THE OPERATION

Incision.—The subumbilical midline incision suits the conditions of outstation surgery best. There are many against this incision, holding that it gives rise to incisional hernias. However, gynaecologists still use it to good effect and it gives clear and rapid exposure of both iliac fossae and the pelvic cavity. The moderately expert surgeon may prefer a paramedian incision on the affected side. One has been really red in the face using this incision and finding that the opposite side is affected or, as in one of our cases, there was an ectopic pregnancy on either side!

We will not go into the minutiae of the operation, but will mention points.

(1) Blood is sucked out of the pelvis. With the advent of antibiotics there is a recent trend to leave free blood in the peritoneal cavity where the iron content is eventually re-absorbed. It is of course necessary to obtain a clear view of both tubes. So far we have not tried this method of therapy.

(2) Both tubes and adnexae are examined. It is fairly frequently observed that an haematosalpinx is present in the remaining tube. At all costs this must be recognised and care taken that only the tube with the ectopic pregnancy is removed.

(3) The affected tube is removed. In most cases this is very easy, applying two large haemostats in a "V" on either side of the offending area and removing it. The cut edges are closed with haemostatic sutures.

The distal end can be turned back like a cuff instead of merely tying it off. It may be helpful to hitch the ovary up into a position near the tubal remnant.

POSTOPERATIVE THERAPY

Blood transfusion may be necessary. Antibiotic therapy is instituted, especially if the needle aspiration test has been employed. We have found a combination of penicillin and streptomycin adequate. Iron is supplied by Imferon intramuscular injection or by tabs-ferrous sulph orally.

CONCLUSION

Every medical officer is faced by this problem. He must act at once. Operation is life-saving, and the more bled out the patient the faster he must act. If he does not operate the patient will very probably die, but if he operates she has every chance of living. Not to operate constitutes an act of negligence. The oft in-superable question of blood supplies can be overcome by autotransfusion. Let us stress that we do not advocate autotransfusion where blood supplies are available, but it is for use in circumstances where no supply is to hand.

Acknowledgment

Our thanks are due to Mrs. B. Lawson, F.R.C.S., M.R.C.O.G., consultant to the Llewelin Hospital Department of Obstetrics and Gynaecology, for her help and advice in the preparation of this paper.

A Decade of Steroids*

By M. E. L. TONKIN, M.B., B.CH. (Rand.)

Ten years have elapsed since cortisone was first given by Hench and Kendall and their co-workers at the Mayo Clinic to a patient with rheumatoid arthritis, with the well-known dramatic results, and ten years of experience in the use of the adrenal corticoids are now available to us.

As with any new drug, there are three phases:

(1) Firstly, the stage of discovery, with its attendant drama.
(2) Secondly, the phase during which the drug is used for every illness.
(3) And thirdly, the stage of analysis and retrospection.

We have now reached this last stage. But before discussing it, it is pertinent to observe that so much controversy and conflicting reports from either sides of the Atlantic probably stem from the fact that the Americans had an almost exclusive reserve on Stage 2. Whilst they were trying cortisone for every disease, due to difficulties of production and supply, England and Europe had only very limited allocations of cortisone until 1953, and in fact it was not generally made available to practitioners until the end of 1955. As a consequence, England's meagre supplies probably resulted in very carefully screened usage, whereas freedom of supply in the United States probably accounted for grossly excessive dosage regimes and a legacy of side-effects. No wonder there have been differences of opinion.

NATURAL STEROIDS

The first diagram (1) shows the products of the adrenal cortex.

* A talk, illustrated with slides, given to the Southern Rhodesian branch of the British Medical Association in November, 1959.
Cortisone, hydrocortisone and desoxycorticosterone have, of course, also been synthesised and, for obvious reasons, the sex corticoids have been omitted.

The next diagram (2) shows the typical steroid molecule which is composed of three six-sided carbon rings and one five-sided carbon ring, and is the basic steroid known as pregnane.

By altering the structure of pregnane we proceed from one steroid to another.

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**Diagram 1**

<table>
<thead>
<tr>
<th>Naturally occurring</th>
<th>Glucocorticoids</th>
<th>Mineralocorticoids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosterone</td>
<td>Prednisone</td>
<td>Desoxycorticosterone</td>
</tr>
<tr>
<td>Cortisol</td>
<td>Prednisolone</td>
<td></td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>Triamcinolone</td>
<td>9-alpha fluoro-hydrocortisone</td>
</tr>
<tr>
<td>(Cortisol)</td>
<td>Methylprednisolone</td>
<td></td>
</tr>
</tbody>
</table>

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**Diagram 2.** Pregnanne.

By adding a double bond between carbon atoms 4 and 5 and by adding oxygen to carbon atoms 3 and 20 we get progesterone, and by adding an hydroxyl group at carbon 21 we get desoxycorticosterone or DOCA in its acetate form, which is, of course, a mineralocorticoid causing sodium and water retention and potassium loss (Diagram 3).

Corticosterone or Compound B (Diagram 4) has an hydroxyl group at carbon position 11, and this was perhaps the toughest nut the pharmaceutical firms had to crack. It led to expeditions to various parts of the world in an endeavour to find a natural plant steroid already provided with this modification. Ox bile was the original starting point for the production of cortisone, and the Mexican yam and heco-genin from sisal have all been utilised in turn. More recently, microbiological fermentation has been used to modify the steroid molecule.

Corticosterone has all the side-effects but none of the anti-inflammatory properties of hydrocortisone.

The next diagram (5) shows hydrocortisone with an hydroxyl group at carbon 17, and cortisone with an oxygen atom instead of an hydroxyl group at carbon atom 11.

It is probable that hydrocortisone is the main natural hormone of the body and that cortisone is relatively inactive, but must be converted to hydrocortisone before exerting its effect. Cortisone is used, however, because it is easier and cheaper to make than hydrocortisone.

These then are the natural steroids, but what are their effects?

**Steroid Effects**

Broadly, of course, they fall into four main groups:

- Anti-inflammatory;
- Anti-allergic;
- Metabolic; and
- Electrolytic;

but the following is a more detailed classification of the effects of the steroid molecule on the body:
(a) Its effect on carbohydrate metabolism causing in excess, hyperglycaemia and glycosuria—the so-called diabetogenic effect.

(b) On protein metabolism, with consequent katabolism or failure of anabolism, giving muscle wasting, osteoporosis, ecchymoses and striae. (Increased nitrogen excretion and loss of creatinine acid and amino acids in urine.) Large doses inhibit growth, hence great care must be taken with children on steroids.

(c) Its effect on fat metabolism, giving the typical Cushing's redistribution of fat.

(d) It affects electrolyte balance with sodium retention and oedema, and in some circumstances sodium loss by increased filtration. It is interesting to speculate whether "moon facies" is due to oedema or a redistribution of fat.

(e) Its effect on collagen tissue, where it inhibits the reactivity and hyperactivity to injurious stimuli with depression of local inflammatory response, depression of phagocyte activity, depression of polymorphs, eosinophils and lymphocytes.

(f) Its effect on lymphoid tissue which atrophies (also the spleen).

(g) Its effect on blocking the allergic and hypersensitivity response.

(h) In acute infections, the signs of which it masks.

(i) Its depressant effect on the pituitary and ACTH production.

(j) It tends to cause atrophy of the adrenal cortex.

(k) The thyroid which it depresses.

(l) During degradation of cortisone, signs of androgenic excess may appear (masculinisation in females).

(m) On the cardiovascular system; it can increase the blood pressure.

(n) On the gastrointestinal system where it helps ulcerative colitis, but HCl and pepsin secretion are stimulated.

(o) Its effect on the central nervous system with euphoria and sometimes a frank psychosis.

**SYNTHETIC STEROIDS**

Turning now to the synthetic steroids once more, an examination of their chemical structure shows that:

The delta-1 analogue of cortisone is prednisone, and of hydrocortisone is prednisolone (Diagram 6). Probably the best known and certainly the first of these to be synthesised were Meticorten and Meticortelone.

A second double bond between carbon atoms 1 and 2 has converted cortisone into prednisone and hydrocortisone into prednisolone.

From hydrocortisone comes 9-alpha fluoro-hydrocortisone (fludrocortisone) (Diagram 7) by inserting a halogen atom at the 9-carbon atom position. Of all the halogens used experimentally, fluorine proved to be the most potent.

9-alpha fluoro-hydrocortisone is, of course, a mineralocorticoid, and because of its very marked sodium-retaining property should not be used except as replacement therapy in Addison's disease or after adrenalectomy, and also for its pituitary suppressive function in order to distinguish between adrenal tumours and hyperplasia.

Also using this fluorine at carbon atom 9, and by adding an hydroxyl group at carbon atom 16 to prednisolone, we get triamcinolone, or 16 hydroxy-9 fluoroprednisolone, known in trade terms as Aristocort, Kenacort or Leder-cort, depending upon which pharmaceutical company makes it.
Diagram 7.
9-a-fluorohydrocortisonc (fludrocortisonc).

Diagram 6.
Prednisolone.

Diagram 8.
Dexamethasone.
Methyl-prednisolone (or Medrol) has a methyl radicle at carbon atom 6 and now the latest steroid, dexamethasone, which is 16-methyl-9-fluoroprednisolone, has fluorine at carbon atom 9 and a methyl group at carbon atom 16 (Diagram 8).

It is interesting that dexamethasone was discovered simultaneously by Schering as Deronil and by Merck-Sharp & Dohme as Decadron. Since then other firms have followed suit and a whole host, such as Dexa-cortisyl and others, have appeared on the market.

Dexamethasone is comparatively new and has not yet had the long-term assessment which other steroids have had, but, as with the newer steroids, it appears to have very little, if any, sodium-retaining effect. It is, however, very potent and has a pituitary depressing value which varies according to different workers from 9 to 30 times that of prednisone (Bunim, Slater, 1959), and hence great caution should be observed during withdrawal, which must be done very gradually.

Next is a diagram showing the relative potencies of the various synthetic steroids:

- Dexamethasone is—
  - 5 x as potent as Triamcinolone;
  - 5 x as potent as Medrol;
  - 7 x as potent as Prednisone and Prednisolone;
  - 28 x as potent as Hydrocortisone;
  - 35 x as potent as Cortisone;

or put in another way:

- 0.8 mg. dexamethasone (Deronil) is equivalent in anti-inflammatory activity to—
  - 4 mg. of Medrol or Triamcinolone;
  - 5 mg. of Prednisone or Prednisolone;
  - 20 mg. of Hydrocortisone;
  - 25 mg. of Cortisone.

The next diagram shows the usual dosage forms available:

- Cortisone ... ... ... 25 mg.
- Hydrocortisone ... ... ... 10 and 20 mg.
- Prednisone ... ... ... 1 and 5 mg.
- Prednisolone ... ... ... 1 and 5 mg.
- Triamcinolone ... ... ... 1 and 4 mg.
- Methylprednisolone ... ... ... 2 and 4 mg.
- Deronil ... ... ... 0.4 and 0.8 mg.
- Decadron ... ... ... 0.5 mg.

**Clinical Indications**

Now what are the clinical indications for steroids, and in discussing them we must remember that their action is suppressive and not curative?

(1) First and foremost, of course, as replacement therapy for any condition of adrenal insufficiency—par excellence in Addison's disease or for adrenalectomy. In adrenalectomy, Howard (1959) says that mineralocorticoids must be given as well as glucocorticoids, although if the adrenalectomy is subtotal the remaining tissue will probably take over. One word of caution: in patients without adrenals, extra coverage must be provided in conditions of stress, such as infection, operation, pregnancy and so on. In acute crisis there are excellent preparations for intravenous use. For details of dosage regimes I refer you to the excellent recent articles—one by Stuart Mason et al., of the London Hospital (1958), and the other by Howard, of Johns Hopkins (1959). I was interested, too, to read of a case of Cushing's disease syndrome in an African described by Turner and Hurley (1959).

The adrenal insufficiency of overwhelming infections is another indication.

(2) Secondly, in allergic states. All asthmatics do not require or respond to steroids. In status asthmaticus steroids have proved their place, but opinion varies as to their value in chronic asthma. Long-term therapy should be avoided, if possible, but short courses—for, say, three months at a time—may be helpful.

Here, for once, American exuberance and British conservatism have changed places. The Americans are pointing to the increasing death rate and enquiring whether steroids have something to do with this, but the British declare that steroid treatment is undoubtedly a most valuable method of treatment for severe chronic asthma and status asthmaticus (British Medical Journal leading article, 17th May, 1958).

(3) In collagen diseases, such as rheumatoid arthritis, there is no doubt that steroids have rendered life habitable and pleasant for otherwise crippled and useless patients. The trend to-day is to start with small doses and build up to a maintenance level rather than the reverse. In other collagen diseases, such as disseminated lupus erythematosis, periarteritis nodosa and dermatomyositis, steroids are life-saving and mandatory. The results in scleroderma, however, have, I think, been disappointing.

(4) I do not know whether there are any dermatologists here, but I wonder if they would cross swords with me if I said that almost every skin disease is to-day treated with steroids? However, there is perhaps about a 25 per cent. justification for this, for according to a recent American author (Stoughton, 1959) about 25 per cent. of all skin cases are eczematous and most of the eczematous diseases respond to topical steroid therapy. In pemphigus and exfoliative dermatitis, systemic steroids are mandatory. Hydrocortisone is probably the steroid of choice for topical therapy and a new aerosol form will be watched with great interest. Used topically,
there is rarely any danger of systemic absorption and side-effects and the patient requires far less supervision. The skin diseases associated with the systemic collagen diseases obviously require systemic therapy.

The danger of local infection with topical therapy is minimal, surprisingly so in view of the contrary which obtains with bacterial infection in systemic therapy. The exception to this is herpes simplex.

Steroids combined with antibiotics are probably of little value in preventive therapy, but are indicated where the lesion is secondarily infected.

(5) Turning briefly to gastro-intestinal diseases, there is no question that steroids are helpful in ulcerative colitis. Truelow (1958) has recently described careful controlled work with hydrocortisone hemisuccinate given as a rectal drip, in which he demonstrates clearly good remissions, but no apparent influence on the relapse rate. Sprue remains a question mark. In virus hepatitis—not all cases, but the very ill ones—steroids have been life-saving.

(6) In pulmonary disease, for example, pulmonary emphysema and fibrosis. I will come to the question of tuberculosis later.

(7) In the nephrotic syndrome; Nabarro, of the Middlesex Hospital (1959), has published disappointing results recently with dexamethasone, but his case numbers were very small. Dramatic improvements have occurred with other steroids, and some American workers are using ACTH (100-200 units daily for 10-20 days) to induce diuresis, followed by oral cortisone (400 mg. daily) for three successive days of the week for at least a year, before tapering off (Lange et al., 1957). Growth seems not to be impaired in children by this intermittent method of therapy.

(8) In eye diseases; here again steroids have been tried for almost every eye disease under the sun, but the object of treatment should be to suppress the symptomatology until the disease, if it is self-limiting, runs its course, leaving an intact eye. Indications should be symptomatic, not disease indications, i.e., inflammation, allergy, oedema, granulation tissue, certain infections (with chemo-therapy).

(9) In blood diseases such as acute idiopathic haemolytic anaemia and idiopathic thrombocytopenic purpura, steroids have undoubtedly controlled the auto-immune process with or without splenectomy, and in agranulocytosis and certain leukaemias they have been useful in causing remissions.

(10) For its suppressive effect on the pituitary steroids are used in the adrenogenital syndrome and, of course, for diagnostic purposes to distinguish between hyperplasia and tumour.

(11) Infectious diseases, for example, tuberculous meningitis.

(12) In rheumatic fever the subjective is controversial. We are all aware of the Medical Research Council’s Anglo-American trial of ACTH, cortisone and aspirin, in which no superiority of cortisone or ACTH over aspirin could be shown. However, since no untreated control group was included, it could be assumed that either—

(1) each treatment was helpful in lessening cardiac damage; or

(2) That none of the treatments was effective; and in reviewing this work recently, McEwen (1959), of New York, suggests that it is possible that corticosteroids may be of value early in carditis, through suppression of the acute exudative phase of the inflammation.

Illingworth et al. (1957) in England went further than this, saying that “Cortisone with salicylates, especially in high dosage, was more effective than any other treatment, including cortisone alone, and that cortisone alone is superior to salicylates alone.”

A word of warning, however, on the use of steroids in general in children. Since growth may be retarded, the advantages must be weighted against the disadvantages. Steroids should not be given continuously for long periods; give rather for a period of say, three months, discontinue, and then start again.

(13) Finally, a word on pulmonary tuberculosis. From initially being a contraindication, opinion has swung around so that to-day many people are giving steroids with the appropriate chemotherapy. The Scottish Tuberculosis Society in a controlled study (1957) has found that prednisolone has a definite effect in hastening improvement, but that whilst initial progress is more rapid, there is no evidence that the ultimate result is any better.

I see that Angawa and Haynes (1959), at the chest hospital in Mombasa, found encouraging results with steroids given to very ill patients combined, of course, with antituberculosis therapy, and opinion is growing of the value of steroids in tuberculous effusions.

In South Africa the Government Chief Tuberculosis Officer is conducting a statistically controlled trial of prednisone in tuberculous pleural effusions, in which condition many workers have stressed the value of prednisone.
Shubin et al. (1959) describe the use of steroids in tuberculosis and claim:

1. They are life-saving in the acute forms.
2. They are valuable in assisting desensitisation in patients allergic to antituberculous drugs.
3. They are helpful in chronic treatment-resistant cases.
4. They are beneficial in acute sarcoidosis.

Contraindications
While on the subject of contraindications, there have been several interesting publications recently which challenge existing views. Several authors (among them Kupperman, 1959; and Mickerson, 1959) have written of the value of steroids to augment diuresis in intractable congestive cardiac failure, and the latest indication, rather than contraindication, for the use of steroids was an article by Oakley et al. (1959) describing the use of prednisone in insulin-resistant diabetics, evidently on the basis that insulin antibodies are built up, and in such cases prednisone produced a dramatic fall in insulin requirements. It seems, therefore, that the steroid story is only just beginning to unfold.

Precautions
A word now on precautions to be taken in steroid therapy.

Weight and blood pressure should be taken regularly and oedema watched for. Urine must be tested and the electrolytes studied where possible. Evidence of virilism, dyspepsia and any change in the mental outlook carefully studied. It is astonishing that practitioners continue to give cortisone without any appreciation of its mode of action or dangers. I heard the other day of a patient who had been on cortisone for six years without a single check-up from his practitioner.

The Question of which Steroid to Use?
Apart from one exception, I think it can honestly be said, "You pays your money and you takes your choice." The newer synthetic steroids by and large have overcome the earlier sodium-retaining disability. Increased appetite and weight gain seem to be a feature of dexamethasone. With triamcinolone care should be exercised, since many articles are appearing in the literature showing that muscle weakness and wasting are very marked with this drug. Otherwise there seems to be very little to choose between them. Some suit individual patients better than others, and it may be advisable to switch until the right one is found.

What Steroid Form to Use?
They are put up in the free form, as an alcohol, as acetates or as other esters, such as phosphates and hemisuccinates, the main difference lying in their solubility, especially in water. It is greatest in the hemisuccinate, which is the steroid for intravenous use, and least in the acetate.

The intramuscular injection obviously takes longer to act than oral forms, but for quicker action give the intravenous form.

For joint injection the least soluble should be used to prolong effect, and hydrocortisone rather than cortisone. For enemata, use the hemisuccinate. For skins, hydrocortisone is put up in strengths from 1 to 2½ per cent., with or without antibiotics, such as neomycin, tetracycline, polymixin, bacitracin and as creams, lotions or aerosol sprays.

For eye work there are ointments and drops, and the hemisuccinate can be injected subconjunctivally.

For the nose, sprays, insufflations and drops can be used.

The Question of Withdrawal?
Never stop suddenly; always withdraw over a period of 10 days. In prolonged treatment decalcification may occur, so it may be advisable to give anabolic hormones—one injection of testosterone or oestrogen every two or three weeks. It seems that the practice of giving ACTH to stimulate the adrenals is falling away, and Barach (1959) has stated that on long-term steroid therapy the adrenals have probably atrophied to the extent that a therapeutic response to ACTH is unlikely.

The Question of Surgical Procedures?
There is no question but that coverage is essential, even in patients who have been on steroids as long ago as 18 months to two years. Every anaesthetist to-day should ask his patient, "Have you had cortisone?"

I have already dealt with increased coverage for those already on cortisone.

Summary
Ten years of experience with the adrenal steroids are now available to us. The earlier hopes of producing steroids entirely devoid of side-effects have not been realised. It is important, therefore, to recognise the risks of long-term steroid usage and to weigh them against the advantages. The consensus of opinion to-day is that the advantages outweigh the risks in carefully selected cases and in carefully controlled cases.
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The Diagnosis and Treatment of Depressive States

BY
Consultant Psychiatrist, Salisbury.

There is no objective test for depression. Whether or not a patient is depressed is a clinical judgment made from his statements, appearance and behaviour, together with relevant facts in his past and family histories. Some confusion is caused by the use of the word "depression" for both a symptom and a psychiatric syndrome. Thus some patients who complain of "depression" are not suffering from a depressive illness and many patients in the throes of severe melancholia may neither complain of depression nor admit to it if directly questioned.

Where the possibility of depression exists, the following questions require to be answered:
(a) Is the patient depressed?
(b) Is the depression endogenous, reactive or secondary?

(c) If secondary, what is the underlying condition?

Is the Patient Depressed?—Although the previous history and likely genetic constitution will influence the physician's opinion, a conclusion that depression is present will seldom be arrived at in the absence of at least one of the following features:
(i) An appearance of sadness.
(ii) A complaint of lack of interest, hopelessness, "heaviness," "dullness," or excessive fatigue.
(iii) Suicidal thoughts or suicidal intent.
(iv) Motor retardation.
(v) Retarded thinking.
(vi) Restless agitation.
(vii) Persistent hypochondriasis.
(viii) Feelings of depersonalisation.
(ix) Delusions of unworthiness or self-reproach; hypochondriacal delusions.
(x) Diminution or loss of sexual desire.
(xi) Disturbance of sleep.

In those patients presenting with hypochondriasis there may be no other indication of depression; in such cases, once an organic or other likely psychiatric explanation has been excluded, it is permissible to use ECT as a therapeutic test.

Is the Depression Endogenous, Reactive or Secondary?—Endogenous depression arises "out of the blue" without psychological cause; reactive depression is attributable to adverse circumstances; both are primary psychiatric syndromes. Secondary depression is a symptom of some other disorder—psychiatric or somatic. Involutional, puerperal, post-operative, post-infective and drug-induced depressions belong in the endogenous group; they do not, as a general rule, represent reactions to psychological setbacks. Where the childbirth, operation or infective illness entails some especial unhappy significance for the patient, there may be an admixture of reactive factors.

Controversy exists as to whether endogenous and reactive depressions are, in fact, qualitatively different. It is suggested that the obvious endogenous depression and the obvious reactive depression are at the extreme ends of a scale representing relative degrees of constitutional predisposition and environmental stress. Lewis (1934), in a detailed clinical study of 61 cases, concluded that there was no real difference between endogenous and reactive depressions. More recently, Hamilton and White (1959), in developing a rating scale for depression, isolated a statistical factor which appears to be a mea-