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A.C.T.H. AND CORTISONE IN THE TREATMENT OF ACUTE COMPLICATIONS OF LEPROSY¹

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INTRODUCTION

Recent researches on the hormones of the anterior lobe of the pituitary and of the adrenal cortex have resulted in the production of two very valuable drugs, the therapeutic efficacy of which has been proved in a variety of diseases, especially rheumatoid arthritis, hypersensitive and allergic conditions, and inflammatory eye diseases, etc.

ACTH is a protein which is obtained from the pituitary glands of pigs. Cortisone is one of the steroids extracted from adrenal cortex, but which is now being synthesised from deoxycholic acid obtained from the bile of animals. The action of ACTH depends on stimulation of the adrenal cortex, which results in the increased production of cortisone and other steroid hormones. The final action therefore of both cortisone and ACTH is the same. They do not have any effect on the aetiological process of the disease, but act by changing the response of the patient to disease through depressing or abolishing the excessive tissue reaction. They are therefore of value in the diseases characterised by excessive inflammatory or allergic response on the part of the tissue. The effects are temporary, and the action ceases when treatment is stopped; however, this temporary action during the active phase of a disease may be of considerable value not only in tiding over and ameliorating the acute symptoms, but also in preventing permanent tissue damage.

¹ Reprinted, with permission, from *Leprosy in India* **25** (1953) 123-140, somewhat condensed. A four-page tabulation of cases has been omitted and the data presented otherwise, and four full-page charts have been simplified and reduced. Addenda have been provided by the author.—EDITOR.

During the long and protracted course of leprosy there are often seen certain acute complications which bear some resemblances with the conditions known to be benefited by ACTH or cortisone. It was therefore natural that these remedies were put to trial in these acute complications of leprosy. It is proposed to summarise herein the results of the small number of trials reported so far, and then to present the findings made by the author.

PREVIOUS WORK ON THE SUBJECT

Roche *et al.* (1951) from Venezuela were perhaps the first to report on this matter. They treated with ACTH 6 cases of lepra reaction in patients with lepromatous type of leprosy, in doses of 40 to 80 mg. per day for a maximum period of 7 days. "In all cases there occurred a rapid regression of the reaction symptoms, and in most of them the temperature fell to normal within 24 hours. Iridocyclitis present in one of the patients, and peripheral neuritis present in two others, were rapidly benefited. Most of the symptoms returned a few days after cessation of therapy." They considered that "through the rapid control of the reaction symptoms, ACTH may contribute in an important way to the treatment of leprosy, particularly in those cases where the reaction is an obstacle to continued administration of a chemotherapeutic agent."

An editorial in *International Journal of Leprosy* (1951) called attention to a note by Koff, *et al.* (1950) on the favourable effects of subconjunctival injections of cortisone in iritis. In reply to a request from the editor, Koff (1952) referred to an article of Duke-Elder containing a symposium on about 600 cases treated with ACTH and cortisone in England. "In this article Duke-Elder state that in their experience the subconjunctival method is the method of choice in dealing with inflammation of the anterior segment, particularly iritis." Roche (1952), also in reply to an enquiry from the editor, stated that all of their cases had relapsed within short periods after the drug was discontinued, but that iridocyclitis which was present in one of them remained quiescent for about 3 months, and after that the symptoms had been kept controlled by instillation into the eye of a dilute solution of cortisone. Regarding the subconjunctival injection of cortisone according to the Koff method, Roche reported his experience with 5 cases who had responded extremely well to it.

Melsom (1952) recorded a case of lepra reaction in a patient with lepromatous leprosy with an apparent favourable response to ACTH. The patient became afebrile as early as the second day, and his general condition gradually improved. A striking feature in this case is the very small dose of ACTH used—4 mg. daily in the first week, 3 mg. daily in the second week, and 2 mg. daily in the third week, these very small doses used by mistake. However, it is significant to note that even these minute doses were effective. The author does not draw any conclusions and states, "It is impossible to conclude whether the effects observed . . . were due to the drug, or if [the treatment] coincided accidentally with a spontaneous remission of the reactional process." The patient remained afebrile for about 4 months, a fresh febrile attack was again successfully treated

with ACTH, and the patient had remained afebrile till the time of writing, about 4 months.

Lowe (1952) has reported on the results in 38 cases of acute complications treated with cortisone or ACTH: sulphone dermatitis, etc., 4 cases; acute neuritis, 8; acute leprous eye inflammation, 7; lepromatous reaction, 16; tuberculoid reaction, 1; leprous elephantiasis, 1; acute leprous arthritis, 1. In 4 cases of leprous eye inflammation cortisone was applied locally; in the others the hormones were injected. In case of ACTH, to begin with a total daily dose of 50 mg. was given because of inadequate supplies, later the total daily dose was raised to 100 mg., but when some bad results were seen smaller doses were resumed. In case of cortisone a total daily dose of 200 mg. was used to begin with, but later smaller doses were used in an attempt to minimise the bad effects. The following results were reported in the various conditions:

All 4 cases of sulphone dermatitis were of the serious exfoliative type with fever, enlarged liver and spleen, and other symptoms. All responded satisfactorily to cortisone treatment.

In acute neuritis, immediate response to ACTH or cortisone was excellent in all cases. However, the ultimate results were good in only 4; in the remaining 4 the ultimate results were considered bad. In them recurrence followed the cessation of hormone treatment, and they were then given 3 to 5 short courses. "In three of these four cases there was some evidence that the hormone treatment had aggravated the leprosy. In one the attacks of neuritis appeared more frequently after the hormone treatment than before it; in the other two the neuritis was relieved, but reaction and iritis recurred."

Of the 7 cases of leprous eye inflammation, the 3 more serious ones were treated with injections of ACTH, and the other 4 with cortisone eye drops. The first 3 showed a good early response, with absence of pain within 24 hours and visible improvement in 24 to 48 hours. "In two of the three cases, however, while the eye inflammation was controlled, the hormone treatment was followed by other complications—in one case reaction, and in the other reaction and neuritis." The 4 cases treated with eye drops responded well and had remained well for several weeks. Lowe considers that local hormone treatment of leprous eye condition is likely to be of great value.

In all 16 cases of acute lepromatous reaction, the acute symptoms disappeared rapidly. However, in 12 the symptoms recurred a few days later, and in some further recurrences were seen; each recurrence was only temporarily controlled by the hormone treatment. "As the work progressed it became clear that, while acute symptoms were being controlled temporarily, the condition of several of the patients was definitely worse than before treatment, and that reaction was becoming more common and more severe." An assessment of the results "indicated that the hormone treatment of lepromatous reaction is attended by considerable danger of aggravating both the complications and the underlying disease, and is therefore contra-indicated."

One case of apparently leprous arthritis was treated successfully. One of leprous elephantiasis of the legs showed marked temporary improvement followed by relapses, and further courses were followed by general reaction. In one case of reaction in tuberculoid leprosy, there was

considerable alleviation of the symptoms with one short course. "Further courses were regarded as undesirable in this localized and usually benign form of leprosy because of the danger of abolishing the cellular reaction which localizes the disease in such cases."

As a result of his experience Lowe recommends the use of hormone treatment only in two complications: (1) sulphone sensitivity, with drug fever, dermatitis, and hepatitis; and (2) acute and subacute leprosy eye inflammation, in which condition the local use of cortisone appears to be effective and safe. Otherwise, he considers the hormone treatment contra-indicated because, while the acute manifestations of leprosy can be readily controlled, "there is a grave danger of aggravating the underlying disease."

PRESENT STUDIES

MATERIAL AND METHODS

Number of patients.—The study reported here is based on the findings in 18 cases, 13 in-patients and 5 out-patients. All were undergoing chemotherapy, either with sulphone or thiosemicarbazones.

Nature of complications.—The acute complications treated were: acute febrile reaction, 8 cases, in 2 of which there was present severe iritis, and in 1 severe neuritis; afebrile reaction in the form of erythema nodosum nodules, 3; acute iritis without any fever, 3; severe sulphone dermatitis, 2; and reaction in cases of the tuberculoid type, 2.

Preparations.—ACTH was used in the majority of cases, and cortisone in some cases only for local application in the eye. The preparations of cortisone used were a 2.5% ophthalmic suspension of Cortone acetate (Merck) as drops, and a saline suspension of the same substance (20 mg. per cc.) for the subconjunctival injections. In case of ACTH two preparations have been used—ACTH in watery solution for most of the cases, and Acthar gel (20 mg. per cc.) in a small number of cases. Acthar gel is a repository preparation in gelatin and propylene glycol.

The ACTH used in this investigation was supplied free by Messrs. Biddle, Sawyer & Co. and by the Organon Laboratories, to whom my thanks are due. The supply was obtained in ampoules containing 10 mg. (10 I.U.) each, together with an equal number of ampoules containing the solvent. The Acthar gel, as also the Cortone ophthalmic and saline suspensions, were bought from the market.

Dosage.—In case of the watery solution of ACTH, the usual initial dose was 10 mg. four times a day, *i.e.*, a total of 40 mg. for 2 or 3 days; later the dose was reduced to 10 mg. two or three times a day; and generally a total of about 16 injections, *i.e.*, 160 mg. was used in each case. In the case of Acthar gel, 1 cc. a day containing 20 mg. was used, and treatment was continued for about a week. A few drops of ophthalmic suspension were instilled into the eye, at first every hour and later less frequently. For the subconjunctival injection about a quarter cc. of the saline suspension was used after properly anaesthetising the eye. A 20 gauge hypodermic needle was used for the injection, which was repeated at about weekly intervals, two or three injections being usually sufficient.

THE RESULTS

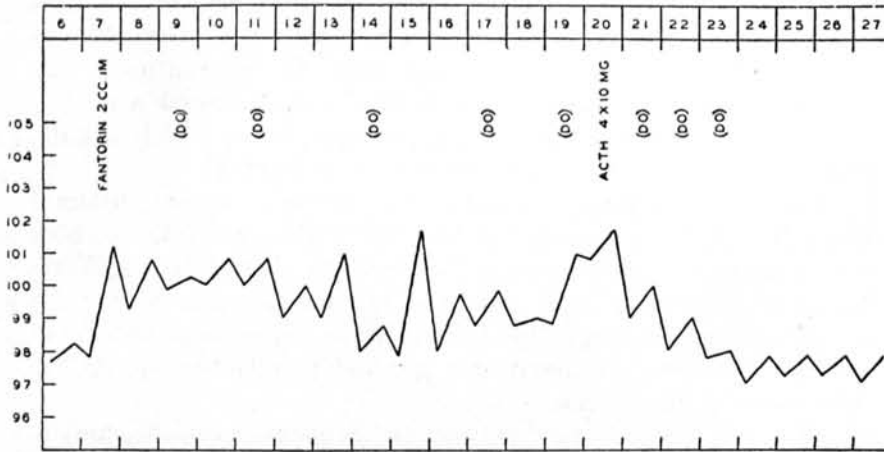
Lepra reaction.—The reaction in lepromatous cases was found to respond very readily and very quickly to ACTH. The relief of pain and temperature was immediate within the first 24 hours, and most of the other symptoms were gradually relieved within the next two or three days. If the treatment was stopped a little too early, there immediately followed a rise of temperature and recurrence of other symptoms, which equally readily responded to further treatment (Chart 3).

The effect of this treatment was specially evident in the 4 cases in which the condition had been unsuccessfully treated with calcium and antimony for the previous several days (Charts 1 to 4).² These patients had been having sleepless nights for days together, because of the pain in spite of the usual treatment for the reaction; on the first night after initiation of ACTH they enjoyed good sleep.

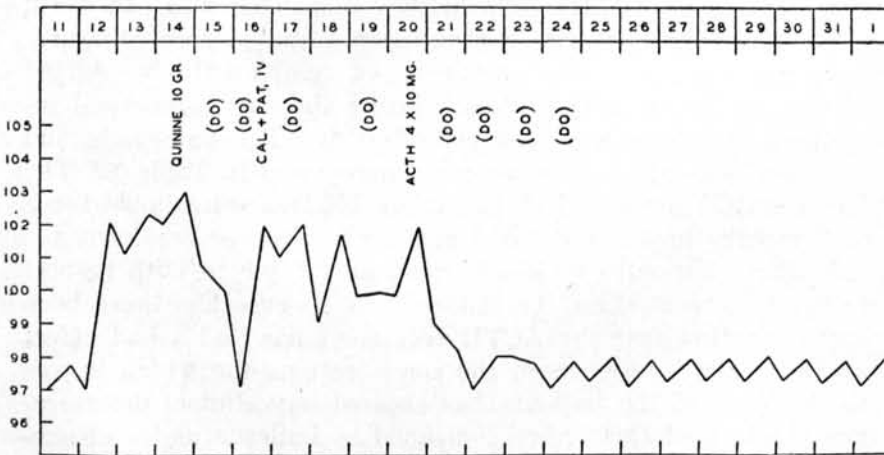
Of the 8 cases, 5 were subject to frequent reactions, and in 2 they were very frequent, occurring almost every other month. In these cases cessation of treatment was sooner or later followed by a relapse, but the relapses in the post-ACTH period have been on the whole less frequent and less severe. If mild these relapses were treated with antimony, if severe with another course of ACTH to which they responded well. In the 2 cases in which iritis was a troublesome and prominent symptom, this condition was only relieved temporarily by ACTH injections. Later, with cortisone drops and subconjunctival injections, the relief has been more lasting. The immediate and late results in all the 8 cases are summarised in Table 1.³ The late results (to the end of December 1952) are available for 8 to 9 months in 4 cases, for 4 months in another case, but for only about 3 months or less in the other 3, which with respect to the late results may be ignored. In no case has there been any indication that the ACTH treatment has had a bad effect on the basic disease or on the complications for which it was used. None of the patients has showed any clinical deterioration, and all of them have continued to improve under chemotherapy. Neither was there any deterioration indicated by the results of bacteriological examination.

² Two of these cases had preliminary treatment with quinine as the symptoms started with rigor suggesting an attack of malaria, and there was considerable enlargement of the spleen (Charts 2 and 4).

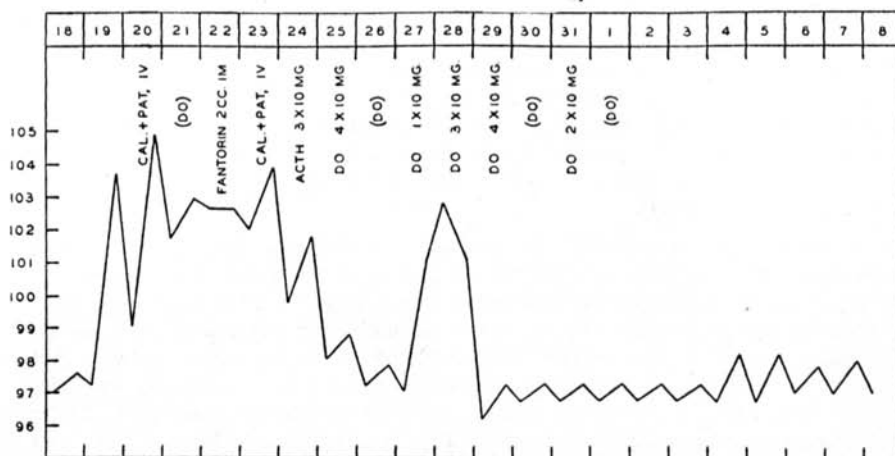
³ Table omitted. The essential data therein, together with notes from the original charts, are given in the case notes provided.—EDITOR.



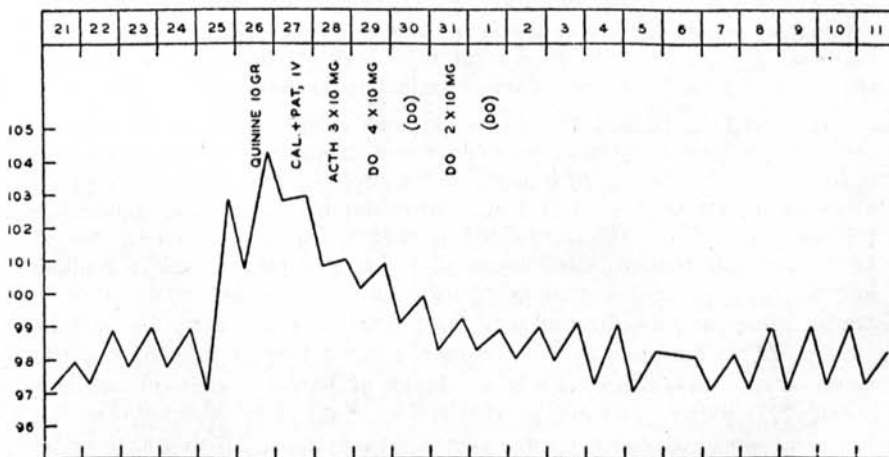
TEXT-FIG. 1. Temperature chart, Case 1, March 6-27, 1952. ACTH first administered March 27.



TEXT-FIG. 2. Temperature chart, Case 2, March 11-April 1, 1952. ACTH first administered March 20.



TEXT-FIG. 3. Temperature chart, Case 3, March 18-April 8, 1952. ACTH first administered March 24.



TEXT-FIG. 4. Temperature chart, Case 4, March 21-April 11, 1952. ACTH first administered March 28.

CASE C.L. (Chart 1).—This patient had fever, severe pain of the extremities, generalised painful nodules, and insomnia due to the pain. Beginning 20/3, ACTH was given, 16 doses of 10 mg. in 4 days. The temperature became normal in 2 days, and the nerve pain subsided on the 5th day. Notes: 20/3: Slept well, nerve pain less. 21 & 22/3: Improvement maintained. 23/3: Slight pain, but slept well. 24/3: Pain relieved. 26/3: Nodules rapidly subsiding. Previously the patient had had frequent reactions. No relapse occurred to the end of December 1952. Due to nephritis, antileprosy treatment was discontinued in October, but the bacteriological index is practically unchanged, 1.3 against 1.1 before the treatment. *Further follow-up* (May 1953): No further reaction. Bacteriological index now 2.0.

CASE N.B. (Chart 2).—Generalised painful nodules, iritis of both eyes, synovitis of both knee joints, pain all over the body, and enlargement of the spleen and liver; quinine given for 3 days. ACTH begun on 20/3, 20 x 10 mg. in 5 days. Temperature normal in 2 days, and joint pains, nodules and iritis subsided in 6 days, although a few transitory nodules and slight nerve pain continued. Notes: 21/3: Some relief, especially swelling and pain, after 4 injections. 22/3: No pain in knees; slept well. 24/3: Further improvement; iritis cleared. 1/4: A few fresh nodules. There was a relapse on April 6, eleven days after the ACTH treatment was stopped [duration not stated], and another in August of 12 days duration, a less frequent occurrence than previously; reactions had been very frequent, 6 during 1951 and 1 in 1952 before the one treated in March. There have, however, been frequent attacks of iritis and conjunctivitis, but these have been controlled with cortisone. Bacteriological index 2.8 before ACTH, now 3.0. *Further follow-up* (May 1953): There have been four more reactional episodes. However, the iritis and conjunctivitis have not so far reappeared since the subconjunctival injections of cortisone, even during the recent febrile reactions. Bacteriological index now 2.1.

CASE N.D.G. (Chart 3).—Fever, a fresh crop of nodules, generalised erythema, intense body pain, joint pain and swelling of both legs. ACTH begun 24/3, 27 x 10 mg. in 9 days. Relief of fever and general symptoms after 12 injections; the ACTH was then stopped for a day. Immediate relapse occurred, but this responded quickly to further treatment. Notes: 24/3: Relief of pain within 3 hours of the first injection. 25/3: Nodules and swelling of legs subsiding. 26/3: All-round relief. 27/3: Painful fresh nodules and swelling of legs reappeared 12 hours after the last injection. 28/3: Pain and swelling reduced after 3 further injections. 29/3: Improvement maintained. 30/3: Swellings of legs and pain almost subsided. This patient had not previously been subject to reaction, and has had none since. Bacteriological index decreased from 2.0 to 1.6. *Further follow-up* (May 1953): No further reaction. Bacteriological index unchanged.

CASE M.R. (Chart 4).—This reaction was severe, with nodules and body pain; because of rigor at an early stage, and palpable liver and spleen, quinine was first given. ACTH begun 28/3, 15 x 10 mg. in 5 days. Subsidence of fever and general symptoms in 4 days; the iritis persisted. Notes: 29/3: Some relief from pain. 30/3: Pain much relieved, nodules subsiding. 31/3: Practically no pain; episcleral nodule still present in only

one eye. 1/4: No pain; all-round improvement (which was maintained). Relapse occurred on 19/4, 18 days after suspension of ACTH; duration, 5 days. Three further relapses occurred: in June (4 days duration), in August (immediately responding, in 2 days, to ACTH), and in November (also responding, in 3 days, to ACTH although iritis persisted). ACTH injections afforded only temporary relief for the very frequent and troublesome iritis; cortisone injected subconjunctivally on three occasions (11/11, 2/12 and 20/12) have afforded more lasting relief. This patient had had very frequent reactions, 7 in 1951, with particular involvement of the eye. Bacteriological index 2.3 before ACTH, now 2.6. *Further follow-up* (May 1953): Has had two reactions in January and February, but milder than before, multiple nodules but no fever. The eyes remained clear during these episodes. Bacteriological index now 3.0.

CASE H.M.—Fever and general symptoms. ACTH begun 2/8, 27 x 10 mg. in 8 days. The condition was quickly relieved, but the treatment was prolonged to safeguard against immediate relapse. Patient not subject to reactions previously, and has had no recurrence. Bacteriological index 1.8 before ACTH, now 1.1. *Further follow-up* (May 1953): No further reaction. Bacteriological index now 1.8, as originally.

CASE R.C.B.—Patient subject to frequent reactions. ACTH begun 9/9, 7 x 20 mg. given [number of days not indicated]. The intense pain was relieved within ½ hour; the temperature and nodules subsided on the 4th day. A relapse occurred on 21/9, but responded immediately to ACTH, which was given until 26/9. Another occurred 10 days afterward, on 6/10 [duration not stated]; not treated with ACTH.

CASE B.S.—Subject to frequent reactions. ACTH begun 16/9, 7 x 20 mg. given in 7 days. Temperature normal on the 3rd day; all symptoms and nodules had subsided after the 7th day. Relapse occurred on 14/10, 22 days after the ACTH was discontinued [duration not stated]; not treated with ACTH.

CASE S.G.—In March this patient had had a very severe reaction, with very high temperature (105°F) and large blisters which on bursting left extensive raw surfaces. In the treated reaction, ACTH was begun 11/11, 16 x 10 mg. in 5 days. Temperature became normal after 3 days, rose again after early suspension of treatment, but was again promptly controlled. The nodules subsided, but inguinal adenitis persisted for about another fortnight. *Follow-up* (May 1953): A febrile reaction occurred, April 17 to May 5, after an increase in dosage of thiosemicarbazone. Bacteriological index decreased from 2.5 before ACTH to 1.6.

Short-lived painful nodules.—Another reactive condition which is often seen, and which should be differentiated from acute febrile reaction, is the appearance of fresh nodules of the nature of erythema nodosum. They are more frequently seen in patients under chemotherapy than otherwise. In this condition, which is usually afebrile, the patients who are otherwise improving get crops of small, painful, short-lived red nodules or raised patches. This subacute afebrile reaction is usually considered to be of good prognostic import.

ACTH was tried in 3 such cases. Each patient was in the first instance given a course of four days treatment (40 mg. daily, divided into 4 doses), and all of them responded well, the nodules disappearing after the first injections. However, about 4 to 10 days after the stoppage of the treatment the nodules began to appear as before. They again subsided and disappeared during the second course of treatment of the same duration, making their appearance as before after the stoppage of treatment.

It was therefore concluded that ACTH treatment was not suitable for this kind of reaction. However, observation of these cases for about 6 months after the treatment did not reveal any deteriorating effect on the course of the disease.

Acute iritis.—The effects of ACTH and cortisone have been tried in acute eye complications occurring both during the general reaction and apart from it. Acute iritis was a prominent symptom in 2 of the 8 cases of lepra reaction already described. In these cases the relief in the eye symptoms accompanied the general relief following ACTH injections. However, the condition soon reappeared after stoppage of the treatment, but later, with local treatment with cortisone drops and subconjunctival injections, the beneficial effects have been more lasting.

The effect of the treatment has been tried in 3 cases of iritis occurring apart from general reaction. In one case only ACTH injection was given, in another the injections were followed by local treatment with cortisone, and in the third only local treatment with cortisone was given.

In the first case the eye condition had appeared suddenly and was not of long standing. He was treated with ACTH for 4 days, 4 x 10 mg. daily. Watering and pain decreased immediately and subsequently disappeared; but the congestion, though decreased, cleared up only gradually. In the nearly 6 months since the treatment there has been no clinical or bacteriological indication of deterioration of the disease; on the other hand there has been some improvement.

The second case suffered from a chronic eye condition which was subject to frequent acute exacerbations. During the chronic phase of the disease he was given 2 courses of 4 days' treatment with ACTH (4 x 10 mg. daily) at short intervals, i.e., a total of 320 mg. ACTH. No appreciable improvement was seen in the eye condition. About 2 months after the second course the patient had a febrile reaction with acute flare-up of the chronic eye condition. ACTH injections were given for 4 days (4 x 10 mg. daily); the fever and acute eye condition subsided. This was followed up with local treatment with cortisone; the eyes apparently cleared up and have remained free from trouble (2 months). There has been no indication of deterioration of the disease (5 months after ACTH was first given). As

a matter of fact, there has been improvement. (It is not suggested that this improvement has been caused by ACTH.)

Because of the experience in the above two cases the third case received only local treatment with cortisone, with good results.

Drug dermatitis.—Drug dermatitis is frequently seen during treatment with sulphones, but in this country we do not come across the very serious exfoliative type reported by Lowe. The condition seen usually responds readily to antihistamine drugs; however, sometimes it is more severe and persistent and may necessitate the suspension of sulphone treatment. Two such cases, which did not respond satisfactorily to antihistaminics, cleared up quickly with ACTH.

In one case watery ACTH was given for 2 days and no further treatment was necessary. In the other patient, in whom the condition was more severe, and who was an out-patient, treatment was given once daily with Acthar gel (20 mg.) and had to be continued for 5 days.

Reaction in tuberculoid cases.—Reaction in cases of the tuberculoid type is of comparatively shorter duration, is usually not so troublesome, and is considered to exert a beneficial effect on the disease. The condition therefore does not call for any very special steps for treatment. However, sometimes the condition persists for a long time and something may have to be done, specially if there is danger of permanent damage to an affected nerve. Two such cases have been treated with ACTH. There was satisfactory response, but it was slow and the treatment had to be prolonged for about 8 to 10 days.

DISCUSSION

General.—There is general agreement regarding the early beneficial effects of treatment with ACTH and cortisone in cases of leprosy with certain acute complications, though there is some difference of opinion regarding the late results. As far as the early results are concerned the most remarkable effects are seen in the lowering of elevated temperature, relief of pain, inhibition of inflammation and swelling whether in joints, eyes, or elsewhere, and subsidence of nodules. The action of the hormones is temporary, and lasts only as long as they are administered. However, the benefit affords considerable relief to the distressing symptoms and is of definite value in that respect.

Need for caution.—There are certain features regarding this method of treatment which make it necessary that great caution should be exercised. For example, it is known that these hormones may mask the symptoms and lower resistance to infec-

tion, so that the disease may actually be getting worse while the patient is having a false sense of comfort and well being. Healing of wounds and injuries is also known to be delayed.

The hormones are known to lead to sodium, chloride and water retention, and therefore are in some cases likely to cause edema and puffiness of the face. This symptom was seen in a number of cases reported here, but was of mild extent and did not call for any special treatment. To counteract this tendency it has been recommended that during treatment the salt intake should be low, and there should be moderate restriction of fluids. If edema does appear, potassium chloride with diuretics is recommended; if the edema is excessive then the dose of ACTH has to be reduced or its use may have to be suspended. The condition quickly clears up on the stoppage of treatment.

As a result of its influence on carbohydrate metabolism there is often produced hyperglycemia, and in some cases glycosuria. If the treatment is unduly prolonged there is danger of the development of an insulin resistant type of diabetes.

In one case of allergic dermatitis treated with ACTH, but not included in the series reported herein, the blood sugar was found to be 175 mg.% after a course of ACTH with a total dose of 300 mg. A month later the blood sugar was still high, being 110 mg.%, and came down to 100 mg.% after about another 3 weeks. When the blood sugar was 175 mg.% the cholesterol content of the blood was also high, 250 mg.%; with the fall of blood sugar to 110 mg.% the cholesterol content also came down to 175 mg.%.

Prolonged treatment with ACTH may give rise to hypertension. This treatment is therefore not advised in persons with high blood pressure. Prolonged treatment may also sometimes give rise to mental changes such as restlessness, and maniac or depressive psychotic changes.

It would therefore be apparent that treatment with these hormones should not be prolonged beyond the relief of acute symptoms, and that the dose should be kept at a minimum. The case report of Melsom gives a useful indication regarding the reduction of the dosage used so far. He used very minute doses through mistake, but it is possible that very small doses may be effective. If it were so, the treatment would be made not only much safer, but also less expensive.

Late bad results.—Our experience does not agree with that of Lowe, who reported that the late results are often bad, leading to aggravation of the underlying disease and deterioration of the patient's condition. In none of our 18 cases has there been any indication of clinical or bacteriological deterioration

of the disease, or any harmful effect in the complications for which ACTH was used. In the cases subject to frequent febrile reactions the treatment has not prevented the recurrence of reactions (it was not expected to), but the relapses in the post-ACTH period have on the whole been less frequent and less severe. Most of the patients have continued to improve under chemotherapy. For the present it is not possible to explain this difference in the experiences at the two different centres.

Indications for treatment.—According to Lowe the only two indications for treatment with these hormones are sulphone sensitivity and acute and subacute leprosy eye inflammation, and possibly certain cases of acute neuritis. We agree with Lowe regarding the two conditions in which these hormones are indicated, specially the leprosy eye inflammations. We also agree that in the inflammatory eye conditions the local use of cortisone appears to be more effective. However, our experience differs regarding the effects in the acute febrile conditions in which Lowe regards the treatment contraindicated.

In India, although we occasionally get sulphone dermatitis, it is usually mild in nature; therefore while the hormones may sometimes be called for in the treatment of this condition, it does not constitute a common indication for their use in this country. We have had no experience in the treatment of acute neuritis occurring apart from the acute febrile reaction, but this condition is quite likely to be benefited by this mode of treatment. In our experience the two conditions that constitute a special indication for this treatment are: (1) acute febrile reaction, and (2) acute or subacute inflammatory conditions of the eye.

In the treatment of the febrile reactions with ACTH injections we have used an initial dose of 4 x 10 mg. daily, continuing the treatment for about 5 days with some reduction in the dose in later days, and the total dose has usually been about 160 mg. However, it is possible that the initial as well as the total dose could be reduced.

In case of iritis and iridocyclitis associated with febrile reaction, in addition to the injections of ACTH given for the general reaction, cortisone ophthalmic suspension can with advantage be used for instillation into the eye. This treatment may have to be followed up with subconjunctival injections of the saline suspension of cortisone. In case of the eye inflammation occurring apart from febrile reaction, the injection treatment with ACTH is not indicated.

SUMMARY

1. Previous reports on the use of ACTH and cortisone in the treatment of complications of leprosy are reviewed.

2. The results of treatment with these hormones in 18 cases are presented. The acute complications treated were: acute febrile reaction, 8 cases; afebrile reaction in the form of erythema nodosa nodules, 3 cases; acute iritis without fever, 3; severe sulphone dermatitis, 2; and reaction in cases of the tuberculoid type, 2.

3. The acute febrile reaction in lepromatous cases responded very readily to ACTH, with immediate relief of pain and temperature and subsidence of other symptoms, including iritis and neuritis, during the next two or three days. The effects of the treatment are only temporary, and in cases subject to frequent reactions it did not prevent the occurrence of relapses; however, the relapses have on the whole been less frequent and less severe. No bad late effects have been noted.

4. Short-lived painful nodules in afebrile patients disappear soon after the institution of treatment, but they begin to reappear soon after the stoppage of treatment. This method of treatment is not therefore considered suitable for this condition.

5. Leprous iritis and iridocyclitis respond very readily to ACTH and cortisone. The effects after local use of cortisone by subconjunctival injection are more lasting than after the routine injections of the hormones. In case of these eye conditions associated with general reaction the treatment may be initiated with injections of the hormones, to be followed up by local treatment. In case eye complications occur apart from general reaction, injection treatment is not indicated.

6. Drug dermatitis frequently met with during chemotherapy of leprosy responds very readily to this treatment, and severe cases of this condition provide a suitable field of application for these hormones.

7. The hormone treatment may sometimes be indicated in certain other acute complications such as leprosy neuritis, adenitis, etc.

8. In our experience the two main indications for the use of these hormones have been: (1) acute febrile reactions, and (2) acute or subacute eye complications apart from general reaction.

9. This method of treatment serves only to ameliorate the acute complications, and is not a treatment for the disease as such. There is need for great caution in the use of these hor-

mones since they are known to mask the symptoms and lower resistance to infection; the treatment should never be prolonged and minimal effective doses should be used.

10. It is concluded that ACTH and cortisone, used with discrimination and with the knowledge of their limitations and possible dangers, provide a valuable method of treatment for certain acute complications of leprosy.

ADDENDUM

Since this report was written, in December 1952, most of the patients have been observed for a further five months, through May 1953. In none of the cases has there been seen any evidence of bad late results of the treatment. Further data on six of the cases of febrile reaction in lepromatous leprosy are supplied.⁴

The 3 cases which were treated for the nonfebrile erythema-nodosum type of reaction (two 4-day courses of 40 I.U. of ACTH per day) have all continued to show clinical and bacteriological improvement under chemotherapy. Their bacteriological indices have changed from 2.6, 1.5 and 2.3 before ACTH to 1.6, 0.5 and 2.0, respectively.

In all of the 3 cases treated for acute iritis in the absence of general reaction, the eye condition has remained subsided and there has been clinical and bacteriological improvement. The bacteriological indices of two of them have changed from 2.8 and 2.1 before ACTH to 1.3 and 0.6, respectively.

Six more cases of general reaction in lepromatous leprosy have been treated, and the data on them are given below. Three of them were treated with the aqueous solution of the hormone, and the other three with the Acthar gel. In one of the latter cases there was also used, for re-treatment of a relapse, a form called ACTH Prolongatum. In this substance, a product of the Fredericksberg Chemical Laboratories, Ltd., ACTH is conjugated with carboxymethyl cellulose. Because of the size of the molecule it is absorbed slowly from the site of injection and has a more marked depository effect than Acthar gel. We are making further observations with this product.

CASE A.M.—The reaction started on 9/3 with fever to 102°F, nodulation, etc. Treatment with Acthar gel was begun on 25/3, 0.5 cc. (10 I.U.) twice daily for 3 days. Fever and pain had subsided on the third day and the drug was discontinued, but the condition relapsed on the following day

⁴ These data are incorporated in the case notes inserted in the body of the article.—EDITOR.

and irregular fever continued for 10 days. In this case 60 I.U. in the gel form was insufficient. ACTH Prolongatum was then started, 1 cc. (20 I.U.) every other day for 3 doses. Temperature and pain subsided and remained so; patches subsided, with desquamation.

CASE G.M.—The reaction started on 1/4 with nodulation, pain, and slight rise of temperature. On 7/4 Acthar gel was begun, 0.5 cc. daily for 4 days. Pain and nodulation subsided completely after the 3rd injection. In this case—the patient a child of 12, the reaction mild—40 I.U. in the gel form was sufficient.

CASE B.I.S.—This patient was subject to frequent reactions, and stood sulphones very badly, even a dose of 10 mg. of DDS being liable to start a fresh reaction. Acthar gel was given over a period of four weeks, 0.5 cc. daily in the first week, 0.5 cc. on alternate days in the second week, and 0.5 cc. twice weekly in the third and fourth weeks. During this period 1 tablet of Sulfadione (DDS, 10 mg.) was given daily and tolerated perfectly. The same dose was given for the next four weeks, without ACTH, then increased to 2 tablets a day for another four weeks, and recently to 3 tablets a day. There has been no reaction during the past 3 months, and the patient has stood the treatment well and has shown improvement.

CASE M.R.—A reaction began on 8/3 with fever to 102°F and severe pain, especially in the ulnar nerves. (The patient had suffered severe right ulnar neuritis before the reaction, and had been relieved to some extent by 2 injections of 5 cc. of 2% procain into the nerve.) Under antimony treatment the temperature came down to 99°F on 19/3, but severe nerve pain persisted. Beginning 2/4, ACTH solution was injected, 1 cc. (10 I.U.) twice daily for 3 days. This almost completely relieved the pain, although a dull burning sensation in the forearm continued. Another 3-day course was begun on 8/4, and the nerve disturbance cleared up entirely.

CASE S.P.—Reaction, with fever and nodulation, began 7/4, after an increase in dosage of thiosemicarbazone. Beginning 9/4, watery ACTH, 1 cc. twice daily, was injected for 2 days. The temperature became normal and the nodules began to subside, but on the day after the treatment was suspended new nodules appeared and the temperature tended to rise. In this case 40 I.U. in watery solution was obviously insufficient.

CASE H.A.—On 4/4, three days after the dosage of thiosemicarbazone was increased from 100 mg., which the patient had been receiving for some time, to 150 mg. a reaction started. There were fever, a few fresh nodules, severe nerve pain, and pain in the extremities below the knees and elbows. (This patient was especially prone to ulnar neuritis, and had received procain injection into the nerves on three occasions.) Beginning 13/4, ACTH solution was given, 1 cc. daily for 7 days, together with 150 mg. of thiosemicarbazone daily. The temperature became normal after 1 day and the pain subsided to some extent, but the temperature again rose to 100°F on 16/4. It appeared that even with the help of ACTH the 150 mg. dose of thiosemicarbazone was not tolerated, so it was reduced to 100 mg. and has been continued at that level.

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