without the devoted efforts of the secretarial staff of the Tuberculosis Research Unit, who have been responsible for the considerable and often tedious clerical work required in conducting this type of investigation.

REFERENCES

- Bernstein, J., Lott, W. A., Steinberg, B. A., and Yale, H. L. (1952). *Amer. Rev. Tuberc.*, 65, 357.
 Elmendorf, Du M. F., jun., Cawthon, W. V., Muschenheim, C., and McDermott, W. (1952). *Ibid.*, 65, 429.
 Goulding, R., King, M. B., Knox, R., and Robson, J. M. (1952). *Lancet*, 2, 69.
 Grunberg, E., and Schnitzer, R. J. (1952). *Quart. Bull. Sea View Hosp.*, 13, 3.
 Hobby, G. L., and Lenert, T. F. (1952). *Amer. Rev. Tuberc.*, 65, 771.
 Knox, R., MacLean, K. S., and Robson, J. M. (1952). *British Medical Journal*, 1, 1081.
 Medical Research Council Investigation (1948). *Ibid.*, 2, 769.
 — (1950). *Ibid.*, 2, 1073.
 — (1952). *Ibid.*, 1, 1157.
 Middlebrook, G. (1952). *Amer. Rev. Tuberc.*, 65, 765.
 Pansy, R., Stander, H., and Donovan, R. (1952). *Ibid.*, 65, 761.
 Robitzek, E. H., Selikoff, I. J., and Ornstein, G. G. (1952). *Quart. Bull. Sea View Hosp.*, 13, 27.
 Steenken, W., jun., Meade, G. M., Wolinsky, E., and Coates, E. O. (1952). *Amer. Rev. Tuberc.*, 65, 754.

A.C.T.H. AND CORTISONE IN TREATMENT OF COMPLICATIONS OF LEPROSY

BY

JOHN LOWE, M.D., M.R.C.P.
Specialist, Nigeria Leprosy Service

The chemotherapy of leprosy with sulphone is now being widely practised, with good results. The thiosemicarbazones also are being used with promising results, and other chemotherapeutic agents are under study. Leprosy treatment is becoming established on sound lines, and the outlook is very encouraging.

Certain complications of leprosy are still very difficult to treat, and, because of their nature, may be precipitated or aggravated by chemotherapy, rendering treatment of the underlying disease difficult. A further difficulty of chemotherapy, particularly with sulphones, is that occasionally a patient after a few weeks' treatment becomes intensely allergic to the drugs used, and this allergy shows itself by drug fever, dermatitis which may exfoliate, and hepatitis which may be severe and lead to liver necrosis, the whole condition sometimes being so severe as to result in death.

These complications are not fully understood, but there are certain resemblances between them and those conditions which are alleviated by A.C.T.H. and cortisone, and a trial of these hormones was therefore strongly indicated. The value of A.C.T.H. and cortisone in the treatment of hypersensitive states and drug allergy showing itself as dermatitis has been clearly demonstrated, and the hormones are obviously worth a trial in the potentially dangerous condition of allergy to sulphones.

There were, however, certain obvious dangers. Leprosy, like tuberculosis, is a disease in which troublesome symptoms may sometimes be caused by excessive tissue reaction to the bacilli and their products. This I believe to be true, though in widely varying degree, in all forms of leprosy. The action of A.C.T.H. and cortisone apparently consists largely in reducing this tissue reaction and thus alleviating symptoms so long as the action of A.C.T.H. or cortisone lasts. But it is this same tissue reaction which is needed to localize the infection and, in time, to overcome it. The question therefore arose whether A.C.T.H. and cortisone might not, while relieving symptoms, aggravate the underlying disease by reducing the tissue reaction which was keeping it in check. A good discussion of the action of

cortisone and A.C.T.H. in tuberculosis appeared in a leading article in the *British Medical Journal* (1951) outlining the difficulties and dangers. It seemed probable that the use of these hormones in leprosy would be attended by the same difficulties.

It was, however, thought there were factors which favoured the use of A.C.T.H. and cortisone in the treatment of complications of leprosy, the main one being that these complications, when untreated, usually last only a week or two and then subside, although they often recur; therefore a few days' treatment, repeated later if necessary, might tide the patient over the natural period of the complication but not be sufficient to aggravate the underlying disease. Further, it was thought that by continuing chemotherapy during hormone treatment, and even perhaps increasing the dose, any tendency to aggravation of the disease by the hormones might be overcome. These hopes were not fulfilled.

Nature of the Complications

Sulphone Dermatitis, etc.

This syndrome, which includes drug fever, a generalized dermatitis which goes on to exfoliation, inflammation of mucous membranes, a general lymphadenitis, and hepatitis with jaundice which may be latent or overt, has constituted the main difficulty of mass sulphone treatment here in Nigeria, where it has been seen in about 2% of treated cases. It is not a true toxic effect of sulphones; it is caused through the patient becoming allergic to sulphones, as is indicated by the following facts. (1) It occurs between the third and ninth weeks of treatment, and if it does not occur then it will not occur at all. (2) A patient who has been taking full doses, such as 200 mg. a day, without trouble, will, when he has become allergic and has later recovered from the dermatitis syndrome, get a recurrence after a single small dose, often as low as 20 mg., of sulphone; the same patient after desensitization will tolerate full doses again without difficulty. (3) The condition is exactly the same as is seen in sulphonamide sensitization. The administration of a single tablet of any sulphonamide will cause an immediate recurrence of symptoms in a person who has recovered but not been desensitized, and a severe aggravation in a person still suffering from sulphone dermatitis. (4) Antihistamine drugs are of value in the treatment of this condition.

This condition demands early recognition, the immediate cessation of sulphone treatment, the avoidance of all sulphonamides, treatment with antihistamines, and good nursing. Even with these the patient is seriously ill and recovery takes several weeks. Without these the condition may cause death, particularly when experienced physicians are not available. So far the treatment of this condition has been along the lines indicated, and recovery has been very slow.

Acute Leprous Neuritis

A chronic neuritis is common in leprosy of all types. In the lepromatous type, with which we are almost exclusively concerned in the present study, leprosy involvement of certain nerve trunks, particularly the ulnar and peroneals, is almost always present. Histopathological studies show large numbers of bacilli lying in the epineurium, perineurium, and endoneurium of the nerves, and usually there is little tissue reaction to these bacilli, and swelling of the nerve is not marked. At certain phases of the disease, and particularly in the middle or towards the end of the long chemotherapy of the disease, such nerves may suddenly become very thick, painful, and tender. The pain may be extremely severe and persistent, and without powerful analgesics the patient may be in agony for several days, or even weeks, until the inflammation spontaneously subsides. This it always does; but before this happens irreparable damage to nerve fibres often occurs, and trophic lesions and deformities follow.

The cause of these attacks of neuritis is not clear. There is no reason to believe that they are due to any increase in the leprosy infection in the nerve, for they frequently occur when the leprosy infection throughout the whole body is steadily being controlled by chemotherapy. The probable explanation is that the interstitial cells in the nerves suddenly and temporarily acquire the power to react violently to the leprosy infection present.

In the past no effective treatment was available; surgical removal of, or making multiple longitudinal incisions in, the nerve sheath, with relief of pressure and of pain, offered a good measure of success, but this was obviously not to be undertaken by anyone anywhere. Recently I have been using with much success injections of procaine (3 to 4 ml. of 2% solution) inside the nerve sheath of the affected portion of nerve, the nerve being punctured through the skin at two or three places an inch (2.5 cm.) or so apart, and 1 to 2 ml. of the solution being injected at each place. The affected nerves are usually so thick that location and injection are easy and cause little pain, especially if the first injection is given proximally, to produce a blocking effect. The effect of the injection lasts two to three days, by which time the neuritis may be subsiding, though two, or even three, injections may have to be given before subsidence occurs. It seems possible that the effect of the procaine is a double one—an analgesic action and an antihistamine action. The antihistamine action of procaine is now widely recognized.

The nature of this complication, and the facts outlined above, clearly suggest that cortisone or A.C.T.H. might be of value in its treatment.

Acute Leprous Eye Inflammation

In the majority of cases of leprosy of the lepromatous type there is leprosy involvement of the eye, both superficial and deep, in the form of keratitis, scleritis, and uveitis. These can be detected by special methods of examination (for example, the slit-lamp); ordinary clinical examinations may not reveal them. The vision is often very little affected. Here again, as in neuritis, this chronic infiltration may suddenly develop into acute or subacute inflammation, with obvious leprosy lesions in the sites mentioned, causing deformities and opacity of the coverings of the eye, and inflammation and adhesions of the iris, often with secondary glaucoma.

These acute or subacute attacks may be extremely distressing, and may last for several weeks or months and lead to partial or complete blindness. In the long run chemotherapy will arrest the leprosy process in the eye, but attacks of eye inflammation may occur during treatment and sometimes seem to be precipitated by treatment.

Here again it would appear that the attacks are caused by the temporary increase in response of the tissue cells of the eye to the leprosy bacillus and its products rather than by an actual increase in leprosy infection; in other words, the attacks indicate some kind of sensitization, and A.C.T.H. and cortisone are therefore worth trying.

Lepromatous Reaction

This, probably the commonest complication of leprosy, is known as leprotic fever and erythema nodosum leprosum. It often occurs entirely apart from, though it may be precipitated by, chemotherapy. Some workers have claimed that the naturally occurring reaction and the reaction produced by chemotherapy are different, but I have not been able to differentiate them.

A typical case shows fever, usually irregularly remittent or intermittent, headache, pains in limbs, malaise, and anorexia. There is often some inflammatory reaction in the leprosy lesions of the skin and mucous membranes, as well as in the nerves, the lymph nodes, the eye, and elsewhere. Sometimes the lesions of the skin and mucous membrane become very swollen and may ulcerate.

In addition there is usually a crop of "new" lesions which take the form of areas of inflammatory induration in the skin and, still more often, in the subcutaneous tissue.

(These swellings give rise to the name erythema nodosum leprosum.) They are commonest in the limbs and on the face, less common on the trunk.

The condition usually lasts a week or two, and then subsides, often to recur later. In a few cases reaction is continuous for months. Unless it involves delicate tissues, such as the nerves and the eye, it may do little immediate harm. In the untreated disease, however, reaction is usually accompanied or followed by clinical deterioration. In patients receiving chemotherapy, reaction is usually followed by clinical improvement—in fact, it has been stated that in many lepromatous cases reaction is "the inevitable accompaniment of any successful treatment." Nevertheless it can be a very troublesome condition and have serious physical and psychological effects on the patient; it can greatly handicap attempts at chemotherapy. A reliable method of mitigating its frequency and severity is urgently needed.

The causation of the reaction is not fully understood. Certain features, such as the appearance of new lesions, suggest that lepra bacilli are being disseminated by the blood stream; other features suggest that the tissues temporarily acquire the power to react to the lepra bacillus or its products, whose previous presence had provoked little such tissue reaction. Probably both these factors play a part in causing the reaction.

Roche *et al.* (1951) recorded the beneficial action of A.C.T.H. on the reaction, with iritis also present in one case and neuritis in two cases. The symptoms were promptly relieved, but they returned in a few days. This temporary relief was thought to be of value.

Treatment

The number of cases treated with hormones up to February 10, 1952, was 38, made up as follows: sulphone dermatitis, etc., 4 cases; acute neuritis, 8; acute leprosy eye inflammation, 7; lepromatous reaction, 16; tuberculoid reaction, 1; leprosy elephantiasis, 1; acute leprosy arthritis, 1.

Apart from four cases of leprosy eye inflammation treated with cortisone applied locally, all hormones were injected (only injectable hormones were available). The initial recommended dose of A.C.T.H. for full effect is 50 mg. six-hourly, and of cortisone 100 mg. 12-hourly. In our work the dosage used has varied widely. Only small supplies of A.C.T.H. were at first available, and rigid economy was essential. The dosage used was 25 mg. twice daily, and the response was good in most cases. Later, when adequate supplies reached us, the dosage was increased to 25 mg. six-hourly, with still better early response. Later still, when some bad late results were seen, smaller doses were resumed so as to prevent these. The work with cortisone was started with full doses (100 mg. 12-hourly), but later, in an attempt to minimize the bad effects, smaller doses were given.

The period of administration was as short as possible, only sufficient to relieve fully all acute symptoms. Two or three days at full doses usually sufficed to produce a marked improvement, though a further two days' treatment at diminishing doses was sometimes given. When smaller doses were used the period of administration was four or five days, the last day or two being at very low dosage.

When symptoms recurred after the initial short course of treatment the course was repeated, in some cases several times, with modifications to correspond to the clinical condition.

During hormone treatment the chemotherapy of leprosy (except in cases of sulphone dermatitis) was continued at full doses in the early phases of the work. Later it was found necessary to reduce the dose in some cases.

Results

Sulphone Dermatitis, etc.

Four cases of this complication have been treated with hormones. In all four cases cortisone was given—100 mg. 12-hourly for two days, 50 mg. 12-hourly for one day, and

then stopped. The response was in all cases dramatic. The following is a typical case report.

The patient was admitted from an out-patient clinic with a history of sulphone treatment for leprosy having been started recently, and an illness of nine days' duration, with fever, much irritation of the skin, followed by blister formation and exudation of fluid.

On admission he showed inflammation of the skin of the whole body; in some areas there was a follicular dermatitis, with much oedema of the skin, in other areas blister formation, and in still other areas desquamation of blackened epidermis, leaving a raw surface. There were puffy swelling of the face and conjunctivitis; the lips were black and cracked, and the mucous membranes of tongue and mouth were red and inflamed. The spleen, liver, and lymph nodes were enlarged. There was remittent fever, 100-103° F. (37.8-39.4° C.). The patient was extremely miserable, and complained mainly of skin irritation, causing sleeplessness, headache, and soreness of the mouth, making eating and drinking very difficult, and loss of all appetite.

Cortisone, 100 mg., was given twice daily for two days, and on the third day the dose was halved. Within a few hours the patient felt better, and said the irritation was less, though there was no visible improvement. Within 24 hours he looked better and the fever had stopped. During the next two days' treatment improvement continued, with extensive desquamation of the skin. Appetite returned. After the hormone treatment was stopped, improvement continued, and there was no tendency to recurrence; dead epidermis peeled off extensively, exposing healthy but rather red and raw skin underneath. At the end of one week desquamation had finished except on the palms and the soles, and the mucous membranes were normal.

Thus recovery was, for practical purposes, complete in a week and there were no untoward symptoms. In previous cases, without hormone treatment, this degree of recovery required at least a month, and the antihistamine drugs, if used for long periods, produced toxic effects, mainly severe depression.

All the four cases of sulphone sensitization treated with cortisone responded in the same way. In three of them one single short course of three days' treatment was enough to control the condition and see the patient well on the way to recovery, and no recurrence has followed the cessation of treatment. In the fourth case a mild recurrence necessitated a second short course of treatment. This hormone treatment was not enough to exert any ill effect on the leprosy.

All the four cases were of several days' duration before hormone treatment was started. If hormone treatment could be instituted within 24-48 hours of the onset, the complication could, it is felt, be rendered benign.

These findings are considered to be of great practical importance, removing the one real danger associated with sulphone treatment.

Acute Neuritis

Eight cases of acute leprosy neuritis have been treated with short courses of A.C.T.H. or cortisone by the methods outlined. In all these cases the immediate response has been excellent. Within a few hours the pain was less, and within 24-48 hours it had gone or almost gone, and the affected nerves were much less thick and tender. In four the cessation of treatment was not followed by an early recurrence, although in three of them there was a recurrence a month or more later, in each case milder than the original attack. In the other four recurrence did follow the cessation of hormone treatment, and they were then given three to five short courses of hormone treatment. 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 frequent after the hormone treatment than before it; in the other two the neuritis was relieved, but reaction and iritis recurred.

Thus of these eight cases of acute neuritis the ultimate results of treatment may be considered good in four, but in the other four the results appeared to be bad. It is noticeable that the better results were seen in those four patients who received only one short course of hormone treatment. It seems that cortisone and A.C.T.H. treatment may be justified so long as only one short course is given. If recurrence follows, further courses of hormone treatment

are contraindicated. On the other hand, the efficacy of injecting procaine into the nerve as already described should not be overlooked. This procedure is much simpler and safer, and, on evidence available, remains the treatment of choice for acute leprosy neuritis. Short courses of hormone treatment might, however, be justified in persons with acute neuritis in the facial nerve, for this may cause severe and permanent disfigurement, and even blindness following inability to close the eyes.

Leprous Eye Inflammation

In all, seven cases of this nature have been treated with hormones. Three had injections of A.C.T.H. and four had cortisone eye drops. All three treated with A.C.T.H. showed a good early response, with lessening of pain within 24 hours and visible improvement in 24-48 hours, and reduced inflammation. When the short course of hormone treatment was completed all acute signs had gone, though the chronic lesions remained. A few days later the symptoms returned and the short course was repeated. One case had three recurrences and the other two had four, each recurrence getting milder and finally ceasing. 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. Of these three cases, the most striking is here described.

A very severe long-standing lepromatous case with severe eye affection; the right eye was completely blind because of chronic leprosy inflammation of cornea and of uveal tract; the left eye showed severe chronic inflammation of cornea and iris, and a small leprosy nodule at the corneo-sclerotic junction; there was still useful vision in this eye. Sulphone treatment had been given for three years, with marked improvement in lesions of skin and mucous membranes, and the leprosy process in the left eye had been arrested, but slight attacks of inflammation had occurred several times.

Suddenly the left eye became acutely inflamed, the nodule became much larger, and the eye showed severe congestion, both superficial and deep, with intense photophobia and headache. Treatment along the usual lines with atropine and other general measures was given for 10 days, but the condition grew worse and the vision rapidly deteriorated.

A.C.T.H., 25 mg. twice daily, was given for two days. There was symptomatic relief in a few hours, visible improvement in 24 hours, and still further improvement in 48 hours. The signs of acute inflammation disappeared for one week. A relapse was then treated as before, with similar results—subsidence for one week, followed by relapse, necessitating further treatment. In all, three relapses occurred, and four two-day courses of A.C.T.H. were given. After the fourth course the condition remained quiescent; the patient has now been free from all acute symptoms for three months, and vision is no worse than before the attack. Chemotherapy (TBI) was continued throughout.

It is considered that hormone treatment almost certainly saved this patient from complete blindness.

The other four cases of less acute leprosy eye inflammation were treated with cortisone eye drops, used, so far as was possible, every hour by day and less often at night. None of these cases were as severe as the case already described; all four responded well to treatment, which was continued for three days, and later resumed when there were mild recurrences. All four patients have now been free from acute symptoms for several weeks. Further cases, more severe and more typical, are needed for further study, but they are not at present available here.

The present study indicates that hormone treatment of leprosy eye inflammation is likely to be of great value. Injected hormones, however, have tended to aggravate other manifestations of leprosy. The local use of cortisone is likely to be the method of choice, but our experience of this method has so far been limited by lack of suitable cases.

Lepromatous Reaction

In all, 16 cases of acute lepromatous reaction have been treated. In every case the acute symptoms disappeared rapidly under hormone treatment, given for two or three days. In 12 out of the 16 symptoms recurred a few days later, and further courses of treatment were given. Further

recurrences were seen in some of the cases, and each recurrence was only temporarily controlled by 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. The investigation was stopped and the position assessed. Of the 16 patients, six appeared to have benefited (all of these had only one or two short courses); in four the results were doubtful (these had one to four courses, average three); in the other six the results were regarded as bad (these had between one and nine courses, average five). All attempts to improve the results by smaller total dosage and tapering off the dose failed.

These 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 contraindicated. It does more harm than good.

Other Complications

One case of apparently leprous arthritis, which previously had often occurred, was apparently cured by one short course of hormone treatment.

One case of leprous elephantiasis of the legs showed marked temporary improvement followed by relapse, and further courses were followed by general reaction; the result was therefore bad.

One tuberculoid case of leprosy (the only one in the present series) came in the phase of acute tuberculoid reaction with marked inflammation of the skin lesions, of the affected mucous membranes, and of the nerves. One short course of hormone treatment brought considerable alleviation of symptoms, but 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.

General Conclusions

While the acute manifestations of leprosy can be very readily controlled by hormone treatment, there is a grave danger of aggravating the underlying disease, particularly in those receiving repeated short courses of treatment, and even of aggravating the particular symptoms to alleviate which the hormone has been given. Thus the early results are good, and the late results too often bad.

Attempts to minimize the bad late results by modified dosage and by energetic chemotherapy during hormone treatment have met with little success. Nevertheless, in two complications of leprosy and its treatment, both of them serious, the results are striking and are usually attained with such small doses that hormone treatment is fully justified. These two complications are: (1) sulphone sensitivity, with drug fever, dermatitis, and hepatitis, and (2) acute and subacute leprous eye inflammation, in which condition the local use of cortisone appears to be effective and safe, and is to be preferred to injection.

Apart from these two conditions the use of hormone treatment of leprosy is usually contraindicated. In some cases of acute neuritis, carefully selected as showing only mild residual leprous infection after chemotherapy, one short course might be justified, but other methods of treatment appear preferable.

I am greatly indebted to Nyegaard and Co., of Oslo, Norway, for free supplies of their "nyco" brand of A.C.T.H., with which the work was started; and also to the Medical Research Council for supplies of A.C.T.H. (Armour) and cortisone (Merck). All three preparations appeared to be fully active.

REFERENCES

- British Medical Journal (1951), 2, 1570.
Roche, M., Convit, J., Medina, J. A., and Blumenfeld, E. (1951). *Int. J. Leprosy*, 19, 137.

PNEUMONIAS ARISING DURING THE COURSE OF UPPER RESPIRATORY INFECTIONS

BY

J. P. P. BRADSHAW, M.D., M.R.C.P.

Captain, R.A.M.C.

C. A. B. BERNSTEIN, M.R.C.S., L.R.C.P.

Lieutenant, R.A.M.C.

AND

E. BOWERS, M.B., B.S., B.Sc.

Captain, R.A.M.C.

(From the Military Hospital, Shorncliffe)

During the period from August, 1950, to May, 1951, 393 Service men from Shorncliffe Camp reported sick with coryzal symptoms. Their ages ranged from 17 to 44. Of these cases 126 were referred to the Shorncliffe Military Hospital either because they were unfit for duty for longer than 48 hours or because they were suspected of having pulmonary complications. Of those referred, 48 were found to have abnormal chest radiographs: the seasonal incidence of these opacities is shown in Table I.

TABLE I.—Seasonal Incidence

	Virus Pneumonias	Other Opacities	Other Upper Resp. Infections Admitted to Hospital
August, 1950 ..	0	2	4
September, 1950 ..	0	1	3
October, 1950 ..	1	4	8
November, 1950 ..	0	7	8
December, 1950 ..	1	3	4
January, 1951 ..	0	8	11
February, 1951 ..	0	7	13
March, 1951 ..	1	7	4
April, 1951 ..	0	4	12
May, 1951 ..	0	2	11

Three of these cases were diagnosed as virus pneumonias. They showed marked constitutional symptoms, with a pyrexia of above 103° F. (39.4° C.), which failed to respond to combined sulphadimidine and penicillin therapy. No pathogenic bacteria were isolated from their sputa, and they demonstrated a neutropenia in association with a raised erythrocyte sedimentation rate. Two developed cold agglutinins to titres of 1/2,560 and 1/512 respectively. Serological investigations in the third case, in which cold agglutinins were not found, were negative on the fourth and tenth days for influenza A and B, ornithosis, the lymphogranuloma venereum group, Q fever, and the streptococcus MG.

In the remaining 45 cases examination of the sputum revealed a mixed growth of throat commensals, and the course of the disease was unlike that of the virus group by reason of the minimal constitutional symptoms, the rapid response to sulphonamides, and certain other features that are described below. They were divided into two groups on the basis of the total neutrophil count, which was considered to be a more reliable guide than the total number of white cells. In Group I (17 cases) the neutrophil count was below 7,500 per c.mm., and in Group II (28 cases) it ranged from 7,500 to 25,000 per c.mm.

It is the purpose of this paper to discuss both groups, but especially Group II, with reference to aetiology and