<td>1000</td>
<td>250</td>
<td>250</td>
<td>250</td>
</tr>
<tr>
<td>DOCA</td>
<td>50</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Cortisone</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Prednisone</td>
<td>12</td>
<td>32</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>15</td>
<td>40</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>F-Prednisolone</td>
<td>250?</td>
<td>500?</td>
<td>500?</td>
<td>500?</td>
</tr>
</tbody>
</table>

This brief and general review of comparative properties permits us to turn to the next and perhaps even more confusing aspect which is the nature and names of the
many proprietary preparations now on the drug market. Dr. Ensign has been kind enough to agree to bring some sense out of this apparent turmoil.

**Dr. Ensign:** It is a turmoil all right, as this batch of sheets will indicate, torn from the last issue of one of the throw-away medical magazines. These are just the ads that had to do with the steroids in this last month’s issue. In spite of the great numbers of pages involved they pertain to just about two products. The confusing thing, of course, is that these drugs were released before being given official designations at the American Rheumatism Association Meeting. The names used first were not the more chemical terms which were finally adopted. The fortunate company that released its product to the market first in commercial quantities chose the catchy name of Metacorten®, which is what most people think of as the representative of this steroid group. The official name that was later selected is a somewhat more difficult one to pronounce and to remember, namely, prednisone. I think physicians are getting used to it. Prednisone and prednisolone are the official designations for the delta derivatives of cortisone and hydrocortisone, respectively. Prednisone is marketed under the names Metacorten®, Deltra®, and Deltasone®. It is present in Cordex®, which is one of the several “super” aspirins. It is presented in a buffered form with aluminum hydroxide and magnesium trisilicate as Co-Deltra®. In the prednisolone group we have Metacortelone®, Hydeltra®, Delta-Cortef® and Sterane®, which are often advertised as the most potent anti-rheumatics. Prednisolone is marketed in a buffered form under the names of Co-Hydeltra®. Prednisolone is the chief ingredient of the “super” aspirin put out by another company under the name of Sigmagen®. I think the deceptive aspect is that most of these advertisements speak about drug safety. If one takes the time, however, to read the little circular incorporated in the package, he finds that the same precautions have to be used and that the same side effects can occur as with cortisone and hydrocortisone. After all, these are very potent steroids. True, they are roughly four times as potent in their anti-inflammatory effects as our older friends, cortisone and hydrocortisone, but they are also four times as dangerous in some of the side effects. Even though activity is less with respect to sodium retention, this can still be a problem. The chief point in taking this much time is to make emphatically clear that behind all the new names we really have only two practical new steroids, namely, prednisone and prednisolone. They are extremely useful drugs in given situations but their use is fraught with the same dangers attending cortisone and hydrocortisone therapy.

**Dr. Smith:** Thanks very much, Dr. Ensign. The panel spent some time in preparing questions to best cover the subject of the hour, which is how we are using these preparations and not why. Which agents do we select? What are the therapeutic programs and what are we encountering as to side effects? These are to be answered in the light of experience by representatives of divisions of the Hospital. It was interesting to see how the thinking went. The first question to come up almost immediately from several quarters was: “Is there any basis for the preferential use of one or another of the parent compounds or their derivatives?” This is a question which we might direct to Dr. Ensign first since he has been so kind as to open the discussion.

**Dr. Ensign:** First of all, just to make myself clear and not to indicate that I am
advocating these drugs as a “cure” for arthritis, I might show you the outline of our current therapy for rheumatoid arthritis. Our basic program which has been a development over many years has been unaltered by the appearance of these new drugs. All of the steroids, both the old and the new, are used only as supplemental

PROBLEMS IN ADRENAL STEROID THERAPY

OUTLINE OF TREATMENT OF RHEUMATOID ARTHRITIS

BASIC PROGRAM

Orientation of Patient and Family

Diagnosis

Nature and course of disease
— no known cause, hence no “cure”
— but some relief possible for all
— a long term (usually life-long) program

Objective of treatment

— relieve symptoms
— improve general health level
— prevent crippling
— arrest disease if possible
— improve function of damaged joints
— educate patient in adjusting to any uncorrectable residuals.

Symptomatic Therapy

Rest
— mental
— physical
— local — splints in acute stage, with joints in optimal position

Aspirin or sodium salicylate to tolerance
Codeine — if necessary for pain relief during night

General Measures

Correct or improve personal and environmental stress factors wherever possible
Provide adequate diet
— supplemental vitamins or minerals if indicated
Insure proper elimination
Remove obvious focal infection
— antibiotics prophylactically
Rest — continuing definite program
— frequent rest periods preferable
— correct faulty joint positions
— proper supports if necessary

Local Measures

Corrective exercises
— detailed program
— all joints, through maximum range of motion
— daily, repeated several times, increasing as tolerated
Other physical therapeutic measures
— heat, dry or moist
— massage — avoiding tender joints
Joint aspiration and intra-articular hydrocortisone TBA — selected cases

Medications

Aspirin (or sodium salicylate)
— regular maintenance dosage
— enteric coated or buffered
Sedatives
Codeine
— sparingly for severe pain
— avoid other narcotics
SUPPLEMENTAL PROGRAM (Useful only as additions to basic program)

**Special Measures**
- Gold salts
  - Best available "stopping mechanism"
  - Safe if used with due precautions under direct personal supervision of physician
- Steroids and hormones
  - Cortisone
  - Hydrocortisone
  - Newer synthetic steroids
  - ACTH
- Phenylbutazone — if effective and well tolerated
- Blood transfusions
- Change of climate

**Reconstructive Measures**
- Surgical correction
- Rehabilitation
  - Physical therapy
  - Occupational therapy
- Devices to aid the use of handicapped joints

measures in selected cases. I think that we are undoubtedly using more of the newer preparations than we are of hydrocortisone in the long-term care of the patients who are receiving the steroids. We do not use steroids in every patient with rheumatoid arthritis; however, we are still using hydrocortisone in those who were started on it and have been taking it without appreciable side effects. One of our reasons for using more of the newer agents is to find out more about their properties, particularly as to whether the buffer coating which is offered gives any greater protection against some side effects. If I were treating a new patient and were not trying to learn more about the newer steroids, I probably would use hydrocortisone first. If the patient did well on a moderate or small dose and was not having any appreciable side effects, the hydrocortisone would be continued. If there were difficulty with sodium retention, I would naturally switch to one of the newer compounds. In our experience there is not much to choose between prednisone and prednisolone, with the exception that we do find the odd patient who apparently tolerates one better than the other or who responds to one better than to the other. Yet, there is nothing consistent about it to enable us to choose between the two.

*Dr. Smith:* Why would you start with hydrocortisone in preference to one of the newer agents?

*Dr. Ensign:* Because we know more about it and we have been working with it for a good many years. It is the naturally-occurring hormone of the adrenal gland. I think that when it works, it works as well as any other.

*Dr. Smith:* Perhaps Dr. Monto would like to say something about his experiences with the various steroids and whether he has any preference for one or another.

*Dr. Monto:* The steroids are the hematologist’s best friend and the closest to our heart is cortisone. We find these agents extremely useful in the management of the lymphomas and leukemias, in the hypoplastic states of bone marrow, as well as in idiopathic thrombocytopenic purpura. Perhaps my thesis is best illustrated by brief comments on a group of patients with idiopathic thrombocytopenic purpura. A regularly encountered response to steroid therapy in thrombocytopenic purpura, whether the latter is secondary or idiopathic, is the very prompt rise in platelet counts.
In one particular patient on about 80 mg. of hydrocortisone daily, however, there was an inadequate platelet response. The dosage was doubled without a further change. When cortisone in doses of 300-400 mg. was administered, we then noted a fair response. Another patient received prednisone at a level of 40 and later 80 mg. a day. There was no appreciable response. With 200 mg. of cortisone daily, however, a satisfactory effect was obtained and since this patient was an adult, splenectomy was done when we reached platelet levels of 150,000. There are exceptions, however, and cortisone may give only a temporary and inadequate response.

Dr. Smith: Would you say from this experience, Dr. Monto, that you would advise others not to begin therapy with hydrocortisone or prednisolone?

Dr. Monto: Yes, I feel very strongly that cortisone is the agent of choice. There is something peculiar about the hematopoetic tissue. Perhaps it is the lack of anti-inflammatory response that makes it different. We feel that cortisone is not only a stimulus for the various cell groups in the bone marrow but it also has a specific action upon the terminal vascular bed which is beneficial in the group of patients which we encounter.

Dr. Smith: Is this the general consensus in hematological practice?

Dr. Monto: Yes.

Dr. Smith: Dr. Keyes, perhaps you would like to comment on whether you feel there is some basis for the selective use of one or another of these steroids in the rheumatic fever problem.

Dr. Keyes: I would first like to make one point clear. All the members of this panel probably use these steroids many more times than do we. Where we have encountered acute inflammatory disease, however, such as in acute carditis, we have used cortisone probably to the greatest extent, simply because of the few cases that have reached us since the acceptance of the newer derivatives. Our experience with prednisone has been rather small. It would seem, however, that the preference of prednisone over cortisone would be determined mainly by whether or not you are concerned that sodium retention is going to be a factor in the outcome of the treatment. In the absence of congestive failure or imminent congestive failure I believe cortisone will give as satisfactory a response. The newer preparations should be used if there is any cardiac failure or if you suspect that sodium retention is already occurring.

Dr. Smith: Before passing on to hear what Dr. Shaffer is using in his allergy practice, I should like to make one comment. Increasing the potency of a pure drug from 10 to 100 times, let us say, in itself is not a strong justification for its selective use. Even if aspirin were ten times more potent, it would not necessarily be a better drug. The primary advantage that has come from the discovery of prednisone and prednisolone is, of course, in having corticoids of lower sodium-retaining potencies. As I mentioned briefly in the opening comments, there is a tremendous amount of false security in the minds of practitioners because they have heard that these agents have fewer side effects. It must be kept in mind that as we have increased the therapeutic potency five-fold, we have increased the chance for major side effects to the same degree.

Dr. Shaffer, do you have a particular preference for any one of the steroids in your allergy practice?

Dr. Shaffer: We use several of these preparations rather regularly but our preference
is for prednisolone. With 15 mg. of this steroid daily, we can control our patients very well and get the desired anti-inflammatory effect on an allergic type of reaction. In more severe cases, we may possibly use 20 mg. in a 24 hour period. In our experience, 3 or 4 days of therapy with that dosage level will give us the desired effect and then we can appropriately cut the dosage. We have some patients who are on a maintenance dose as low as 2.5 mg. per day. Since most of our patients are treated on an outpatient basis, the lack of sodium retention is very important for our particular group. We are very much aware of the other side effects and take steps to reduce them as much as possible. We have had considerable experience with hydrocortisone and continue to use it now. The intravenous form is helpful in severe allergic reactions where rapidly achieved high levels of steroid are needed. In such instances, 100 mg. of the free hydrocortisone in alcohol solution, given intravenously in 600 c.c. of glucose and water over a six to eight hour period, has been found satisfactory. On that type of therapy patients do well in a 24 hour period and may be practically symptom-free of severe allergic reactions, such as to serum or antibiotics. Our experiences with ACTH were among the first in the hospital. We use it now primarily to stimulate the adrenal gland at the end of a course of steroid therapy. Whether that is the correct technique or not, I do not know. I hope this point will be discussed today.

Dr. Smith: Yes, we will come to that in a few minutes. Briefly, would you say that there is general unanimity about the selective use of steroids in the field of allergy?

Dr. Shaffer: There is unanimity of opinion among the top flight allergists that one or another of the steroids is the last preparation to be used in treating an allergic individual. Unfortunately, it is the first and only thing that has been prescribed for many of the patients who later come to us. The most difficult patients we have to treat are those who have been given long-term cortisone therapy elsewhere for a year or so. They are very resistant to the usual measures, and since they continue to have allergic symptoms such therapy is certainly not the answer to the problem.

Dr. Smith: Dr. Livingood, it is said that dermatologists are using a sizeable fraction of the total steroid production in this country. Would you give us some ideas as to what preparations you are now using in the Dermatology Clinic and as to your preferences?

Dr. Livingood: Dr. Smith, dermatologists alone are not using all the steroids that are applied topically. This applies to such use by all physicians. As all of you know, topical steroid therapy, to a certain extent, has revolutionized the management of certain types of skin diseases. It has not replaced other time-honored remedies for these conditions but it certainly is here to stay. Cortisone has no effect whatsoever when applied topically except in the eye, as was first shown at this hospital, so we can dismiss that. Hydrocortisone was the first steroid to show therapeutic effects when applied topically, and even now it remains the agent of choice. Fluorohydrocortisone is about 10 times as potent in its topical effect but curiously enough one reaches a maximum effect. In other words, you do not increase the effectiveness of the fluorohydrocortisone significantly by increasing its strength above 0.25 percent. Roughly speaking, 2.5% hydrocortisone is equal to 0.25% fluorohydrocortisone and increasing the percentage of either does not increase their therapeutic effects significantly. The delta compounds have not been investigated thoroughly as to their effectiveness when applied topically, but the evidence to date would indicate that the effect of prednisolone

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topically is roughly the same as the effect of hydrocortisone. We see an occasional patient who obtains a therapeutic effect with the delta compound and not with hydrocortisone but we also see instances which are the exact opposite. The same applies to fluoro hydrocortisone. Occasionally we see patients who respond satisfactorily to fluoro hydrocortisone and not to hydrocortisone. Again, sometimes it is the other way around.

Now, a word as to the percentage strengths of these compounds in the various preparations. The classical treatment when using topical steroid therapy is 1% hydrocortisone ointment. I should say that in as many as one of ten patients, increasing the concentration to 2.5% will assure a more satisfactory therapeutic result than with the 1% preparation. The great majority of patients, if they respond at all to such therapy, will respond to 1% concentrations. Decreasing the percentage strength to, say, 0.5 decreases the therapeutic effect in a very significant manner. It is true that some patients respond to 0.5% but, by and large, they do not.

The base used in the preparation makes a difference. Sometimes patients respond better when the hydrocortisone is incorporated in a grease or petrolatum type base, the base of Cortef®, for example, which is sold commercially. Sometimes patients respond better when a vanishing base or a lotion type base is used. An experienced dermatologist has an opportunity to select the right type of base and the optimum steroid concentration for the individual patient. Often, patients are helped by selecting the appropriate preparation, even though topical hydrocortisone previously was unsuccessful. What I am trying to say is that if one is to achieve the maximum therapeutic effect from this very potent topical agent, one must be prepared to run the gamut of the presently available preparations, using the three different types of bases and employing both fluoro hydrocortisone and hydrocortisone. You might say, “Why don’t you use fluoro hydrocortisone exclusively if it seems to be just as effective in smaller doses?” Well, in the first place, the cost is about the same so you do not save anything by using smaller doses. In the second place, and this is the most important consideration, there is sufficient absorption of fluoro hydrocortisone in some patients to result in a systemic effect and sodium retention. One is not obligated to consider the topical dosage of hydrocortisone if it does not exceed, say, 500 to a 1000 mg. a day. One must consider the topical dosage of fluoro hydrocortisone, however, even when it is as low as 7 or 8 mg. per day in lotion form, because of this real danger of sodium retention.

Dr. Smith: Would you say, Dr. Livingood, that perhaps as much as 2-3% of topically applied hydrocortisone is absorbed, and that there is a rate limitation which is the reason we do not gain more therapeutically by increasing the potency of these preparations?

Dr. Livingood: Well, Dr. Smith, currently in our department we are making an effort to determine the exact percentage of hydrocortisone absorbed during topical application. Dr. Hildebrand and I are making these studies in conjunction with the physics department of the Upjohn Company which has supplied us with C¹⁴-tagged Cortef®, (Upjohn Company hydrocortisone). It does appear, in preliminary experiments at least, that absorption is probably of the order of 2-4%, which is significant. There is also some work to show that when the hydrocortisone is applied to mucous membrane
areas, such as the perianal region, absorption is increased significantly and I think this must be taken into account.

**Dr. Smith:** Dr. Mellinger, we have not heard from you and I am wondering if you would comment briefly on the use of interval ACTH injections for patients on long-term steroid therapy in whom one wishes to maintain a reactive adrenal.

**Dr. Mellinger:** I do not believe there is a compelling reason to use interval ACTH for patients on long-term (adrenal-suppressive) therapy with any of these steroids. There is certainly no advantage to be gained by awakening the adrenal one day only to put it to sleep the next. There is small likelihood of maintaining an adrenal responsive to endogenous ACTH in patients receiving interval ACTH injections while on long-term adrenal suppressive doses of the steroids. I do not believe any of us would suggest this as a practical approach to the problem. When cortisol or any of the corticoids are to be discontinued, at that time there may well be reasons to use ACTH to achieve a responsive adrenal. The decision as to whether or not you will use ACTH at the end of steroid therapy will depend on such factors as the duration of the steroid therapy and the disease under treatment. Ordinarily, in a self-limited disorder that is over in three weeks, there would be no apparent reason to use ACTH at the termination of that therapy, simply because the adrenal-pituitary axis would not be sufficiently involuted to prevent its normal spontaneous activation. If one is treating a disease such as gout or asthma which might flare up during the steroid withdrawal period, then ACTH may well be given at the end of even a short period of steroid therapy. I would think that in any patient who has received steroids for a prolonged period, and by that I mean for 3 weeks or more, ACTH should be given at the termination of therapy until there is a reasonable demonstration that the adrenal is once more responsive to small amounts of ACTH.

**Dr. Smith:** Would you be willing to suggest a program as to the amounts of ACTH you would use at the end of, say, six months of prednisone therapy?

**Dr. Mellinger:** Before discontinuing the steroid therapy, I would begin ACTH in a dose of 40 units of the gel twice daily. Of course, you can vary this scheme according to your own experience. I think it is reasonable to maintain the ACTH therapy throughout the last 4 to 6 days of the tapering steroid therapy and perhaps the same number of days beyond. When using as large a dose as 80 units in 24 hours, there is little reason for continuing more than four days after cessation of steroid therapy. Even a patient with panhypopituitarism and long-standing adrenal involution is responsive within 48 hours to the latter ACTH stimulation. One can determine whether or not the adrenal is responsive to a lesser ACTH stimulus by appropriate tests but that actually would not be necessary in clinical practice.

**Dr. Smith:** One of the more important aspects of this topic is the problem of complications which are encountered in patients receiving prednisone and prednisolone. Do they differ from those experienced with the parent steroids? Dr. Ensign, do you have some ideas on this, particularly as to the problem of ulcers? What have you encountered?

**Dr. Ensign:** I have no specific data as yet but I am sure we are seeing more ulcers with the prednisone and prednisolone than we did with hydrocortisone. It may be a matter of relative dosage. It is quite disturbing to note the way these newer derivatives are being abused by the profession in general, lulled as we are by this feeling of false security which is unfortunately fostered by the advertisements. We
certainly are seeing everything in the way of side effects from these drugs that we ever saw with cortisone and hydrocortisone, with the exception of sodium retention. I feel as Dr. Shaffer does, that our biggest problem is weaning patients from such therapy.

Dr. Smith: Dr. Monto, have you had any problems with edema in patients receiving prednisone or prednisolone? We hear claims that they should not produce sodium and water retention but is this true to form?

Dr. Monto: Actually, I would willingly trade a little mooning of the face or some ankle edema for a remission in acute leukemia or a response in hypoplastic anemia. As I tried to point out in my opening remarks, I prefer cortisone to prednisone and for that reason have little experience with the latter to report. Our early results of therapy with these newer steroids were so poor that we quickly reverted to cortisone.

Dr. Smith: Associated with the problem of sodium and water retention is the problem of potassium loss. Dr. Keyes, would you make some comment as to whether or not we have to consider this problem in patients receiving prednisone or prednisolone?

Dr. Keyes: We do see rather severe potassium deficiencies. The experience in our own division with the newer derivatives is small, although we have had patients referred to us for electrocardiograms who have displayed evidences of hypokalemia, several, rather marked. Arrhythmias are a very common manifestation of hypokalemia, particularly ventricular extrasystoles. As far as our own routine practice is concerned, where large doses of any of the steroids are employed, supplemental potassium chloride therapy is prescribed in the dosage of 10 to 15 grains four times a day. It can become a real problem as Dr. Smith and Dr. Ensign have stated, particularly in the use of these more potent preparations. Where there is less sodium retention, there may be greater potassium excretion, simply because the catabolic effects are greater. It is a real problem and everyone should be aware of it.

Dr. Smith: With cortisone and hydrocortisone therapies we could protect against potassium loss to some extent by a rigorous restriction of sodium in the diet. Not only did we prevent or minimize the edema, but also we induced a lesser tendency for potassium excretion, although potassium supplements were still needed. With prednisone and prednisolone, there is not the problem of sodium retention, but this does not mean that the immediate potassium loss is not as great. Inasmuch as we have a more potent catabolic preparation, we have a real indication for the potassium supplements. I certainly agree that the level employed should be about what we use with cortisone and hydrocortisone, i.e., a gram four times a day.

Dr. Monto, do you have any other comments as to other supplementary measures you would prescribe for a patient receiving prednisone or prednisolone, or perhaps one of the parent steroids? What about the diet and sodium intake?

Dr. Monto: It has been our policy to use relatively large doses of corticoids for short periods of time and as a clinical remission is obtained to taper the steroid therapy accordingly. We operate then on the thesis that we should use the smallest possible maintenance dose and I think this has helped to avoid complications from some of the newer steroids. In addition to the potassium supplements, we have our patients routinely on diets containing 1 gram of salt.

Dr. Smith: Is that with the prednisone and prednisolone, as well?
Dr. Monto: Yes.

Dr. Smith: I wonder if the panel agrees that such salt restriction is necessary for patients receiving the newer derivatives.

Dr. Ensign: The patients we treat over many months are on relatively minor doses of these steroids. We have not been too strict about the salt restriction, certainly not as low as Dr. Monto mentioned. I always advise these patients to avoid excess salt and, if they develop any trouble, we do restrict, the intake of course.

Dr. Smith: The sentiment of a number of clinicians is that we need not go to 1 gram. Perhaps something can be said for a diet of no added salt. Excuse me for interrupting, Dr. Monto. You have some further comments.

Dr. Monto: Our patients are rather unique. Usually when we put them on steroids they remain on steroids until their demise. I think our problem is a little bit different from that of the rheumatologist and the allergist. Now, I would like to make a short comment about patients with disseminated lupus erythematosus. In that group of patients, we prefer prednisone and we find that the high anti-inflammatory potency makes it a very satisfactory drug. We do not use antibiotics prophylactically in patients on long-term therapy. We treat the acute infections as they appear.

Dr. Smith: We have considered the diet in terms of sodium intake. What about the level of protein and total calories? Would you comment on that, Dr. Mellinger?

Dr. Mellinger: Inasmuch as the therapeutically effective corticoids are essentially catabolic agents, one can routinely expect that there will be nitrogen loss through protein breakdown which can be protected against to some degree by a high protein diet. This should be prescribed just as routinely as a restricted salt diet.

Dr. Keyes: On a strict 1 gram salt diet, it is difficult to maintain a very high protein intake because the higher the protein intake in the diet, particularly in meat, the higher the sodium content.

Dr. Smith: High protein intake seems to be a more reasonable program with prednisone and prednisolone therapy. That is, one can hold the protein intake at a good level with no added salt, and calories roughly in keeping with the total activity and basal metabolic needs.

Briefly, Dr. Mellinger, what about thyroid and testosterone as supplementary measures? We heard quite a bit about this initially and yet it seems to have quieted down recently. Are you still using thyroid as a supplementary measure?

Dr. Mellinger: I treat very few patients with large doses of the adrenal steroids. Most of our patients with endocrine disorders are receiving replacement amounts. There probably is such a thing as corticogenic hypothyroidism and a patient who is receiving the compounds for many months or years may well be benefited by 30 to 60 mg. of thyroid daily. Certainly where it is tolerated and not otherwise contraindicated, supplemental testosterone can be prescribed for the same reasons we discussed under the high protein diet. Many of the patients who have had long-term steroid therapy we see in consultation because of such complications as osteoporosis and other wasting disorders. These can be avoided almost completely if testosterone supplements and a high protein diet are maintained. One hundred mg. of a long-acting testosterone preparation intramuscularly every 2 to 4 weeks is recommended, particularly for a female or elderly patient receiving steroid therapy. For a vigorous young male, perhaps this is not justified.
Dr. Smith: I do not wish to differ much with my associate but suggest that instead of avoiding the protein-wasting effects we would probably delay or minimize them. It is doubtful whether we can reverse the catabolic or wasting properties of the adrenal steroids when they are used in the usual therapeutic doses.

We have now exhausted the time allotted to the panel for formal questions and in closing we would all like to hear from Dr. Mellinger a little more about what Dr. Shaffer was saying in respect to the use of the intravenous preparations of the steroids. Occasions come up in our hospital practice where the patient goes into "shock." We often do not know what the reason is and wonder whether we should use steroids for the hypotensive state. We may see a patient with adrenal insufficiency and some of the questions are: "What steroid should I use?" "Should I go the intramuscular route or the intravenous route? If so, what preparations are available?"

Dr. Mellinger: Of course, any patient in shock should receive his medication intravenously or he probably will not get it. The hospital now has two preparations available for intravenous steroid therapy. There is free hydrocortisone, 100 mg. in alcohol solution, which can be given I.V. in glucose or saline over several hours. There is also available hydrocortisone hemisuccinate which can be given directly and intravenously by syringe. The effect of these compounds is relatively evanescent so that the preparation has to be covered by depo-therapy such as intramuscular cortisone acetate. Hydrocortisone is probably never detrimental to anybody in shock. As a matter of fact, if it is not strictly indicated because of no adrenal insufficiency, it may be indicated because it potentiates the action of pressor agents such as nor-epinephrine. A combination of these drugs in postoperative or other types of vascular shock is well recognized, acceptable therapy.

Dr. Smith: The program is now open for questions from the floor.

Dr. Haubrich: I have one comment and one question. I will comment very briefly in regard to the "buffered" agents. It is my feeling that the introduction of the "buffered" compounds constitutes primarily an admission of guilt and does not appreciably protect the patient. Conceivably, it might protect a very small fraction of individuals who have never had any experience with ulcer disease. In an individual, however, who has a past history of ulcer disease, it is doubtful that the "buffering," as constituted in these tablets, alters appreciably the ulcerogenic potential of these steroid preparations. Therefore, the patient must be put on a definite program in that regard.

My question is this. In the early years of the corticosteroid age, so to speak, we were given a choice usually between ACTH and cortisone. At that time I was inclined, in most instances, to use ACTH because I had an idea that this was a more physiological approach. With the introduction of these newer compounds, we are hearing less and less about ACTH. I would like to ask the panel what the preference is in regard to ACTH as opposed to these newer steroids.

Dr. Smith: I certainly agree with you. We would all like to maintain a near physiological status for the patient during adrenal steroid therapy. We of the Endocrine Clinic were the last in submitting to prednisone and prednisolone, indeed, to the parent steroids, as preferable to corticotropin. We felt that some of the other steroids of the adrenal, such as the so-called adrenal androgens and estrogens, might have a favorable or buffering effect on the patient at the same time as we were getting a
pharmacological effect from the released hydrocortisone. That concept is hard to prove and is still tenuous. The difficulty with ACTH is in the practical aspects of therapy, such as with the patient who has to self-administer the drug or with the frequency one had to give it in the office. Occasional refractoriness to the ACTH occurs even with the best of preparations. Then, what seems to be a most troublesome problem is trying to standardize a unit ACTH given versus the unit response of the patients. One patient may respond by x milligrams of hydrocortisone output and the next person by 2 x. Even though we are giving 40 units to each we are not getting the same pharmacological effect. Finally, as to sodium retention, and there is no question about it, we run into more difficulty with edema and hypertension with ACTH than we do with prednisone. It looks as though we are giving up the ghost. However, ACTH still has a role, as Dr. Mellinger pointed out, in recovering adrenal cortical function. Dr. Ensign, do you want to add to that?

Dr. Ensign: No, I think that in our long-term therapies it is the practical part which is the most important one. To add just a little to what Dr. Haubrich said about the “buffering” of the steroid preparations, I certainly agree with him that it is an admission of guilt. However, the buffer provided is not enough. We have had some very interesting experiences with patients who have developed ulcers while on therapy with the newer steroids. These have been healed by proper management with the aid of our Gastrointestinal Division. The routine use of large doses of buffering material and protective diets are going to be very important for most patients on long-term steroid therapy.

Dr. Dumke: After seeing how many patients are given cortisone therapy, I am wondering whether significant adrenal suppression goes hand in hand with this therapy? Should I routinely, as many anesthesiologists are doing today, administer cortisone preoperatively as we administer atropine or scopolamine? Is there any way in which I can tell whether the patient so treated has adrenal insufficiency? Do you tell the patient he is getting cortisone so that when I see him preoperatively he will be able to tell me? I know you protect him fairly well for elective procedures but we also handle emergency procedures. Quite often the medical record is voluminous and it is difficult to find out just what the patient is getting. Is there any harm in giving 200 mg. of cortisone the night before and then administering an intramuscular dose in the morning at surgery to meet the stress that we produce?

Dr. Smith: Certainly, if there is the slightest indication from the history of any steroid being used recently, I would recommend intramuscular cortisone as you suggested.

Dr. Mellinger: I certainly agree but doubt that you need to give it the night before. The morning of surgery is time enough to give steroid support. In line with the other comment, we actually have cards to give our patients on long-term steroid therapy to carry in their wallets. These cards indicate that the patient is receiving steroid medication, just as the diabetic patient carries a card which says that he requires insulin. It is very important for each patient to be instructed that in event of emergency he must take additional steroid medication. His doctor and family should know it. We do provide that information for the patient to carry on his person.

Dr. Coates: Dr. Monto, you seem to feel quite strongly that cortisone is preferable. Do you feel there is any special attribute of cortisone in hematological disorders, or malignant diseases in general, which the other compounds do not have?
Dr. Monto: I doubt if anyone is aware of the mode of action of the steroids. In hematology we are no exception. All I know is that our results speak for themselves.

Dr. Brush: I have now done six gastric resections with vagotomies on patients who have been on long-term cortisone therapy. After the operation they can be continued on steroid preparations as needed and I would like to point out that the Department of Surgery is available for these operations.

Dr. Smith: We will certainly keep that in mind, Dr. Brush.

Dr. Miller: A question to Dr. Mellinger. There has been some talk about the pituitary being suppressed, i.e., the output of endogenous ACTH being suppressed, as a factor in the unresponsiveness of the adrenal after steroid therapy. Of course, ACTH would not affect this. I would like your opinion.

Dr. Mellinger: Essentially, all the adrenal suppression is indirect and through the pituitary. There is no evidence that cortisone affects the adrenal gland per se except through the pituitary. Does that answer the question?

Dr. Miller: Not quite. I mean, is there evidence that the production of endogenous ACTH does not come back promptly after the adrenal steroids are discontinued?

Dr. Mellinger: There is some evidence that it does not come about promptly due to changes in the pituitary or the hypothalamus but the adrenal response is also not prompt. For the latter reason we administer large amounts of exogenous ACTH and begin it before the steroids are discontinued. We certainly cannot stimulate the pituitary, however, by any of these means.

Dr. Smith: With these comments the morning activities are completed.