

1-3-1957
S. Paolo

INTERNATIONAL JOURNAL OF LEPROSY

VOLUME 24, NUMBER 2

APRIL-JUNE, 1956

c 1 CLINICAL STUDIES IN THE USE OF CORTISONE AND
CORTICOTROPIN IN THE REACTIVE
EPISODES OF LEPROSY

JOHN S. SHUTTLEWORTH, M. D.¹

Erythema nodosum leprosum (18) occurs as an acute, subacute or chronic reaction characterized by the occurrence of erythematous nodules, which appear most commonly on the extensor surfaces of the extremities, the face and the trunk. These nodules are usually painful. The reaction is often associated with fever, malaise, nausea, vomiting and some loss of weight. Occasionally the reaction may recur at frequent intervals or, in the more chronic form, it remains active for long periods of time. In untreated cases the fever usually decreases by lysis. With repeated acute attacks, or in the more chronic form, there is a tendency for the lesions to develop pustulation and for chronic induration of the skin to occur. Approximately 63 per cent of lepromatous cases have erythema nodosum reactions at some time during their illness, and approximately 93 per cent of these occur after the institution of sulfone therapy (18). In a small percentage of the cases of erythema nodosum leprosum the reactions are of such severity and frequency that it becomes impossible to continue sulfone treatment. In some cases involvement of the nerves by the reaction results in an intense neuritis, and this can predominate in the clinical picture. It is usually of short duration, however, differing from leprosy neuritis in which the process is of much longer duration and frequently results in loss of nerve function.

Histological studies of erythema nodosum lesions show vascular changes in the smaller subcutaneous blood vessels and their branches in the corium. These vessels show endothelial proliferation, and there is edema and infiltration of cells and inflammation in the perivascular areas. The most striking change, however, is the marked edema in the corium. The possibility of an allergic basis for the erythema nodosum leprosum reaction, related in some way to sulfone therapy or to the *Mycobacterium leprae*

¹ Formerly chief of medical service, U. S. Public Health Service Hospital (National Leprosarium), Carville, Louisiana.

itself seems quite logical, for in many respects it resembles a Schwartzman phenomenon (17), and in other respects is similar to the Herxheimer reaction (7).

Many forms of therapy have been used for this reaction, particularly stibophen (fuadin) which in acute cases frequently will give dramatic relief. However, in some cases which have had repeated acute episodes or have the chronic form of the condition that drug is ineffective. In such patients hormone therapy has been considered in an effort to control the reactions and allow the patients to continue sulfone therapy.

The effectiveness of the adrenal steroid hormones in hypersensitive disease states has been well established (1, 12, 14, 15, 16), although the mechanism of the beneficial effect is not entirely clear (5, 6, 9, 15). The literature contains conflicting reports on the effect of these agents in leprosy and its complications (2, 3, 4, 8, 10, 11, 13). The present study was undertaken to try to reach a better understanding of the effects these drugs may have in leprosy. The following case reports give a representative sample of the results obtained in classical erythema nodosum leprosum, and also in several reactions which resembled acute exacerbations of lepromatous leprosy (Case 6) and erythema multiforme (Case 1) with severe systemic symptoms. Because of the protean nature of these latter episodes, all of these cases are being classified under the general heading of reactive episodes of leprosy.

CASE 1 (No. 2204).—A 30-year-old white female developed lepromatous leprosy in 1946. Sulfoxone sodium (diasone) therapy was begun in 1952. Her first erythema nodosum reaction was in February 1954, with high fever, chills, malaise, nausea, vomiting, and a generalized eruption of tender erythematous subcutaneous nodules. The sulfone was discontinued, and she responded to stibophen therapy. She was discharged from the infirmary after eight days hospitalization, and diasone treatment was resumed. She then had very little difficulty except for an occasional erythema nodosum lesion associated with mild chills and fever. In March 1954, she had an acute reaction resembling erythema multiforme which failed to respond to stibophen, but subsided spontaneously after fifteen days in the hospital. Sulfone therapy was discontinued. She remained asymptomatic until April 20, when she again had an acute reaction.

The patient was then treated with cortisone orally, 50 mgm. every six hours, and by the second hospital day her temperature had returned to normal, and she remained afebrile. She was out of bed and eating on the next day, and her skin lesions had disappeared by the sixth day of therapy. The dose was then decreased to 25 mgm. every six hours for two days, then to 12.5 mgm. twice daily for two days, after which it was discontinued. The patient remained asymptomatic, and on instructions took no more diasone until July 1. Skin tests for *M. leprae* remained positive. Her leprosy was of the same clinical degree as before cortisone therapy was given. On July 1, 1954, the sulfone treatment was resumed and has been continued, and there have been no further erythema nodosum reactions to the time of writing.

CASE 2 (No. 2144).—This 52-year-old white female developed lepromatous leprosy in 1946, which was moderately severe when she was admitted to Carville in May 1951. On May 26 treatment with glucosulfone sodium (promin) was begun. On June 27 the patient had her first erythema nodosum leprosum reaction. The sulfone was discontinued and the patient was given amithiozone (tibione) from July 7

through November 23, 1951. In January 1952 diasone therapy was begun and has been continued to the present time except for frequent intervals when acute reactions occurred.

At first the reactions responded well to stibophen therapy, but finally the outbreaks of erythema nodosum became so frequent that the patient developed the chronic form with nearly continuous fever, marked induration of the skin of the extremities, and subcutaneous suppuration. On November 23, 1953, she was readmitted to the infirmary with an acute exacerbation of the chronic reaction. She was given two courses of stibophen, which resulted in temporary improvement; but the febrile episodes, with chills and systemic symptoms, returned after each course. Between November 23 and January 6, 1954, the patient lost approximately ten pounds in weight and the subacute erythema nodosum continued.

Cortisone was then administered, 100 mgm. twice daily. Within two days the patient became afebrile; there was a marked clearing of the erythema nodosum lesions; her appetite improved and her mental attitude changed completely. The dose was gradually decreased and she was maintained on 50 mgm. twice a day for a month; but within three days after cortisone was stopped the fever returned and reactivation of the erythema nodosum began. Cortisone treatment was reinstituted, but following the first dose there developed abdominal pain, tachycardia and a shock-like syndrome. The possibility of sensitivity to cortisone was considered, and this treatment was discontinued. On supportive therapy the abdominal symptoms subsided, but the erythema nodosum lesions became progressively more severe. She again began to lose weight rapidly, ten pounds in about a week.

Treatment was begun again but this time, because of the possibility of sensitivity to cortisone, corticotropin was used, 10 units every six hours intramuscularly, later increased to 15 mgm. every six hours. This dose was continued for a week and the patient again showed very dramatic improvement, becoming afebrile within two days. Corticotropin, 20 mgm. daily in divided doses, was continued for approximately a month. The skin became completely clear, the weight returned to normal, and the patient was asymptomatic. This treatment was discontinued on March 15, 1954.

During the period since November 23, 1953, all sulfone therapy had been withheld. On April 1 the patient was started again on diasone. She was asymptomatic until June 1, when an occasional erythema nodosum lesion appeared with no systemic reaction. She has continued to take diasone regularly. The leprosy remains active, but with no clinical evidence of aggravation due to the hormone therapy.

CASE 3 (No. 2217).—This patient developed lepromatous leprosy in 1945 and was admitted to Carville in April 1953. Acetosulfone (promacotin) treatment was started in May. In August 1953 she had her first acute erythema nodosum reaction. Under stibophen the reaction subsided within six days. She continued to have an occasional erythema nodosum lesion but without marked systemic symptoms, so she continued to take acetosulfone fairly regularly. In October 1953 the reactions became more severe and frequent, and finally, in June 1954, she sought medical assistance. The patient was then moderately ill and had lost about ten pounds in weight. There were numerous erythema nodosum-type lesions over the extremities and trunk and a dusky cyanosis of both malar areas. She had discontinued therapy because it aggravated her symptoms. She was admitted to the infirmary with a moderate intermittent fever.

On June 23 she was placed on cortisone therapy, the dosage as in Case 1, and within five days her temperature was normal and the erythema nodosum lesions had disappeared. On July 16 another acute reaction occurred, and she was placed on stibophen therapy for three days; there was slight decrease in the fever, but she remained acutely ill. On July 27 cortisone therapy was again started. The fever promptly dropped by crisis, and the systemic symptoms subsided. The patient was maintained on cortisone, which was gradually decreased to 50 mgm. daily. Her skin was clear of erythema nodosum lesions, she remained afebrile, and her weight returned

to normal. Minimal to moderate numbers of new nodules began to appear in spite of cortisone, so the dose was gradually increased to 50 mgm. four times daily, and on that dosage schedule it was possible to keep her completely free of lesions.

Diasone was then added to the treatment regimen, and for seven months it has been possible to continue this therapy and to keep the erythema nodosum reaction satisfactorily suppressed. Her weight and blood pressure have remained stable. She has remained nearly free from erythema nodosum lesions and has been able to tolerate the sulfone, and her general appearance and outlook have improved greatly. Skin smears are still strongly positive for *M. leprae*, but there has been no clinical evidence of aggravation of the leprosy.

CASE 4 (No. 2003).—This 25-year-old male developed lepromatous leprosy in 1948 and was admitted to Carville in February 1949, when diasone therapy was instituted. In December 1950 he had his first typical erythema nodosum reaction, which was controlled by stibophen. He continued on the sulfone for three years, and during this period had very little erythema nodosum. In April 1954, however, he developed an acute erythema nodosum reaction. Stibophen therapy then proved ineffective.

The patient was started on cortisone, as in Case 1. Within three days he was asymptomatic, and was discharged after seven days hospitalization. From then until August he continued diasone treatment with no further erythema nodosum reactions. The leprosy remains at the same clinical level of activity as before cortisone therapy.

CASE 5 (No. 2101).—This 24-year-old male was admitted to Carville in 1950 with lepromatous leprosy. Promin therapy was started and continued for four years without difficulty. Skin smears became negative in June 1953, and in May 1954 his disease was apparently arrested and preparations were made for his discharge. The patient then began to complain of pain along the distribution of the left ulnar nerve, with slight edema of the forearm and hand. Symptoms increased in severity, and within five days there was moderate edema of both forearms. Both ulnar nerves were moderately enlarged and acutely tender. There were fresh infiltrates with irregular borders on both forearms, about the left elbow, and on both legs. Scrapings from these lesions revealed small numbers of *M. leprae*. The results of a skin biopsy of one of these lesions were consistent with active leprosy, probably of the dimorphous group.

The patient was hospitalized on May 23 with low grade fever, anorexia and malaise, and was placed on cortisone therapy as in Case 1. He became afebrile by the second day, and the enlarged nerves decreased in size and became nontender; he was ambulant and free of pain by the next day. Maintenance cortisone was continued until June 4, when he was started on heat therapy and muscle exercises, and within two weeks he was entirely asymptomatic. Promin therapy was reinstituted, and no further reactions have occurred.

CASE 6 (No. 2199).—This 44-year-old male developed lepromatous leprosy in 1949 and was admitted to Carville in September 1952. Shortly after admission he had acute intensification of the lepromatous lesions, accompanied by pain in both feet, marked malaise, anorexia and fever. These attacks occurred at three- or four-month intervals and made adequate sulfone treatment difficult. On February 28, 1954, he was admitted to the infirmary with another severe reaction. He ran a septic type of fever with marked skin changes for twelve days, after which the symptoms gradually subsided.

On March 20, another such reaction having developed, cortisone therapy, 100 mgm. three times a day, was started. Within forty-eight hours the patient was afebrile and the toxic state subsided; there was marked clearing of the skin lesions, and the severe nerve pains disappeared. The dosage of cortisone was gradually decreased, and it was discontinued on the fifth day. On May 28 there was another acute reaction, which also responded dramatically to cortisone. In September there

occurred still another reaction, which was again suppressed by cortisone on outpatient treatment.

Long-term cortisone treatment was planned in the hope that further reactions could be suppressed and that a sulfone could be administered simultaneously. It was possible to keep this patient asymptomatic on a daily dose of 100-200 mgm. This treatment was continued until the middle of October, when Cushing's syndrome appeared. Every attempt to decrease the dose of cortisone resulted in the reappearance of a very severe reaction. The drug was gradually withdrawn, however, and the severe reaction which then occurred subsided spontaneously. After that it was decided to discontinue long-term cortisone therapy, and to use it in short-term courses for acute reactions when necessary.

CASE 7 (No. 2186).—This 43-year-old female developed lepromatous leprosy in March 1952, and was started on diasone therapy in May. Shortly afterward she experienced an acute erythema nodosum reaction which responded to stibophen. From that time until May 1954 she had more or less chronic erythema nodosum, and it was necessary to withhold sulfone treatment for long periods of time. The chronic erythema nodosum became so severe that loss of weight became precipitous, and general debility was marked.

An attempt was made to control these reactions by a low maintenance dosage of cortisone, hoping thereby to permit simultaneous sulfone therapy. The patient was hospitalized from May 1954 through March 1955, during which time she was on the cortisone regimen without sulfone. There was improvement in the induration and subcutaneous suppuration as long as the cortisone was maintained at a high dosage level, 300-400 mgm. daily, but as soon as a reduction of the dose was attempted there would be an exacerbation of the lesions. A course of corticotropin therapy was also tried, with similarly disappointing results.

Finally the patient was put on cortisone in a dosage of 400 mgm. daily for a month. During this period her skin condition was markedly improved, and she was relatively asymptomatic. After that an attempt was made to begin diasone treatment, but the patient again began having difficulty with erythema nodosum-type lesions in spite of the large doses of cortisone. Cortisone therapy having proved impractical in this case, it was gradually discontinued. There was a reappearance of the chronic erythema nodosum lesions that were noted prior to the cortisone treatment, but the patient has remained afebrile.

CASE 8 (No. 2022).—This 53-year-old female noted the onset of the disease in 1945 and was admitted to Carville in 1949, with advanced lepromatous leprosy. Promacatin treatment was begun in August 1949, and was soon followed by repeated erythema nodosum reactions. The treatment was continued until July 1951, and during this period the patient had a nearly continuous chronic erythema nodosum reaction, with acute exacerbations which were controlled by stibophen. In January 1952 promin treatment was started. The erythema nodosum remained in a chronically active stage, with frequent acute exacerbations which were fairly well controlled by periods of rest from sulfone treatment plus stibophen.

In February the patient was again admitted to the infirmary with an acute exacerbation of erythema nodosum. The sulfone was discontinued and cortisone was administered as in Case 1. The response was dramatic; no new erythema nodosum lesions appeared and the chronically indurated skin became much softer. The patient was discharged after eighteen days of treatment, and she remained asymptomatic for about two months. She then began to notice occasional reappearance of the lesions, and finally an acute erythema nodosum reaction occurred in July 1952. This was adequately controlled by stibophen during the immediate post-therapy period, but since then she has continued to have chronic erythema nodosum as before the cortisone treatment.

CASE 9 (No. 2033).—This 23-year-old white male was admitted to Carville in 1949 with lepromatous leprosy, and diasone treatment was started. In January 1950 he began having frequent episodes of severe peripheral neuritis, particularly of the ulnars, with fever, malaise, nausea, vomiting and characteristic erythema nodosum lesions. During these attacks he was treated symptomatically and with stibophen. The reactions continued at frequent intervals, and the danger of narcotic addiction became paramount.

In April 1954 there was another acute attack of severe nerve pain, with low-grade fever and systemic symptoms. The ulnar nerves were acutely tender and nodular, and easily palpated into the axilla. The median, superficial peroneal, posterior tibial, and sural nerves were similarly affected. The patient was started on cortisone therapy as in Case 1. Within twenty-four hours there was marked decrease of the pain, and the fever and the erythema nodosum lesions subsided; methadon became unnecessary. After two days the nerves were no longer tender, and they decreased considerably in size.

Shortly after discharge, however, there was recurrence of nerve pain and tenderness, and throughout May cortisone was administered in doses between 25 and 100 mgm. daily. In June, cortisone was replaced with corticotropin, 20 mgm. four times daily for three days, the dose was then gradually reduced over a six-day period and discontinued. Cortisone therapy was reinstituted, and the patient was discharged from the hospital on a maintenance dosage of 25 mgm. four times daily, which was taken regularly through November. The nerves decreased to one-half their previous size, and were nontender. He was able to continue diasone treatment, and analgesics were seldom required.

A comparison of the results of muscle and electrical stimulation testing between the time of admission and prior to the beginning of cortisone therapy showed marked decrease in function. Comparison of these tests at the time cortisone treatment was begun and nine months later, after it was stopped, showed no improvement of function despite the clinical improvement mentioned.

In January 1955 there was a recurrence of severe pains along both the ulnar and median nerves, and again cortisone suppressed the reaction. During the treatment period a left ulnar nerve transfer was performed. Cortisone was gradually discontinued. Shortly thereafter severe pains recurred, largely limited to the area of the ulnar-nerve transfer, with extension into the axilla and shoulder. Cortisone is again being used successfully to control pain.

CASE 10 (No. 2263).—This 40-year-old white male developed lepromatous leprosy in 1952. When admitted to Carville in June 1954 there was extensive anesthesia to pin prick over the extremities, and both ulnars were enlarged and slightly tender. There was muscular weakness mainly caused by ulnar involvement, with pain and tenderness over both thenar eminences. Electrical and manual muscle-testing showed moderate weakness of muscles innervated by the ulnars, and minimal weakness of those innervated by the median nerves.

Promin therapy was started shortly after admission. Because of the nerve troubles, long-term cortisone treatment was begun in July, and continued regularly with a dose of 75 mgm. daily. The pain in the hands and the ulnar nerves soon disappeared, and the ulnars decreased in size until now they are barely palpable.

In September an ulnar nerve stripping and transplant was performed on the left side. Grossly, the nerve appeared normal, in striking contrast with what is usually found. Since then the cortisone treatment has been continued.

The right arm has been used as a control for comparison with the left arm, which was operated on. Both hands have been treated with moist heat and muscle exercises. Two months after the operation, and four months after the beginning of the cortisone treatment, electrical and manual muscle-testing showed further reduction of muscle function on the left, but slight improvement on the right. There has been

no dramatic response, however, and perhaps the improvement noted on the right side was caused by the decrease of the pain which was present at the time of admission. The patient's leprosy has shown clinical improvement during this period.

DISCUSSION

It has been my experience in treating acute erythema nodosum reactions with cortisone and corticotropin that these drugs have a place in the treatment of these reactions, although definite indications have not been established. No serious complications have occurred, but with the higher doses and when the hormones are used over relatively long periods of time it is necessary to control electrolyte and water disturbances. In cases in which frequent acute reactions occur it appears that short-term courses of hormone therapy would be indicated. Likewise, in the occasional case where the response to stibophen (fuadin) is poor, hormone therapy would appear to be indicated.

The usefulness of hormone therapy in chronic erythema nodosum reactions is much more difficult to evaluate. It seems logical to attempt to control the reaction with hormone therapy, and then by continuing this therapy in a long-term, low-dosage schedule, to add a sulfone to the regimen; but my results were not consistently successful. Cases 2, 3 and 8 seemed to benefit from hormone therapy. The possibility that these reactions would have subsided spontaneously must be considered, but the severity of the erythema nodosum in these cases and the marked improvement that occurred with cortisone seem to make that possibility remote. Case 8 had a good response and had no further reactions for four months after eighteen days of cortisone therapy, but now the patient is beginning to have recurrence of the chronic erythema nodosum. Case 7 is considered a failure because, although the reaction could be controlled with large doses of cortisone, it was impossible to decrease the amount because of a recurrence of the lesions, and continuation of such large doses seemed contraindicated. Case 6 likewise is considered a failure for long-term therapy, but benefit was obtained with short courses of cortisone during an acute reaction. The reactions in this case are difficult to classify, and were probably leprosy *per se* rather than erythema nodosum.

The hormone therapy has shown indications of having its greatest usefulness in leprosy neuritis. In Case 5 there was immediate control of the pain and swelling, and reasonable evidence that severe nerve damage was avoided; certainly the duration of the reaction was shortened. In Case 9 there were erythema nodosum and neuritis, and nerve damage had probably reached an irreversible stage; however, the danger of drug addiction was paramount, and cortisone lessened this danger considerably. In Case 10, which represents a fairly early neuritis, the effects of cortisone have been interesting. At operation the nerve appeared grossly normal, which is most unusual and unexpected and most certainly was caused by hormone therapy. The continued loss of function during the two months following the operation, in which the nerve was stripped and

transplanted, speaks for the fact that nerve stripping is unphysiologic and of questionable benefit. That was evident from the comparison with the opposite nerve which had received only the benefit of cortisone, and which has shown no further loss of function and perhaps some improvement. This approach must be used in a large number of cases, preferably before severe nerve damage has occurred, and the results followed for a longer period of time, before the answer to these questions can be given.

SUMMARY

1. In acute erythema nodosum leprosum, hormone therapy is effective in controlling the reaction. There has been no evidence of aggravation of the leprosy when hormones have been used in short courses as described.

2. In chronic erythema nodosum the results with these drugs have been equivocal, but further experience is needed before their effects in this condition can be completely evaluated. Hormone therapy may be of help in this matter, but the dangers of the treatment must be recognized and long-term therapy should be under close and careful medical supervision, particularly until the effects of this therapy in leprosy are better understood.

3. In leprosy neuritis the hormones seem to be of definite value in suppression of the acute reaction. Also, with the institution of hormone therapy earlier in the disease, and for longer periods of time, it may be possible to prevent severe nerve damage before irreversible changes have occurred. It is hoped that continuation of this study will show that nerve function can be improved in cases that have not progressed too far before treatment is started.

RESUMEN

1. En el eritema nudoso leproso agudo, la hormonoterapia resulta eficaz para cohibir la reacción. No hay datos de agravación de la lepra cuando se han usado las hormonas en series breves en la forma descrita.

2. En el eritema nudoso crónico, los resultados con dichas drogas han sido equívocos, pero se necesitan más observaciones antes de justipreciar definitivamente sus efectos en esa dolencia. La hormonoterapia puede ser de ayuda, pero hay que reconocer los peligros del tratamiento y la terapéutica a largo plazo debe quedar bajo intensa y cuidadosa vigilancia médica, en particular hasta que se comprendan mejor los efectos de este tratamiento en la lepra.

3. En la neuritis leprosa, las hormonas parecen poseer valor bien definido en la supresión de la reacción aguda. Además, con la iniciación de la hormonoterapia en una etapa más incipiente de la dolencia y durante períodos más largos de tiempo quizás sea posible evitar grave lesión nerviosa antes de que ocurran alteraciones irreversibles. Espérase que la continuación de este estudio muestre que cabe mejorar la función nerviosa en casos que no han avanzado demasiado antes de iniciar el tratamiento.

REFERENCES

1. BRADLEY, J. E., HARVEY, A. M., HOWARD, J. E. and NEWMAN, E. V. Preliminary report on the use of ACTH in hypersensitive states. *Proceedings First Clinical ACTH Conference*. New York: Blakiston, 1950, pp. 469-472.

2. DEL POSO, E. C. and GONZALES OCHOR, A. Two cases of prevention and treatment of "lepra reaction" by cortisone. *J. Invest. Dermat.* **18** (1952) 423-424.
3. DHARMENDRA. ACTH and cortisone in the treatment of acute complications of leprosy. *Internat. J. Leprosy* **21** (1953) 201-205.
4. DORENLOT, H. Eight cases of leprosy reaction treated with ACTH. *Bull. Soc. Path. exot.* **46** (1953) 56-65.
5. DOUGHERTY, T. F. and WHITE, A. An evaluation of alterations produced in lymphoid tissue by pituitary-adrenocortical secretion. *J. Lab. & Clin. Med.* **32** (1947) 584-605.
6. EBERT, R. H. and BARCLAY, W. R. Changes in connective tissue reaction induced by cortisone. *Ann. Int. Med.* **37** (1952) 506-518.
7. HERXHEIMER, K. and MARTIN, H. So-called Herxheimer reactions. *Arch. Dermat. & Syph.* **13** (1926) 115-117.
8. IGLESIA, M. H. Treatment of lepra reactions with cortisone. *Internat. J. Leprosy* **21** (1953) 580-581.
9. KINSELL, L. W. The clinical application of pituitary adrenocorticotrophic and adrenal steroid hormones. *Ann. Int. Med.* **35** (1951) 615-651.
10. LOWE, J. ACTH and cortisone in treatment of complications of leprosy. *British Med. J.* **2** (1952) 746-749.
11. [MADRID CONGRESS] Technical resolutions. Treatment. *Internat. J. Leprosy* **21** (1953) 516-526; *Mem. VI Congr. Internac. Leprol.*, 1953; Madrid, 1954, pp. 87-95.
12. RANDOLPH, T. G. and ROLLINS, J. P. Relief of allergic diseases by ACTH therapy. *Proceedings First Clinical ACTH Conference*. New York: Blakiston, 1950, pp. 479-487.
13. ROCHE, M., CONVIT, J., MEDINA, J. A. and DE BLUMENFELD, E. ACTH in the lepromatous lepra reaction. *Proceedings Second Clinical ACTH Conference*. New York: Blakiston, 1951, Vol. II, pp. 441-444.
14. ROSE, B., PARE, J. A. P., PUMP, K. K. and STANFORD, R. L. The clinical effect of ACTH and cortisone in allergy and other forms of hypersensitivity. *Proceedings Second Clinical ACTH Conference*. New York: Blakiston, 1951, Vol. II, pp. 414-426.
15. SACKS, M. S. ACTH, cortisone and hypersensitive disease states. *Ann. Int. Med.* **36** (1952) 911-915.
16. SHULMAN, L. E., HARVEY, A. M., HOWARD, J. E. and SCHOENRICH, E. H. Clinical studies with ACTH in bronchial asthma. *Proceedings Second Clinical ACTH Conference*. New York: Blakiston, 1951, Vol. II, pp. 401-413.
17. SHWARTZMAN, G. Phenomenon of local skin reactivity to culture filtrates of various micro-organisms. *Proc. Soc. Exper. Biol. & Med.* **26** (1928-1929) 207-208.
18. WOLCOTT, R. R. Erythema nodosum in leprosy. *Internat. J. Leprosy* **15** (1947) 380-388.