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CURRENT LITERATURE

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General and Historical

Brown, David H. Ocular leprosy in Hawaii: the past. Ann. Ophthalmol. **7** (1975) 1025-1030.

Leprosy in Hawaii dates back to about 1840. The first recorded ocular leprosy is from the 1880's. Robert Louis Stevenson and Jack London both wrote descriptions of the ocular signs of leprosy. Pinkerton in 1927 and Van Poole in 1934 reported large series of patients with ocular leprosy. In 1973 there were about 2,168 cases of leprosy in the 50 states. Most ophthalmologists practice in areas where there are leprosy patients.—Author's Summary

Tisseuil, Jean. La régression de la lèpre ne fut-elle pas aussi fonction de l'évolution économique au XIV[e] siècle? [Was not lepra regression also a function of the economic development in the 14th century?] Bull. Soc. Pathol. Exot. **68** (1975) 352-355. (In French)

During the century of expansion, bread was regularly more costly and the labor cheap because of surplus population.

During the 14th century, the weather was too rainy and much colder, the corn harvest was too deficient, the mortality rate increased; unfertile ground was deserted; drought and famine followed consecutively. The rats followed the peasantry and transmitted pestilence as a result of which depopulation occurred. Wages doubled while the cost of bread was reduced. Life became better and leprosy began to decline.—(*Adapted from* author's English summary)

Clinical Sciences

Andersen, Johs G. Transverse metatarsal head resection—a radical approach to the problems of forefoot ulceration. Lepr. Rev. **46** (1975) 191-194.

Transverse metatarsal head resection is recommended as a surgical approach to the problem of recurrent forefoot ulceration. This operation combines the soundness of a formal foot amputation with due consideration for the desires of patients. Indications and contraindications are given, and the technic, described in detail, does not require sophisticated orthopedic experience. The final results are extremely encouraging.—Author's Abstract

Chan, W. C., O'Mahoney, Sr. M. G., Yu, D. Y. C. and Yu, R. Y. H. Renal failure during intermittent rifampicin therapy. Tubercle **56** (1975) 191-198.

Two patients who developed reversible renal failure during intermittent rifampicin therapy are described. Both had febrile reactions to rifampicin. The first was also found to have uremia associated with swelling of the glomerular endothelial cells. The second developed tubular necrosis unassociated with hemolysis or shock.

The pathogenesis of the renal lesion in these two patients, as revealed by light microscopy, immunofluorescence studies and electron microscopy, is discussed.—Authors' Summary

Iveson, J. M. I., McDougall, A. C., Leathem, A. J. and Harris, H. J. Lepromatous leprosy presenting with polyarthritis, myositis, and immune-complex glomerulonephritis. Br. Med. J. **3** (1975) 619-621.

A Pakistani man aged 19 years was admitted to a rheumatological unit in the United Kingdom with acute widespread polyarthritis accompanied by night sweats and fever. Preliminary examination suggested Reiter's disease, but further investigation

showed acute glomerulonephritis with uremia. The possibility of periarteritis nodosa, and the prominence of muscle tenderness in the legs, led to biopsies of striated muscle and skin, in both of which were changes typical of lepromatous leprosy, with many *Mycobacterium leprae* on Ziehl-Neelsen staining. Serum showed IgG-IgM cryoglobulinemia without antiglobulin activity, and in the recovery phase renal biopsy showed a resolving proliferative glomerulonephritis with linear IgG and IgM immunofluorescence and granular deposits of C3. Clinical signs subsided rapidly under steroid treatment and subsequent progress on antileprosy drugs was uneventful. The term *erythema nodosum leprosum* is inadequate and misleading as a title for a common and important immune complex reaction of lepromatous leprosy, in which numerous body systems may be involved.—Authors' Summary

McLeod, J. G., Hargrave, J. C., Gye, R. S., Pollard, J. D., Walsh, J. C., Little, J. M. and Booth, G. C. Nerve grafting in leprosy. Brain **98** (1975) 203-212.

The authors, writing from Australia, describe a nerve grafting technic designed to correct sensory loss in leprosy. Median, ulnar, sciatic and posterior tibial nerves were removed from cadavers within 24 hours of death and stored in physiologic saline at 0-10°C for up to two weeks. They were then cut into suitable lengths and the diameters were measured. The nerves were freeze-dried, placed in individually sealed double-layered polythene bags and after irradiation stored at 4°C. Strips of infant dura mater were similarly prepared, and were subsequently fashioned into cylinders of varying lengths and diameters to be used as cuffs to hold nerve grafts in position.

Twenty-three nerve grafts were inserted into the peripheral nerves of 14 leprosy patients suffering from sensory loss: 10 into median nerves, 8 into posterior tibial nerves, 4 into ulnar nerves, and 1 was a branch graft from a median nerve proximally to both median and ulnar nerves distally. Azathioprine was given to each patient for immunosuppression. Results were good in two grafts, fair in seven grafts, poor in eight grafts, and six were failures. Although there was no return of motor function, no patient was worse clinically after the operation than beforehand.

The authors consider these results encouraging but emphasize that the technic of nerve grafting in leprosy is only in the developmental stage and its limitations must be appreciated.—W. H. Jopling (Trop. Dis. Bull.)

Ocampo, J. C., Gatti, J. C. and Cardama, J. E. Tratamiento de la lepra en reacción. [Treatment of leprosy in reaction.] Rev. Leprol. **10** (1975) 269-280. (In Spanish)

A discussion is presented on the recent advances in the pathogenesis of ENL, i.e., the development of immunologic complexes and the possible mechanistic action of thalidomide on its control which would be mainly immunological stabilizing the lysosomic layer.

The treatment of lepromatous leprosy is summarized considering ENL, erythema nodosum polymorphous, acute lepromatization, and the Lucio phenomenon; pointing out the type of biologic immunity attributed to thalidomide, the anovulatory recommended when necessary and without contraindications.

In the discussion of clofazimine the authors mention therapeutic actions, effects on pregnancy, newborns and lactation; its toxicity and contraindications. Special reference is made to corticosteroids and their use in iridocyclitis, neuritis and orchiepididymitis. Reference is also made to the treatment of reactions in tuberculoid and borderline leprosy.—(*Adapted from* authors' English summary)

Pearson, J. M. H. and Ross, W. F. Nerve involvement in leprosy—pathology, differential diagnosis and principles of management. Lepr. Rev. **46** (1975) 199-212.

Nerve damage in nonlepromatous leprosy and in "reversal" reactions is the result of an immune response to the presence of antigenic material derived from leprosy bacilli within nerves. This immune response damages nerves by intraneural epithelioid cell formation, and by compression of Schwann cells due to inflammatory edema. In lepromatous leprosy the presence of leprosy bacilli induces slow damage to both perineurium and Schwann cells. When *erythema nodosum leprosum* (ENL) develops, associated neuritis is probably brought about by the presence of ENL lesions within the nerves.

In the absence of typical skin lesions, the nerve damage caused by leprosy can mimic other conditions. The differential diagnosis in such cases is outlined, and the principles of management of nerve damage due to leprosy are summarized.—Authors' Abstract

Rea, Thomas H. and Levan, Norman E. *Erythema nodosum leprosum* in a general hospital. Arch. Dermatol. **111** (1975) 1575-1580.

We report 32 patients with *erythema nodosum leprosum* (ENL). Twenty-two patients developed ENL before beginning chemotherapy. The recognition that ENL in the absence of chemotherapy is not an uncommon event is of importance, not simply as a fact in and of itself, but because this observation raises provocative questions when placed in the context of current ideas concerning ENL. ENL should be regarded as a manifestation of leprosy, not necessarily as a complication of its therapy.—Authors' Abstract

Reddy, N. Rosi and Kolumban, Steven L. The effects of daily and once per week plaster of Paris cylindrical splinting on contracted proximal interphalangeal joints in leprosy patients. Lepr. India **47** (1975) 151-155.

For the purpose of straightening finger flexion contractures of the proximal interphalangeal joint in leprosy by the use of serial cylindrical plaster of Paris splints, it was found that there is no statistically significant difference between daily and weekly splinting.

This study concerns itself with the straightening of flexion contractures of the proximal interphalangeal (PIP) joints of leprosy patients by the use of cylindrical plaster of Paris (POP) splints. Previously, studies were conducted comparing the straightening effects of daily POP splinting with thrice and twice a week splinting (Kolumban, S. L., 1960, 1967, 1969). The results showed no statistical significance of these three groups. In this study daily POP cylindrical splinting was compared with once per week POP cylindrical splinting.—(*Adapted from* authors' summary)

Sebille, A. L'unité motrice chez les lépreux: résultats d'une étude électromyographique et histologique, comparée aux données cliniques et aux vitesses de conduction motrice. [The motor nerve-muscle unit in leprosy: the results of an electromyographic and histological study compared with clinical data and motor conduction time.] Med. Trop. **35** (1975) 231-247.

This report of an investigation into the correlation of nerve trunk damage and its distal motor and histological effects, is both interesting and important.

Electromyography in 20 leprosy patients (17 lepromatous, 2 tuberculoid, and 1 borderline) of the external popliteal nerve and the muscle it supplies, was supplemented by microscopic examination of muscle specimens. Damage to muscle was mainly due to impairment of nerve function, and not to the rare presence of *Mycobacterium leprae* in the muscles themselves. No correlation was found between the presence and degree of nerve trunk damage and the presence of *M. leprae* in either the muscles or the nerve sheath.

Signs of the nerve trunk denervation were found in early lepromatous leprosy and in the absence of any clinically detectable abnormality of the nerve trunk. These signs revealed by electromyography also preceded histological signs of nerve damage in the muscles supplied.

However, where enlargement of the nerve trunks was already established, then definite reduction in conduction time was evident, accompanied by histologically discernible muscle damage. Slowing of nerve conduction times was most noticeable in the segments of the nerve clinically subject to enlargement, but the actual impairment of conduction time bore no relation to the presence or absence of enlargement of the nerve trunk in these situations.

Subclinical muscle damage was demonstrated by electromyography in 90% of patients, a finding that suggests to the author that such damage may be occurring at the time of the early skin rash of lepromatous leprosy.—S. G. Browne (*From* Trop. Dis. Bull.)

Sheskin, J. The case for invisible leprosy. Int. J. Dermatol. **14** (1975) 345-346.

The author briefly reports three instances of lepromatous leprosy diagnosed in Israel (out of a total of 262 patients known to be suffering from leprosy), in whom no recognizable and diagnosable skin lesions were said

to have been present until, during an episode of *erythema nodosum leprosum,* lesions appeared that were typical and bacteriologically positive. [In some patients, tell-tale evidence of past leprosy, now quiescent, is almost invariably present in either the skin or the peripheral nerves or in both.]—S. G. Browne (*From* Trop. Dis. Bull.)

Shukla, R. K., Viswanathan, M. K., Chaturvedi, S. N. and Gupta, A. K. Preliminary study of opponensplasty using extensor digitiminimi in leprosy. Lepr. India **47** (1975) 170-175.

Extensor digitiminimi was used in 32 thumbs for restoration of opposition. There were 29 leprosy patients, and 3 with poliomyelitis where half of the thenar muscles were paralyzed.

A pulley was not constructed in this operation as the ulna acts as a static pulley; hence the question of migration of the pulley does not arise. The operative technic is simple and it is easy to carry out postoperative management.

The problem of check rein deformity and sublimis minus deformity, as seen in the donor fingers in Brand's procedure, are not observed in this operation. Loss of the independent extension of the m.p. joint of the little finger was the only disability seen in this operation.—(*Adapted from* authors' summary)

Terencio de las Aguas, Jose. Telangiectasias en la lepra. [Telangiectasia in leprosy.] Rev. Leprol. **10** (1975) 179-184. (In Spanish)

The presence of telangiectasia has been studied in 320 leprosy patients; 215 male and 105 female. The presence of these vascular extasias has been observed in 53% of lepromatous cases. The order of preference for the localization of these lesions is: face, supraexternal region, forearm and hand, back, thigh, leg and foot.

These telangiectases are found first of all in the diffuse infiltrative type of lepromatous leprosy of many years duration and with frequent leprosy reactions. The existence of these lesions has also been related to genital and hepatic alterations which can have an influence on their presence.—(*Adapted from* author's English summary)

Usmanov, R. K. Affection of the upper respiratory tracts in lepromatous leprosy and their treatment. Vestn. Otorinolaringol. **3** (1974) 88-92. (In Russian)

On the basis of clinical observations on 536 patients suffering from lepromatous leprosy for a period of ten years with the application of various functional methods, histochemical and histomorphological studies, the author describes a clinical picture of affections of the upper respiratory tracts during the smooth course and relapses of the disease. It was for the first time shown that affection of the upper respiratory tracts at the reactive stage was allergic in character. In patients with relapses of lepromatous leprosy there were no specific affections of the upper respiratory tract clinically, but bacterioscopic examination was always positive, and lepromatous infiltrates were always revealed by histological study. Schemes of combined therapy of affections of the upper respiratory tracts as applied to various stages and phases of the disease were elaborated.—English Summary

Wastie, M. L. Radiological changes in serial x-rays of the foot and tarsus in leprosy. Clin. Radiol. **26** (1975) 285-292.

Most bone abnormalities seen in serial films of the feet in leprosy were static being the end result of old disease. Changes over a period of time were observed in serial films of 214 feet and these changes were due to a combination of infection, neuropathic changes and avascular necrosis occurring in anesthetic feet.

The bone abnormalities seen were absorption of toes and metatarsals, bone destruction, a neuropathic arthropathy of toes and metatarsals, and various patterns of tarsal disintegration.—Author's Abstract

Yassin, A., El Shennawy, M., El Enany, G., Wassef, N. F. and Shoeb, S. Leprosy of the upper respiratory tract. A clinical, bacteriological, histopathological and histochemical study of 20 cases. J. Laryngol. Otol. **89** (1975) 505-511.

Twenty cases clinically diagnosed as leprosy were thoroughly examined for ENT lesions. These lesions were subjected to bacteriological, histopathological and histochemical studies. The results have been tabulated and discussed with special stress on some findings which are of help in diagnosing the disease.—Authors' Summary

Chemotherapy

Allen, B. W., Ellard, G. A., Gammon, P. T., King, R. C., McDougall, A. C., Rees, R. J. W. and Weddell, A. G. M. The penetration of dapsone, rifampicin, isoniazid and pyrazinamide into peripheral nerves. Br. J. Pharmacol. **55** (1975) 151-155.

Dapsone, rifampicin, isoniazid and pyrazinamide were shown to penetrate readily into the sciatic nerves of the dog and sheep.

These findings suggest that the continued persistence of viable drug-sensitive leprosy bacilli in the peripheral nerves of patients treated for long periods with either dapsone or rifampicin is not due to inadequate intraneural drug penetration.—Authors' Abstract

Beiguelman, Bernardo. Terapeutica de la lepra y farmacogenetica. [Leprosy therapy and pharmacogenetics.] Rev. Med. Chile **103** (1975) 344-349. (In Spanish)

Some pharmacogenetic factors influencing the action of 4,4′-diaminodiphenyl-sulfone (DDS), the most widely used drug in leprosy therapy, are genetic polymorphisms of the human species.

In this review article special attention is given to the polymorphism of acetyltransferase, glucose-6-phosphate dehydrogenase and NADH methemoglobin reductase. Besides the review and critical analysis of the pertinent literature, suggestions for further research are made.—Author's English Summary

Chaudhry, S. B. Roy and Desikan, K. V. Sulfone resistance in leprosy. A report of three cases. Lepr. India **47** (1975) 283-290.

The experimental transmission of leprosy to the foot pads of mice has provided a very useful technic to demonstrate the occurrence of sulfone-resistant strains of *M. leprae*. Although this method is at present the most satisfactory laboratory confirmatory test, it is not practicable to apply it to screen a very large number of cases of leprosy under sulfone therapy today. Clinical detection of sulfone-resistance is therefore very essential. Three cases of lepromatous leprosy detected clinically to be sulfone-resistant and proved subsequently by the mouse foot pad are reported.—Authors' Summary

Gelber, R. H., Gooi, H. C. and Rees, R. J. W. The effect of rifampicin on dapsone metabolism. Proc. West. Pharmacol. Soc. **18** (1975) 330-334.

Our studies demonstrate that concurrent rifampicin therapy increases the rate of DDS plasma clearance. This increase appears to be neither a consequence of an increased acetylation rate nor of DDS displacement from plasma protein binding. Rifampicin's effect on DDS metabolism is maintained two days after its discontinuation but not after two weeks. As rifampicin is entirely cleared from the plasma by 48 hours our results suggest that the most likely mechanism of this drug interaction is enzyme induction.

Rifampicin induces its own metabolism, its plasma half-life being shorter after continuous daily administration than following the first dose. Animal and human data have demonstrated that rifampicin induces microsomal hepatic enzymes. Most recently, O'Reilly (1974) has demonstrated that rifampicin therapy decreases the anticoagulant activity and plasma level of warfarin following a warfarin test dose and argues that this is secondary to microsomal enzyme induction. We postulate that the rifampicin-dapsone interaction found in our study is also a result of induction of microsomal enzymes; these most likely increase N-hydroxylation, which unlike acetylation, is known to be microsomal.—Authors' Discussion

Gelber, R. H. and Rees, R. J. W. Dapsone metabolism in patients with dapsone-resistant leprosy. Am. J. Trop. Med. Hyg. **24** (1975) 963-967.

Acetylation of dapsone (DDS) and sulfamethazine (SMZ), and plasma clearance of DDS were studied in Malaysian Chinese with lepromatous leprosy including 40 DDS-resistant and 44 nonresistant patients. Neither a patient's acetylation characteristics (DDS or SMZ), nor his plasma clearance rate, appeared to have predisposed him to the development of DDS resistance. A potentially important drug interaction between rifampin and DDS was discovered. After ingestion of rifampin for a minimum of two weeks, the plasma clearance of DDS was increased and the relative amount of the

acetylated DDS was decreased. The implications of these results for the treatment of lepromatous leprosy are discussed.—Authors' Abstract

Gordon, G. R., Peters, J. H., Ghoul, D. C., Murray, J. F., Jr., Levy, L. and Biggs, J. T., Jr. Disposition of dapsone and monoacetyldapsone in rats (39062). Proc. Soc. Exp. Biol. Med. **150** (1975) 485-492.

Female Buffalo and Lewis rats receiving 1.0 mg DDS/kg ip exhibited higher plasma levels of DDS and its monoacetylated metabolite, MADDS, than did male rats of each strain receiving the same dose. The fraction of the total measured drug in plasma as MADDS at eight hours in female rats of both strains ranged from 43 to 62% compared with a range of 28 to 31% in male rats. Plasma half times of disappearance ($T_{½}$) of DDS ranged from 5.0 to 6.8 hours and were not different among sexes and strains. Deacetylation of MADDS to DDS occurred when equimolar doses of MADDS were administered. An approach to a steady state of acetylation-deacetylation was indicated by comparing the percentage of MADDS of the total drug in plasma in the respective sexes and strains receiving both drugs. $T_{½}$ values of MADDS were significantly lower than values for DDS in Lewis rats. They were not different in Buffalo rats. Protein binding studies in plasma from rats receiving 5.0 mg DDS or 5.8 mg MADDS/kg showed 67 to 72% binding of DDS and 91% binding of MADDS. These *in vivo* observations were confirmed by *in vitro* binding studies. Comparison of these results with those of earlier studies in mice and man indicates that the rat is a better model of man than is the mouse for studies on the disposition of DDS.—Authors' Summary

McDougall, A. C., Rose, J. A. and Grahame-Smith, D. G. Penetration of C^{14}-labeled rifampicin into primate peripheral nerves. Experientia **31** (1975) 1068-1069.

The penetration of C^{14} rifampicin into various tissues, but particularly peripheral nerve, has been studied in the monkey. Penetration into the substance of peripheral nerve internal to the epineurial covering was demonstrated and the significance of this in relation to the treatment of leprosy is discussed.—Authors' Summary

Ohman, Lena and Wahlberg, Ivar. Ocular side-effects of clofazimine. Lancet **2** (1975) 933-934. (Letter to Editor)

Sir: Clofazimine (Lamprene) has been used in the treatment of leprosy since 1962 and it has also lately been tried in some dermatological disorders. It is a phenthiazine derivative and is thought to stimulate phagocytosis. No ocular side-effects were noted.

Eye examinations were performed in 26 patients on clofazimine (100-300 mg daily for 1-15 months). Ten patients, aged 18 to 69 years, showed corneal changes in the form of fine linear brownish subepithelial opacifications. These changes diminished or disappeared within two months of stopping treatment. One patient, aged 41, with corneal pigmentation, who had had normal fundi two years earlier, had speckled pigmentation in the macular area. Another patient, aged 50, without corneal changes, had a clump of fine pigmentations in the macula. The retinal changes remained unchanged after four to six months.—Authors' Letter to Editor

Peters, J. H., Gordon, G. R., Murray, J. F., Jr., Fieldsteel, A. H. and Levy, L. Minimal inhibitory concentration of dapsone for *Mycobacterium leprae* in rats. Antimicrob. Agents Chemother. **8** (1975) 551-557.

To define the minimal inhibitory concentration (MIC) of dapsone (DDS) for *M. leprae* in rats, we determined the relationship between dietary and plasma levels of DDS in uninfected male and female Lewis rats. This knowledge was applied to the design of experiments using rats inoculated in the foot pads with *M. leprae*. The MIC for DDS in male and female rats, respectively, was 1.5 to 4.0 ng and 1.8 to 3.0 ng of DDS/ml of plasma, even though the sexes exhibited markedly different concentrations of DDS when receiving the same dietary level of DDS. These values for the MIC of DDS for *M. leprae* in rats are nearly identical to the previously determined MIC of DDS for *M. leprae* in mice.—Authors' Summary

Peters, J. H., Murray, J. F., Jr., Gordon, G. R. and Jacobson, R. R. The disposition of sulfoxone and solasulfone in leprosy patients. Lepr. Rev. **46** (1975) 171-180.

Sulfoxone was administered to 14 patients

and the levels of dapsone (DDS) and monoacetyldapsone (MADDS) in plasma and urine were determined by spectrophotofluorometric technics. Peak plasma levels of DDS were approximately 600 ng/ml 5-8 hours after treatment with 330 mg sulfoxone. The urinary excretion pattern of DDS and MADDS after this drug was similar to that found after DDS treatment, but total DDS excretion was lower. The results indicate that regular sulfoxone therapy provides plasma levels of DDS that would be expected to be therapeutically effective and to protect patients from the development of DDS-resistant leprosy.

A recently developed high pressure liquid chromatographic fluorometric procedure was used to determine plasma levels of DDS, MADDS and parent drug in six patients receiving solasulfone. After a single 500 mg intramuscular injection, plasma levels of DDS were only slightly above the minimal inhibitory concentration of DDS for *Mycobacterium leprae,* but the concentration increased fourfold after six 500 mg twice-weekly doses. The rate of disappearance of solasulfone was rapid, but concurrent DDS and MADDS clearance times were longer than after DDS treatment. Direct relationships were found between 24 hour DDS and solasulfone levels and among the disappearance rates of DDS, MADDS and solasulfone. Low levels of DDS after a single dose of solasulfone, as may be encountered in interrupted therapy, could be accompanied by an unusually high risk of the emergence or the selection of DDS-resistant *M. leprae* in certain patients.—Authors' Abstract

Quagliato, R., Bechelli, L. M. Almeida, J. O. and Araujo Arantes, M. A. Bacteriological status (point prevalence) of lepromatous outpatients under sulfone treatment. Bull. WHO **52** (1975) 57-62.

The study concerns 337 outpatients with lepromatous leprosy who had been receiving dapsone treatment for 1-26 years: 69% of them regularly and 31% irregularly. Routine bacterial examination (10 minutes per slide) by a paramedical technician showed only 50% of these patients to be bacteriologically positive. This rate attained 99% when each slide was examined for 30-60 minutes by a qualified bacteriologist. Other factors, apart from the limited action of sulfones, might account for these unexpected results: the material was collected by an experienced leprologist; the disease was still clinically active in 75% of the patients; about 25% of them had been treated for only one to four years; and the intake of dapsone in long-term treatment gradually decreases.—Authors' Abstract

Theophilus, S. Clinical observations with clofazimine in the treatment of leprosy. Lepr. India **47** (1975) 267-282.

In the series of 131 cases which were studied, the MI became rapidly negative even with DDS-resistant cases in about six months, though the majority of cases take a longer time which could lead to a suspicion of partial resistance to B663. In ENL, since negativization of the BI takes two years or longer in lepromatous cases with a high BI and consequent heavy bacterial load, B663 should be preferable to DDS or Fanasil to avoid long-term deleterious actions of the drug itself. Again in ENL the total period of hospitalization and treatment is substantially reduced in comparison to DDS or Fanasil.

B663 should be the drug of choice for active cases on the BB-BT-TT side especially with supportive corticosteroid therapy. Ulnar decompression might be used as a routine procedure together with B663 for lepromatous cases with a high BI in which considerable time may elapse before negativization. A special feature is the improvement in the muscles associated with thumb and first two fingers so important in holding and handling small objects.—Author's Summary

Immuno-Pathology

Almeida, J. O. and Kwapinski, J. B. Reatividade de antígenos de actinomicetos com soros de lepra, avaliada por imunofluorescência em suporte de acetato de celulose. [A study of the reactivity of actinomycetes together with lepra sera by means of the immunofluorescent test with cellulose acetate.] Publ. Cent. Estud. Leprol. **14** (1974) 73-90. (In Portuguese)

The immunofluorescent reaction using cellulose acetate discs was negative (less than a Turner fluorometer reading of 50) in 276

normal sera from tuberculin negative individuals. In 24 sera of patients with tuberculoid leprosy, 18 were negative and 6 had a fluorescence between 50 and 100. In 420 sera from lepromatous patients, 310 gave a reading greater than 100, 68 with a fluorescence between 50 and 100, and only 42 with less than 50.

The reproducibility of the reaction was verified by repeating the test in 30 discs with the same negative serum; of these 30 discs, 3 produced fluorescence greater than 100 and 27 showed readings less than 50. In 30 discs of known positive leprosy serum, 24 fluoresced between 300 and 500, 2 had values of 200, and 4 produced fluorescence greater than 500.

Those antigens which inhibit the Rubino reaction produced greater fluorescence than those which did not, either when they were imposed directly on the discs or when serum was added first.

The sera of lepromatous leprosy produced high values of immunofluorescence with antigens of actinomycetales, whether or not inhibiting the Rubino reaction, which were significantly higher than the values obtained with sera from tuberculoid leprosy.

There were no constant relationships between the capacity of antigens to inhibit the Rubino reaction and their precipitation in gel by the antileprosy sera.—(*Adapted from* authors' English summary)

Barnetson, R. StC., Bjune, G., Pearson, J. M. H. and Kronvall, G. Antigenic heterogeneity in patients with reactions in borderline leprosy. Br. Med. J. **4** (1975) 435-437.

Fifteen patients with borderline leprosy who developed "reversal" reactions were studied from the inception of treatment. Thirteen showed an appreciable increase in lymphocyte transformation (LT) when preparations of *Mycobacterium leprae* were used as antigen. The LT responses to either "whole" or "sonicated" preparations of the bacillus in these 15 patients and in 9 others also in reaction correlated with the clinical presentation. Those with skin disease predominating in the reaction showed an appreciable increase in LT when whole *M. leprae* was used as antigen. Those with nerve disease predominating showed an increase with sonicated *M. leprae.* In those with both skin and nerve disease there was an increase with both antigen preparations. The ratios of the LT test results (whole to sonicated *M. leprae*) showed highly significant differences between the three groups.—Authors' Summary

Bedi, B. M. S., Narayanan, E., Doss, A. G., Kirchheimer, W. F. and Balasubrahmanyan, M. Distribution of single lesions of tuberculoid leprosy. Lepr. India. **47** (1975) 15-18.

The unresolved question of the portal of entry of *Mycobacterium leprae* into its human victim may find a partial answer in this study of the distribution of single lesions of tuberculoid leprosy in the skin. The extremely scanty observational indications that the portal of entry is the site of the first or only skin lesion, are supplemented by the conclusions of the authors. Up to the age of 12 years, the male:female ratio of tuberculoid leprosy in a small group of 103 children in an area around Pondicherry (South India) was almost 1:1, and the distribution of the single tuberculoid lesions was very similar. In 212 adults (above the age of 12), however, the male:female ratio was 2.2:1, and females showed fewer lesions on the trunk and lower limbs than males. The authors conclude that this discrepancy may be related to the wearing of clothing by females, which protects the skin from the bites of arthropods that might transmit leprosy bacilli.—S. G. Browne (*From* Trop. Dis. Bull.)

Bedi, T. R., Sama, S. K. and Bhutani, L. K. Hepatitis B antigen and antibody in leprosy patients. Lepr. India **47** (1975) 316-320.

Fifty patients of leprosy were investigated for the detection of hepatitis B antigen and antibody to hepatitis B antigen employing agar gel diffusion, counterelectrophoresis and sandwich solid phase radioimmunoassay technics. HBag and anti-HBag were each positive in 2% of the cases and the results were not significantly different from those seen in normal blood donors from the same section of the population. The findings of the present study do not substantiate the hypothesis that patients with lepromatous leprosy have increased susceptibility to infection with hepatitis virus. The carrier state appears to be a mere reflection of opportunity for infection rather than genetic predisposition.—Authors' Summary

Bergel, Meny. La lepra como enfermedad metabólica. [Leprosy as a metabolic disease.] Rev. Leprol. **10** (1975) 113-149. (In Spanish)

The author reviews an extensive series of theoretical and experimental considerations on etiology, pathogenesis, prevention and treatment of leprosy. Based upon these considerations he concludes that leprosy must be located in the nutritive-metabolic group of diseases and not with infectious diseases. Leprosy is particularly described as an autooxidative disease. General considerations with regard to the present leprological experiences are made, and a critical study concerning the immunologic experiences in leprosy is performed. Special emphasis is made with respect to prevention and treatment of leprosy.—(*Adapted from* author's English summary)

Bernard, Juan C. and Vazquez, Celia A. Alteraciones patologicas adrenales en los lepromatosos. [Pathological changes of the adrenal gland in leprosy patients.] Leprologia **19** (1974) 55-77. (In Spanish)

In studying pathologic changes in the adrenal gland we arrived at the following conclusions.

1. Lepromatous infiltrations are present in 10% of cases. They are predominantly in the cortical and fascicular zone. We observed miliary lepromatas with Virchow cells and bacilli in the cortex.

2. Cortical alipoidosis is the most frequent nonlepromatous leprosy lesion. It was observed in 80% of the cases and was presented in agonic shock and stress cases.

3. Cortical amyloid is in the most important lesion in residual leprosy. It was more frequent than renal amyloid and was found in the cortical zone.

4. Myeloplastic adrenal lesions were present in 25% of all cases. They were more frequent in residual (15%) than in active (10%) cases.

5. Cortical necrosis was present in 6.6% of cases. It was observed in lepromatous cases with ENL and multiforme. We think that these lesions were the most frequent visceral manifestations of allergic lepromatous reaction.

6. Cortical adenomas, nodular hyperplasia and diffuse and metatastic carcinomas were in fifth place.

7. Vascularitis was observed in reactional patients with cortical necrosis.

8. A benign pheochromocytoma was observed in one case.

These are the pathologic lesions not usually described in leprosy, however, we think their documentation is an important step in the understanding of Hansen's disease.—(*Adapted from* English summary)

Chaudhuri, Sachin and Ghosh, Sukumar. Leprosy and tuberculosis: immune allergic relationship. Lepr. India **47** (1975) 295-306.

There is a close resemblance between tuberculosis and leprosy in respect to bacteriology and also probably from the standpoint of pathology, but in regards to immunology there is considerable dissimilarity. The words antagonism and cross-immunity are not substantially proved correct so far. Evidence of a more direct nature will be necessary before any valid conclusion can be made about the detection of presence of cross immunity between the two diseases. This investigation leads to the conclusion that tuberculosis infection offers no protection against leprosy; on the other hand there is a chance of more leprous infection.—(*From* authors' article)

Convit, J., Pinardi, M. E., Arias Rojas, F., Gonzales, I., Corey, G., Arvelo, J. J. and Monzon, H. Tests with three antigens in leprosy-endemic and nonendemic areas. Bull. WHO **52** (1975) 193-198.

A study comparing the 48-hour and 30-day reactions produced by three antigens was made in areas of low and high leprosy endemicity in Venezuela and in areas of Chile, a nonendemic country. The antigens used for the intradermal tests were standard Mitsuda antigen, supernatant from standard Mitsuda antigen, and PPD. The results indicate that there is no difference in the Mitsuda reaction of persons living in areas of high or low endemicity, but they show a statistically significant difference between the reactions in persons who live in endemic areas and those of persons living in a country where the disease has not been described. The difference in the Fernandez reaction obtained with the supernatant was not statistically significant between the two population groups in the endemic country, but was high-

ly significant when comparing the endemic and the nonendemic countries.—Authors' Abstract

Crawford, C. L. Amyloidosis and *erythema nodosum leprosum.* Lancet **2** (1975) 703-704. (Letter to Editor)

Sir: Dr. McAdam and his colleagues (Lancet **2** [1975] 572) conclude from their study of patients with lepromatous leprosy that there is a causal association between amyloidosis and *erythema nodosum leprosum* (ENL). Your editorial in that same issue (p 589) supports this conclusion.

Amyloidosis was probably the major cause of death in lepromatous leprosy in the presulfone era. In Hansen's time the life expectancy of newly diagnosed lepromatous leprosy was about ten years. In the Philippines before sulfones were available the mortality of lepromatous leprosy was five times greater than in the general population. The mortality of leprosy in the USA since the introduction of sulfones is now the same as in the general population, thus strongly suggesting that these drugs have prevented the development of amyloidosis. Therefore, a major risk factor is the absence of sulfone treatment, but Dr. McAdam *et al* neither mention this fact nor give any details about treatment in their patients. Patients admitted to the hospital were "infectious" and it is not clear if they had received any sulfones. Until this issue is clarified it would be most unwise to conclude that there is a causal association between amyloidosis and ENL, especially as in another study of seven patients with ENL none showed any amyloidosis on renal biopsy. Dr. McAdam and his colleagues' statement that 50% of lepromatous patients develop ENL is based on institutional figures. A more accurate estimate is about 5%. Neither has their claim that ENL is associated with recurrent bouts of iritis, orchitis, and nephritis been substantiated. In your editorial you do not question the continued usage of thalidomide in leprosy patients in spite of the fact that the side-effects of the drug on the peripheral nerves are still being ignored by leprologists. Alternative drugs, such as clofazimine and possibly rifampicin, are available for the management of ENL.—Author's Letter to Editor

Desikan, K. V., Ramanujam, K., Ramu, G. and Balakrishnan, S. Autopsy findings in a case of lepromatous leprosy treated with clofazimine. Lepr. Rev. **46** (1975) 181-189.

The first recorded autopsy findings are presented on a young person suffering from intractable lepra reaction treated for four months with clofazimine in a dose of 300 mg daily. Apart from a generalized yellow coloration of fatty tissue, brick red in muscle and viscera, extreme congestion and edema of the mucosa of the small intestine was found, and considered not to be caused by any infectious agent. Deposits of clofazimine crystals were found in the intestinal mucosa.—Authors' Abstract

Fliess, E. L., Bachmann, A. E., Sasiain, M. del C. and Ares, B. R. Exploración inmunologica en pacientes con lepra indeterminada. [Immunological studies in patients with indeterminate leprosy.] Rev. Assoc. Argent. Microbiol. **7** (1975) 81-85. (In Spanish)

The immunological competence of 11 patients with indeterminate leprosy was compared with that of 10 normal volunteers of the same age and sex distribution; these controls had not had previous contact with leprosy.

The following parameters were studied in peripheral blood cells: 1) the percentage of lymphocyte bearing surface immunoglobulins, as revealed by immunofluorescence; 2) percentage of lymphocyte bearing complement receptors, as studied by antibody and complement-coated erythrocyte rosetting; 3) percentage of T cells, as revealed by spontaneous sheep erythrocyte rosettes; 4) blastogenic and mitogenic response of cultured lymphocytes to PHA; and 5) cell migration inhibition test using lepromin (80×10^6 bacilli /ml) as antigen. Skin reactions to lepromin were also assayed. In the six lepromin-positive patients with indeterminate leprosy, no major immunological alterations could be detected. In contrast, the five lepromin-negative patients showed important alterations which could well be considered as precursors of lepromatous leprosy.—(*From* Trop. Dis. Bull.)

Fliess, Enrique L. and Carosella, Edgardo D. Linfocitos T formadores de Rosetas (LFR) en pacientes de lepra incaracterística. [T lymphocyte formation of rosettes in indeterminate leprosy patients.] Rev. Leprol.

10 (1975) 21-25. (In Spanish)

A total of 16 indeterminate leprosy patients were studied by the rosette E formation test, and intradermal reaction to lepromin.

From the results, a correlation was observed between the negative skin test and a depletion in T lymphocyte population of the patients studied. In conclusion, there is a possibility that the study of lymphocyte population by the rosette formation test may be used as a prognosis in the later development of indeterminate leprosy patients.—(*Adapted from* English summary)

Gatti, J. C., Cardama, J. E., Gabrielli, M., Gurrea, M. C., Di Lonardo, A. M. and Bianchi, O. Manifestaciones clinicas de las crioglobulinemias en la enfermedad de Hansen. [Clinical manifestations of cryoglobulinemia in Hansen's disease.] Leprologia **20** (1975) 15-19. (In Spanish)

The bibliography on this subject affords data to the effect that a high percentage of lepromatous and dimorphous leprosy patients show through laboratory testing the presence in the serum of small figures of cryoglobulins, which do not produce clinical manifestations.

When this index increases and above all by individual condition, there appear lesions such as: cyanosis, livor, purpura with necrotic tendency, papules, ulcers, necrosis with spontaneous amputations which may or may not be accompanied by disturbances in the liver, spleen, kidney, and central nervous system, etc.

It seems that the pathogenesis of these phenomena would be due, as shown above, to vascular obstruction with inflammation in the endothelium and accompanied eventually by phenomena of vessel constriction in zones far from the real site of deposit owing to immunologic response (antigen-antibody clash).

The authors present three patients with leprosy with clinical manifestations of cryoglobulinemia. Two of them were male and the other one female. Clinical forms: ENL in one, and dimorphous in reaction in one.—(*Adapted from* English comments and summary)

Haldar, B. and Dutta, A. K. Cutaneous vascular reactivity in tuberculoid leprosy lesions. Lepr. India **47** (1975) 307-315.

In order to study the nervous and non-nervous cutaneous vascular responses in tuberculoid lesions of leprosy under chemical, mechanical and thermal stimuli, the following experimental studies were performed in 38 cases with control study in each: 1) adrenaline-induced blanch reaction and periblanch erythema; 2) focal bleeding time; 3) surface temperature variations and adjustments following local application of cold.

In the lesions the results showed less prolonged blanch reaction and ill-developed periblanch erythema, relatively prolonged focal bleeding time; slightly lesser degree of initial surface temperature, higher degree of declination in surface temperature following cold application and higher level of rise following heat application. Hunting type of reaction after both heat and cold applications was observed in control and test sites almost equally.

The collective results testify the phenomenon of inhibited nerve tonus in leprosy lesions consequent to organic affection of sympathetic fibers resulting in a vascular atomia.—(*Adapted from* authors' summary)

Harman, D. J. Biopsies in leprosy. Lepr. Rev. **46** (1975) 125-134.

This presentation is a nice summary of good, routine procedures for making skin biopsies and preparing the sections. As such it is well worth perusal but is too detailed for abstracting. If the precautions here noted were generally followed there would be many fewer disappointments relating to biopsy results.

The details of paraffin sectioning and embedding are those used by the author and the minor variations found from laboratory to laboratory are unlikely to be of significance. The pathologist should be happy with the results.

The staining described is based on the TRIFF stain (Lepr. Rev. **36** [1965] 37) which is excellent for the purposes described. Many pathologists, however, will be confused by the statement that the TRIFF stain is a combination of Masson's trichrome stain and the Fite-Faraco modification of the Ziehl-Neelsen stain. Though the TRIFF stain is a trichrome stain, of which there are several varieties, it does not include Masson's procedure. There are several differences, perhaps chief of which is the use of saffron as a counterstain in TRIFF procedures whereas Mas-

son's method utilizes aniline blue or light green solutions. In this respect the TRIFF stain more closely resembles Movat's Pentachrome Method. However, since the author presents the TRIFF method in detail the historical trauma is perhaps not more significant than the physical trauma occasioned by a neatly done biopsy as here outlined.—O. K. Skinsnes

Job, C. K. and Verghese, Roy. Schwann cell changes in lepromatous leprosy. An electron microscope study. Indian J. Med. Res. **63** (1975) 897-901.

Biopsies from radial cutaneous nerves of four untreated lepromatous patients were studied using the electron microscope. It was found that *M. leprae* engulfed by Schwann cells grew and multiplied, building up protective responses against the destructive action of the cell by losing their phagosomal membrane and by producing an inert electron transparent substance around them. However, once the organisms were dead they were digested inside phagolysosomes. The electron transparent substance produced by the cell-bacilli interaction might remain inside the cell for a long time giving it a foamy appearance.—Authors' Abstract

John, T. J., Vijayarathnam, P., Verghese, R. and Krishnamurty, S. Lymphoblast transformation in leprosy. Indian J. Med. Res. **62** (1974) 696-698.

Phytohemagglutinin-M induced lymphoblast transformation of peripheral lymphocytes in cell cultures was studied in 21 lepromatous and 7 tuberculoid leprosy patients and in 9 control subjects. There was no appreciable difference in the range or mean of the proportion of blasts in the cultures among the three groups. This indicates that thymus dependent lymphocytes are basically normal in number and function in lepromatous leprosy in our locality.—(*From* Trop. Dis. Bull.)

Kenzhebaev, A. Ya. Some indices of iron metabolism in patients with leprosy. Vestn. Dermatol. Venerol. **2** (1974) 53-56. (In Russian)

The author studied the content of iron in the serum, the general iron-binding capacity (GIBC) of the blood serum, unsaturated iron-binding capacity (UIBC) of the blood serum and percent of transferrin saturation with iron in the blood serum of 91 patients with different types of leprosy and in 40 normal subjects serving as controls.

In patients with leprosy the content of serum iron was found to be decreased depending on the activity and character of the specific process and occurrence of complications. The GIBC of blood on the whole was decreased proportionately to the character of the preceding leprous process and the existence of foci of chronic suppuration. The UIBC of the blood remained normal, and in the anemic syndrome exceeded the normal level. Transferrin saturation with iron was on the whole decreased and in the anemic syndrome—decreased markedly. In female patients with leprosy the content of iron in the serum was significantly lower and the GIBC significantly higher than in the male patients.—English Summary

Kharatiyan, A. A. and Kenzhebaev, A. Ya. The indices of iron metabolism and erythrokinetics in leprosy patients. Geographitcheskaja Patologia Uzbekistana, Taschkent (1975) 183-189.

The concentration of the serum iron, the general and nonsaturated iron-connective ability of the blood serum, the percentage of transferrin saturation with iron, the elimination of iron by urination and the following determination of the iron reserve by the Desfalov test and by the radioisotopic method of the intestine absorption of iron, and the main indices of ferro- and erythrokinetics have been determined in 120 leprosy patients (L-75, T-20, I-25). Also determined were the absolute quantity of iron in the plasma and erythrocytes, the rotation of iron in plasma and erythrocytes, the utilization of iron by the erythrocytes, the synthesis and the dissociation of hemoglobin, the data of erythrocyte equilibrium, and the duration of the life of erythrocytes.

As a result, it was determined that in patients with any form of leprosy the iron metabolism and the erythrokinetics are disturbed, especially so in the progressive stage of the disease and when complicated with anemia during antileprosy treatment.—(*Adapted from* N. Torsuev's summary)

Lancet 2, September 27 (1975) 589-590. Amyloidosis and leprosy. (Editorial)

Leprosy, like other chronic diseases, can cause secondary amyloidosis. Until lately, firm diagnosis of this complication depended on the characteristics of amorphous deposits at various tissue sites. Amyloid material was recognized by positive staining with congo red and by polarization microscopy but was not identified chemically. Since proof of amyloidosis rested on histological examination, it was often obtained only at necropsy; and the incidence of amyloidosis was determined by taking biopsy specimens of gum or rectum. In the past four years much has been learned about amyloid material. The amorphous amyloid deposits have been identified as protein with fibrillary ultrastructure, and from amino acid sequences two chemical types of amyloid fibrils have been identified. In primary and myeloma-associated amyloidosis the fibrils are composed of fragments of immunoglobulin light chains, and in such patients serum immunoglobulin abnormalities are frequent. In secondary amyloidosis, associated with various chronic diseases, an entirely different protein AA has been identified which is unrelated to immunoglobulin: in such cases a serum protein SAA antigenically related to AA is detectable and is presumed to be a precursor to the fibril protein. While the association of amyloidosis with leprosy has been firmly established from most parts of the world where leprosy is endemic, different investigations have shown great variation in frequency of this complication—31% in the USA, 7.5% in India, 6% in Mexico, and 2.4% in Malawi. Explanations have been sought in the wide spectrum of clinicopathological manifestations of leprosy, but a nonleprosy factor which might influence the development of amyloidosis is the high frequency of chronic trophic ulcers resulting indirectly from leprosy neuropathy.

From Papua New Guinea, Dr. McAdam and his colleagues report their quest for risk factors and the mechanisms whereby amyloid is produced in leprosy (this issue, p 572). Noteworthy findings were the high levels of SAA, related to severity of the ENL, and the persistence of detectable SAA for weeks or months after ENL episodes. Furthermore, the correlation between raised neutrophil-counts and raised SAA concentrations suggested that neutrophils are associated with the production of SAA. Although the origin of SAA is still unknown, its relation to AA protein found in amyloid strongly suggests that, by degradation, persisting high levels of SAA give rise to deposition of AA protein in the tissues.

Drugs to prevent or stop further deposition of amyloid are urgently needed, and this adds import to the observation that colchicine prevented development of casein-induced amyloidosis in the mouse. The close correlation between raised SAA and ENL episodes in lepromatous leprosy and the assumed relationship of SAA to the eventual development of amyloidosis, immediately raises the question whether drugs that suppress ENL also diminish protein SAA. The three most powerful anti-ENL drugs are thalidomide, clofazimine, and corticosteroids. Since the mode of action of thalidomide and clofazimine against ENL is unknown and neither of the drugs suppresses other immune complex diseases in man, it will be important now to see whether protein SAA levels are affected in patients receiving thalidomide or clofazimine. Likewise, the suppressive effect of colchicine on experimental amyloidosis warrants a trial of colchicine in lepromatous patients with ENL. Finally, protein SAA estimation must be included in all future investigations concerned with ENL.—(*Excerpted from* Editorial)

Lim, S. D., Kiszkiss, D. F., Choi, Y. S., Gajl-Peczalska, K. and Good, R. A. Immunodeficiency in leprosy. Birth Defects **11** (1975) 244-249.

It is known that the impairment of cell-mediated immunity (CMI) exists in lepromatous leprosy patients. This was shown by 1) delayed skin reaction to various test antigens, 2) decreased transformation of lymphocytes by various antigens, 3) delayed rejection of skin allograft, 4) decreased migration inhibitory factor (MIF) formation, and 5) histologic study of the lymph node. In addition to these previous works, we have studied T and B lymphocytes in peripheral blood of leprosy patients; T cells by the technic of rosette formation, and B cells by staining surface immunoglobulins. The result of our study shows decreased numbers of T cells and increased numbers of B cells in peripheral blood of lepromatous patients. At the same time, we found that allogenic leukocyte infusion treatment reversed T and B-cell abnormalities. We know that repeated infusions of allogenic leukocytes dramatical-

ly brought about improvement of the clinical status of the patients, resolution of skin lesions, subsidence of *erythema nodosum leprosum* reaction, clearance of bacteria from the skin and lymph nodes, and reconstitution of peripheral lymph nodes.—Authors' Abstract

McAdam, K. P. W., Anders, R. F., Smith, S. R., Russell, D. A. and Price, M. A. Association of amyloidosis with *erythema nodosum leprosum* reactions and recurrent neutrophil leucocytosis in leprosy. Lancet **2** (1975) 572-575.

Rectal biopsy in 190 inpatients at a leprosy hospital in the highlands of Papua New Guinea disclosed 16 patients with secondary amyloidosis. This represented 20% of the patients who had had polar lepromatous leprosy for more than two years. Patients with amyloidosis characteristically had either a history of recurrent attacks of *erythema nodosom leprosum* (ENL) reactions or chronic trophic ulcers. Levels of the serum component (protein SAA) antigenically related to the amyloid fibril protein AA were monitored, at varying intervals for three months, in lepromatous patients with ENL reaction. The SAA levels rose during ENL reactions in parallel with the neutrophil count. SAA occurred with greatest frequency among patients with lepromatous leprosy, while most nonlepromatous patients with detectable SAA had chronic trophic ulcers. The correlation between raised neutrophil count and elevated SAA concentration, observed in this and other studies, suggests that neutrophils are associated with the production of SAA.—Authors' Summary

Meneghini, C. L., Angelini, G., Lospalluti, M. and Trimigliozzi, G. Cutaneous responses to irritants and microbial antigens in lepromatous leprosy. St. John's Hosp. Dermatol. Society Trans. **60** (1974) 91-93.

Cutaneous delayed hypersensitivity responses to common microbial agents and chemical contact allergens are known to be depressed in lepromatous leprosy patients. A study was undertaken with benzalkonium chloride 2.5% and potash soap 30% to find out whether the cutaneous inflammatory response to irritants is also depressed; 70 patients were examined. The cutaneous hypersensitivity reactions to microbial antigens (candidine, staphlococcal and streptococcal vaccine, tuberculin and lepromin) were assessed in the same group of 70 patients and in another 36 patients. The inflammatory responses to benzalkonium chloride and potash soap were depressed in the majority of patients, many of whom presented negative or mild reactions to microbial antigens.—Authors' Summary

Nelson, D. S., Penrose, J. M., Waters, M. F. R., Pearson, J. M. H. and Nelson, M. Depressive effect of serum from patients with leprosy on mixed lymphocyte reactions. Influence of antileprosy treatment. Clin. Exp. Immunol. **22** (1975) 385-392.

Mixed leucocyte cultures, from two normal donors, were set up in media containing human serum from one of the following sources: a) a pool of normal group AB donors; b) Chinese, Malay or Indian patients with untreated leprosy; c) the same patients after effective antileprosy treatment; d) control Chinese, Malay or Indian subjects. Transformation was estimated by measuring the incorporation of tritiated thymidine in the last 24 hours of a seven day culture period. Transformation was impaired in sera from untreated lepromatous patients, but was less impaired or not impaired at all in sera from treated lepromatous patients. The loss of depressive activity after treatment was more marked in Chinese and Indian than in Malay patients. Transformation was also impaired, though to a lesser extent, in sera from patients with untreated tuberculoid leprosy; it was still impaired in sera from treated tuberculoid patients. There was no evidence of specificity in impairment of mixed lymphocyte reactivity and lymphocytotoxic antibodies appeared to play no role. The incidences of hepatitis B antigen and antibody and of antinuclear factor were not notably high.—Authors' Summary

Nowicki, L., Behnken, L. and Martin, H. Über die Häufigkeit von Hämoglobinanomalien und Hämoglobinopathien bei moçambiquanischen Völkerschaften. (Mit Vergleich zwischen Leprösen und Nicht-Leprösen.) [Frequency of abnormal and pathologic hemoglobins in different populations from Mocambique (comparison between leprous and nonleprous natives).] Blut **31** (1975) 283-290.

In 588 blood samples of Negroid natives from Mozambique, mostly Chuabo and Macua, hemoglobin analyses were performed. In 21 cases an increase of Hb A_2 was found indicating the presence of heterozygous β-thalassemia; in 1 case the changes in Hb-analysis were typical for β-δ-thalassemia; 18 samples were shown to contain Hb S, typical for the heterozygous sickle cell trait. Furthermore, in 7 cases Hb A_2' was found. In two blood samples hemoglobin variants were observed, which according to their electrophoretical mobility, were assumed to represent Hb D in one case, and Hb G in the other. In the Chuabo population the frequency of the thalassemia gene was found to be more than twice as high as in the Macua population. In nonleprous natives Hb S was observed with a remarkable higher incidence than in those with leprosy.—(*Adapted from* English summary)

Pattyn, S. R., Dockx, P., Jacob, W., Rollier, R. and Rollier, M.-T. *Mycobacterium leprae* in human skeletal muscle. Ann. Soc. Belg. Med. Trop. **55** (1975) 643-646.

Leprosy bacilli were found in 24 of 31 muscle biopsies from treated lepromatous patients. Bacilli were localized within macrophages and endothelial cells of the interstitial connective tissue; none were found inside muscle cells. This may be the result of treatment. Morphological intact bacilli were not observed. The widespread occurrence of leprosy bacilli in the human body is in accordance with the concept that leprosy is a generalized infectious disease.—Authors' Summary

Rea, T. H., Gottlieb, B. and Levan, N. E. Apparently normal skin in lepromatous leprosy. Histopathological findings. Arch. Dermatol. **111** (1975) 1571-1574.

Biopsy specimens of apparently uninvolved skin from 34 patients with lepromatous leprosy were studied histologically. Bacilli were found in 30 of 31 specimens from clinically polar or near-polar lepromatous patients but not in the three from nonpolar patients. A predominantly perivascular distribution of infiltrate and bacilli is consistent with a hematogenous spread of infection. Subclinical, diffuse lepromatous leprosy is found in patients with nodular lesions and may precede the development of nodules. Study of apparently uninvolved skin may be helpful in classifying patients, in interpreting immunologic responses, and in elucidating the natural history of the illness.—Authors' Abstract

Sampaio, L. A., Jr., Schiavi, A., Jr., Macedo, J. A. P. and Miranda, R. N. Contribution to the study of the Mitsuda phenomenon. Publ. Cent. Estud. Leprol. **14** (1974) 94-96.

The purpose of this study was to investigate a possible parallelism between the Mitsuda reaction and late Montenegro reaction in persons suffering from tuberculoid leprosy.

Following the findings of Portugal and Gimenez (1943) and Miranda (1967), 18 tuberculoid leprosy patients were submitted to intradermal reactions with lepromin and leishmanin, the results being considered by both gross and microscopic features.

It was estimated that there was a 65% parallelism between Mitsuda and late Montenegro reactions in tuberculoid leprosy. Further studies may lead to replacement of lepromin by an equivalent antigen.—(*Adapted from* authors' summary)

Saxena, H., Ajwani, K. D. and Vishnoi, K. The nitroblue tetrazolium test in leprosy. Lepr. India **47** (1975) 321-324.

The NBT test was performed in 48 normal healthy people and in 30 leprosy patients. The score of NBT positive cells in normal persons ranged from 1% to 13%, while the score in leprosy ranged from 3% to 28%, with a normal range in 26 leprosy patients and raised in 4 cases of lepromatous leprosy. The NBT test in leprosy has no diagnostic or prognostic value.—(*Adapted from* authors' summary)

Skinsnes, Olaf K. Immunometabolism in leprosy. Ethiop. Med. J. **13** (1975) 111-120.

No clinical manifestation is known for a genetic deficiency in β-glucuronidase, possibly because this metabolic route is not important to the normal metabolism of lipids in men and perhaps such deficiency is not crucial to the development of mucopolysaccharidoses. This whole metabolic area is not adequately understood to permit further correlative speculation. It is, however, not im-

probable that this defect may be related to an inability of deficient macrophages to metabolize the extraneous lipid complexes of *M. leprae,* perhaps because of the formation of relatively insoluble lipicarbohydrate complexes. If this be true, then it would appear that the manifestations of tuberculoid and borderline leprosy may lie within that range of interaction seen between host and challenging dose of pathogen in most infectious disease of low-virulence, while in lepromatous leprosy the pathogen has capitalized on a metabolic defect to perpetuate itself by massive bacillary proliferation in, and discharge from, the conveniently deficient host.

The findings described here, although tentative in some areas, are firm enough *in toto* to warrant the attention of others concerned with the problems of leprosy understanding and treatment and to suggest approaches to the cultivation of *M. leprae.* They also present the determination of a specific effect of vitamin C on an infectious disease.—(*From* text of article)

Srivastava, L. M., Agarwal, D. P., Benkmann, H. G. and Goedde, H. W. Biochemical, immunological and genetic studies in leprosy. III. Genetic polymorphism of C3 and immunoglobulin profile in leprosy patients, healthy family members and controls. Tropenmed. Parasitol. **26** (1975) 426-430.

One hundred forty-eight members from 30 families (64 children) from Ethiopia, where one or more persons were affected with leprosy, were investigated for genetic polymorphism of C3, serum concentration of β1C/β1A-globulin and immunoglobulins A, G and M using high voltage agarose electrophoresis, immunoelectroassay and single radial immunodiffusion technics respectively. The results are compared with related healthy controls. No association between C3 phenotypes and leprosy could be established through family studies. C3 concentration was, however, lower in leprosy patients. Difficulties and drawbacks of such studies with small families are discussed.—(*From* Trop. Dis. Bull.)

Thomas, E. M., Damasco, M. H. dos S., Viana, S. M. and Silva, C. Efeito da talidomida sobre os linfócitos e imunoglubulinas G, A e M no sangue circulante de pessoas normais. [The effect of thalidomide on the lymphocytes and immunoglobulins G, A and M in the blood of healthy volunteers.] Bol. Div. Nac. Dermatol. Sanit. **34** (1975) 73-79. (In Portuguese)

The quantification of T, T-a and B lymphocytes and of immunoglobulins G, A and M of the peripheral blood from 13 healthy volunteers were performed before and after continuous use of 200 mg per day of thalidomide during three weeks. A reduction of about 30% of T lymphocytes and 26% of T-active lymphocytes was observed while there was no change among B lymphocyte percentages. The levels of immunoglobulins did not show any appreciable variation. The authors recall their previous research work in which the drug caused a great decrease among T lymphocytes and almost total suppression of T active subpopulation.—(*Adapted from* authors' English summary)

Wright, D. J. M., Hirst, R. A. and Waters, M. F. R. Neural auto-antibodies in leprosy. Lepr. Rev. **46** (1975) 157-169.

A new axonal antibody confined to peripheral nerve has been found at a significant titer of 1/30 by indirect immunofluorescence. This antibody occurred in 23 of 59 sera from patients with lepromatous leprosy, 2 of 10 sera from patients with tuberculoid leprosy from Malaysia, and 1 of 12 sera from patients with leprous neuropathy from Ethiopia, 4 of 6 sera from patients with post-infective polyneuropathy, and 6 of 271 control sera.

Failure to remove the axonal antibody by absorption with BCG in six sera from patients with post-infective polyneuropathy suggested that this was not a cross-reaction with *M. leprae* or other mycobacteria, but probably occurred as an epiphenomenon following nerve injury. The finding of axonal antibodies at a titer of 1/10 in 43 of 271 control sera (15.8%) also suggests that the antibody's presence is not related to nerve damage. There were no antimyelin antibodies found in any of the sera studied.—Authors' Abstract

Youngchaiyud, U., Panpatana, P., Jatikavanij, V., Thongcharoen, P. and Vibhatavanija, T.-N. Serum immunoglobulin determinations in leprosy patients. J. Med. Assoc. Thai. **58** (1975) 304-307.

The serum immunoglobulins were determined by the single radial diffusion method in 147 cases of leprosy, 49 cases with lepromatous and 98 cases with tuberculoid type. The cases were divided into three groups corresponding to the duration of disease. No significant alteration of serum immunoglobulin G, A, M level was demonstrated in all of the tuberculoid patients and in lepromatous cases with the disease less than five years, but a slight rise in IgA level was found in this group. There was a significant increase in all of the three classes of immunoglobulin in lepromatous patients who had had the disease more than five years. This finding suggested that the duration of the disease may be one of the factors affecting the variation in serum immunoglobulin level in lepromatous patients.—Authors' Summary

Microbiology

Azuma, I., Yamamura, Y. and Mori, T. Chemical and immunologic studies on *Mycobacterium lepraemurium* strain Hawaii cultured on Ogawa's one percent egg yolk medium. Jap. J. Microbiol. **19** (1975) 333-336.

The results described herein indicate that the chemical compositions of the cell wall prepared from the cells of *M. lepraemurium* Hawaii grown on Ogawa's 1% egg yolk medium are almost similar to those of the cell wall prepared from the cells of the same strain grown in C_3H mice. Immunological study suggests that the skin testing peptides prepared from the cells of *M. lepraemurium* Hawaii grown *in vitro* elicited potent delayed-type skin reaction in guinea pigs immunized with the cells of *M. lepraemurium* Hawaii grown *in vivo* or *in vitro,* or *M. avium* 4110.

Recently some similarities were found between *M. lepraemurium* and *M. avium* by biochemical examination. However, Mori *et al* have shown that cytochrome having an absorption peak at 550 mμ was not detected in the cells of *M. lepraemurium* Hawaii grown *in vivo* and *in vitro.* This finding is a characteristic of the cells of *M. lepraemurium* grown *in vivo* or *in vitro,* and this phenomenon may correlate to the difficulty of the culture of *M. lepraemurium in vitro.—(Excerpted from* authors' paper, p 335-336)

Matsuo, Yoshiyasu. Studies of *Mycobacterium* in cell culture. 2. Pathogenicity of *Mycobacterium lepraemurium* maintained in mouse foot pad cell culture and interaction of the bacilli with the infected cells. Jap. J. Microbiol. **19** (1975) 319-325.

A serially diluted bacterial suspension of the Kurume-42 strain of *Mycobacterium lepraemurium* maintained for 1,255 days in a mouse foot pad (MFP) cell culture was inoculated in mice subcutaneously. The ID_{50} value was estimated at more than 10.7 and less than 85 organisms, indicating that pathogenicity of the organism had been maintained well in a long-term cell culture. The cells infected and maintained for a long period in the cell culture showed all the stages of cell mitosis. This suggests that the bacterial increase in cell cultures of *M. lepraemurium* is not only due to rephagocytosis of the bacilli released from the infected cells but also to a constant intracellular growth cycle of the bacilli accompanied by mitosis of the infected cells. In acid phosphatase activity, no appreciable differences were noted between the infected and uninfected cells as far as the present cell culture system was concerned. Most of the bacilli within the cells were ultrastructurally normal. Solid bacilli in phagosomes were surrounded by less electron dense clear zones.—Author's Abstract

Mori, Tatsuo. Successive cultivation of *M. lepraemurium* by bacterial mass inoculation. Lepro **44** (1975) 49-54. (In Japanese)

Since *M. lepraemurium* Hawaii was isolated on 1% Ogawa yolk medium, Kozeki *et al* and Mori succeeded in confirmatory experiments of Ogawa's method. However, successive inoculation with smooth suspension was not successful, as was reported by Ogawa.

It was still not clear why some growth-negative tubes were always observed in cases of successive inoculation and primary isolation, despite massive bacterial inoculation. The difficult problem to be solved is that of single cell culture of *M. lepraemurium.* As it was very difficult to get 100%

success in successive inoculations, even with massive bacterial inoculation, some conditions for achieving more efficiency were carefully studied by the method of bacterial mass inoculation.

1. Successive inoculation of *M. lepraemurium* was not achieved on the 1% Ogawa yolk medium without malachite green.

2. Successive inoculation of *M. lepraemurium* was independent of any modification of the 1% Ogawa yolk media by supplementation with the following substrates: cystin, cystein special agar noble, sodium citrate, sodium α-ketoglutarate, glucose, protoporphyrin and water- or butanol-extract of 1% Ogawa medium on which *M. lepraemurium* had grown.

3. Successive inoculation of *M. lepraemurium* was slightly inhibited on the modified 1% Ogawa yolk medium supplemented with sodium pyruvate.

4. Addition of hemin to 1% Ogawa yolk medium gave a good result for successive inoculation of *M. lepraemurium.*

5. In successive inoculation of *M. lepraemurium,* aeration through a small hole in the gum stopper gave better results than with air-tight condition.

6. The organism from an old culture of over two months was not good for successive inoculation, but the young rough organism from a 30 to 40 day culture was most suitable. Moreover, the organisms should not be scattered on the surface of the medium. It was important to inoculate heavily to achieve good results.—*(Adapted from* author's English summary)

Nakamura, Masahiro. Improvement to the NC-5 medium for culturing *Mycobacterium lepraemurium* (ND-5 medium). Kurume Med. J. **22** (1975) 67-70.

An improved cell-free liquid medium (ND-5) derived from the NC-5 medium is described. For a basal medium, Dubos medium was used instead of Kirchner medium. In this medium, *Mycobacterium lepraemurium* quickly multiplies in the form of binary fission without an extraordinary elongation. A possible generation time can be calculated by repeated experiments as 1.4 – 2.6 days.—(*From* Trop. Dis. Bull.)

Nyka, W. Studies on the effect of starvation on mycobacteria. Infect. Immun. **9** (1974) 843-850.

Ten cultures of *Mycobacterium tuberculosis,* one of *Mycobacterium kansasii* (nonsignificant), and one of *Mycobacterium phlei* were submitted to starvation. As a result they lost first their acid fastness and then all other staining affinities but, in this chromophobic state, they survived for at least two years and, after that time, produced cultures of acid-fast bacilli when transferred onto nutrient media. Chromophobic tubercle bacilli similar to those produced experimentally had previously been demonstrated in caseous lesions of lungs surgically removed from patients under chemotherapy. Since it has been shown that experimentally produced chromophobic bacilli can recover their original biological properties, the opinion is warranted that, under suitable conditions, those in the lung could also become reactivated and cause a relapse of the disease.—Author's Abstract

Olitzki, A. L. Effect of microbial substances of different origins on the growth of *Mycobacterium leprae.* Israel J. Med. Sci. **11** (1975) 896-905.

Mycobacterium leprae multiplied in media enriched with substances originating from other mycobacteria, from non acid-fast *Actinomycetales* or from gram positive or gram negative *Eubacteriales.* Most of the *M. leprae* strains did not grow on a synthetic medium containing the amino acids present in *M. smegmatis,* but the growth-promoting effect of sonic extracts of this organism indicated that substances of bacterial origin, other than amino acids, do act as growth factors. The identification of the growing, acid-fast microorganisms with *M. leprae* was verified by their ability to oxidize D-3,4-dihydroxyphenylalanine (D-DOPA test). *M. leprae* did not multiply on Nakamura medium unless at least 40% of medium NM7 enriched by bacterial substances was present. Adequate aeration was essential for multiplication of *M. leprae* in enriched NM7 and No. 3 media.—Author's Abstract

Stanford, J. L., Rook, G. A., Convit, J., Godal, T., Kronvall, G., Rees, R. J. and Walsh, G. P. Preliminary taxonomic studies on the leprosy bacillus. Br. J. Exp. Pathol. **56** (1975) 579-585.

Antigens extracted from leprosy bacilli obtained from infected human and armadillo

tissues have been examined by immunodiffusion analysis with serum samples from lepromatous patients and with immune sera raised in rabbits. Using the best combinations of serum and antigen extracts, 12 antigenic constituents were found in the leprosy bacilli. Six of these were antigens common to all mycobacterial and nocardiae, four were specific to the leprosy bacillus, and the position of two could not be determined. Groups ii and iii antigens (i.e., those associated with the slow growing and fast growing subgenera of mycobacteria) were not found in the leprosy bacillus, suggesting some relationship with *M. vaccae* and similar strains in which these antigens are also missing. Lymphocyte transformation tests performed on lymph node cells of mice infected or immunized with leprosy bacilli also showed the leprosy bacillus to have a closer relationship with *M. vaccae* than with other mycobacteria.—(*From* Trop. Dis. Bull.)

Yoshii, Zensaku and Nakamura, Masahiro. Growth features of *Mycobacterium lepraemurium* cultivated in NC-5 medium. Kurume Med. J. **22** (1975) 35-56.

Morphologic features of *Mycobacterium lepraemurium* cultivated on a glass slide in a cell-free liquid medium, NC-5, were precisely observed by a scanning electron microscope. As previously demonstrated, elongation of bacterial cell was noted in the second week of cultivation; and thereafter septum formation, division, budding and branching followed. It was obvious that the growth grade of bacilli depended upon the number of bacilli presented on the glass slide; when a small number of bacilli was inoculated on the glass slide a microcolony was formed in ten weeks' cultivation, but further development did not occur even if cultivation was continued.—(*Adapted from* Trop. Dis. Bull.)

Experimental Infections

Closs, Otto. Experimental murine leprosy: growth of *Mycobacterium lepraemurium* in C3H and C57/BL mice after foot pad inoculation. Infect. Immun. **12** (1975) 480-489.

Forty-three female C57/BL and C3H mice were inoculated with 2.7×10^6 *Mycobacterium lepraemurium* into each hind foot pad. The foot thickness and the number of acid-fast bacilli in the foot pad and popliteal and inguinal lymph nodes were recorded. In addition the Morphologic Index and the mean bacillary length were determined in the foot pad and in the popliteal lymph node. The bacilli multiplied in both strains during the first four weeks after inoculation. After that time no further increase in acid-fast bacilli was observed in the C57/BL strain; the bacilli became elongated and the Morphologic Index decreased. These changes were preceded by a local swelling of the foot pad due to the onset of an immune reaction. Thus, under the present conditions, C57/BL mice were able to resist experimental infection with *M. lepraemurium* by developing an immune response. In C3H mice no indication of an immune reaction was detected, and the bacilli continued to multiply throughout the observation period. The mouse foot pad model seems to provide an excellent basis for the use of experimental murine leprosy to study immunity to mycobacterial infections. Certain aspects of the present model are discussed in relation to the mouse foot pad model as used in the study of *M. leprae* infection in mice.—Author's Summary.

Closs, Otto and Kronvall, Goran. Experimental murine leprosy. 9. Antibodies against *Mycobacterium lepraemurium* in C3H and C57BL mice with murine leprosy and in patients with lepromatous leprosy. Scand. J. Immunol. **4** (1975) 735-740.

Sera from C3H and C57BL mice infected with *M. lepraemurium* (MLM) and from human leprosy patients were examined for antibodies against MLM by a crossed immunoelectrophoresis (CIE) technic. Altogether antibodies against six or seven MLM antigens were found in the mouse sera. After a small inoculum of MLM, C3H mice produced more antibodies than C57BL mice. After a large inoculum both strains produced about the same amount of antibodies but showed qualitative differences in their response patterns. A serum pool from patients with lepromatous leprosy contained antibodies against six MLM antigens; five of these were identical with the antigens against which antibodies were found in infected

mice. C57BL mice that had lost their delayed-type hypersensitivity to MLM during the course of a disseminated infection showed a fairly strong antibody response to three antigens and a weak response to three others. Since almost the same spectrum of antibodies, although in lower titers, could be demonstrated in C57BL mice with intact delayed-type hypersensitivity to the bacilli, these antibodies did not seem to interfere with the expression of cell-mediated immunity.—Authors' Summary

Collins, F. M., Montalbine, V. and Morrison, N. E. Growth and immunogenicity of photochromogenic strains of mycobacteria in the foot pads of normal mice. Infect. Immun. **11** (1975) 1079-1087.

Specific pathogen-free CD-1 mice were infected subcutaneously in the foot pad with *Mycobacterium kansasii,* three strains of *M. marinum,* and two strains of *M. simiae-habana,* and the growth of the organisms in the foot pad, the draining popliteal lymph node, and the lung and spleen was followed quantitatively for up to 60 days. The ability of a foot pad inoculum of *M. marinum* to spread to the lung and spleen with the ability of the organism to survive and multiply at 37°C in *in vitro* cultures. The amount of foot pad swelling which developed in the *M. kansasii*- and *M. marinum*-infected mice varied depending upon the strain of organism and the size of the original foot pad inoculum. Injection of dead *M. marinum* into the foot pad also induced an extensive amount of swelling which varied with the strain used, as well as being dose dependent. *M. marinum*- and BCG-vaccinated mice were protected against a later foot pad challenge with *M. marinum* or the highly mouse virulent *M. tuberculosis* strain Erdman. The significance of this finding is discussed in relation to cross-protection studies using a variety of mycobacteria in the foot pad infection model.—Authors' Abstract

Collins, F. M., Montalbine, V. and Morrison, N. E. Growth of *Mycobacterium marinum* in the foot pads of T-cell-depleted mice. Infect. Immun. **11** (1975) 1088-1093.

Mycobacterium marinum strains 1218 and 1219 were inoculated into the hind foot pads of T-cell-depleted specific pathogen-free C57B1/6 mice, and the growth and survival of the organisms at the site of injection, the draining popliteal lymph node, and the spleen and lung were quantitated for up to 70 days. T-cell depletion largely ablated the normal cell-mediated antituberculous response to the *M. marinum* population. The mice were able to control the further growth of the inoculum within the foot pad only after it had reached 5 to 10 times that present in the normal controls. The high temperature-adapted strain (37°C; strain no. 1218) induced an increasing infection in the liver, spleen, and lungs of the THXB mice and the infection eventually spread to the opposite foot pad and to the tail skin. Strain 1219 gave rise to considerable systemic involvement in the THXB host despite its inability to survive at 37°C, but the size of the splenic and lung populations was considerably lower than in the 1218-infected animals. Both *M. marinum* infections persisted in the tissues of the T-cell-depleted mice with no indication of a cell-mediated immune response. Foot pad swelling in the *M. marinum*-infected mice was not greatly reduced by T cell depletion and, if anything, tended to persist at high levels long after the swelling of the control feet had gone into a decline. On the other hand, incorporation of tritiated thymidine by cells within the infected foot pads, the draining lymph node, and the spleen was considerably reduced in the T-cell-depleted host compared with control values. Late in the infection, there was a significant increase in the amount of label taken up by the cells in the foot pads of the T-cell-depleted host. —Authors' Abstract

Fieldsteel, A. Howard and Gartner, Suzanne. Effect of thymectomy and antilymphocyte serum on *M. leprae* infection in mice. Infect. Immun. **12** (1975) 733-737.

BALB/c mice thymectomized at three to five days of age were studied to determine if this procedure would result in enhanced susceptibility to infection with *M. leprae* and, if so, whether or not administration of antilymphocyte serum would further increase this susceptibility. The plateau for growth in the foot pads of intact mice occurred four months after inoculation, whereas in the thymectomized and thymectomized plus antilymphocyte serum-treated groups the plateau occurred between months 11 and 12 after inoculation. Thymectomy resulted in

at least a tenfold increase in the number of *M. leprae* found in the foot pads. Antilymphocyte serum did not appear to further enhance the *M. leprae* infection in the thymectomized mice. Although growth of *M. leprae* in the testes of both intact and thymectomized mice was erratic, the number of organisms reached a higher ceiling in the thymectomized groups. *M. leprae* harvested from all groups was passaged into intact mice at various intervals after inoculation to test for viability. Viable *M. leprae* were found at all intervals tested including 22 months after infection in the intact mice, suggesting that a chronic infection occurred that probably lasted during the entire life of the animals. —Authors' Summary

Haugen, Olav A. and Closs, Otto. Experimental murine leprosy. 6. Cellular reactions in the draining lymph node after injection of *Mycobacterium lepraemurium* into the foot pads of mice. Acta. Pathol. Microbiol. Scand. [A] **83** (1975) 683-692.

The reaction patterns of the draining lymph nodes were studied in C3H and C57/BL mice after foot pad inoculation of *Mycobacterium lepraemurium* (MLM). Bacilli were found in the lymph nodes of both strains already a few days after inoculation, but any marked reaction did not occur until approximately three weeks later and then only in the lymph nodes of C57/BL mice. The reaction involved enlargement, epithelioid cell granuloma formation and proliferation of pyroninophilic blast cells in the T cell area. The lymph nodes in these animals remained large and showed a reactive pattern for up to 230 days. At this stage, bacilli were relatively few. In C3H mice, no reactive changes developed and it was not until much later that they became significantly enlarged. In the advanced stage, normal lymph node structures were replaced completely by giant macrophages loaded with acid-fast bacilli. C3H and C57/BL mice are polar as regards the lymph node reaction against MLM; in C3H mice it resembles the advanced stages of human leprosy while it in C57/BL mice mimics the situation in the BT-TT region. Immunofluorescence studies did not reveal any early proliferation of Ig-containing cells and the lack of cellular immune reaction against MLM in C3H mice cannot be explained as an early B cell reaction to interfere with the development of cell-mediated immunity.—Authors' Summary

Haugen, O. A., Skjorten, F. and Closs, O. Experimental murine leprosy. 8. Ultrastructural features of the inflammatory exudate and bacterial morphology in C3H and C57BL mice after foot pad inoculation with *Mycobacterium lepraemurium*. Acta. Pathol. Microbiol. Scand. [A] **83** (1975) 693-703.

Mice of the inbred strains C57BL and C3H were inoculated in the foot pads with *M. lepraemurium* (MLM) and the inflammatory reaction was studied using light and electron microscopy. In C57BL mice a granulomatous reaction developed three to four weeks after inoculation. The inflammatory exudate at this stage showed numerous lymphocytes, monocytes and macrophages. The latter cell type often contained many lysosomes and appeared activated. The bacilli which were all within phagosomes showed extensive electron dense aggregates of the cytoplasm suggesting severe damage. Lymphocytes and macrophages in close contact with each other were often observed. In macrophages which contained damaged bacilli, spherical lipid-like bodies surrounded by granular endoplasmic reticulum were observed. It is suggested that this cell product could be of some significance for the bactericidal function of the macrophage. Contrary to these findings, the cellular infiltrate developing in C3H mice showed no lymphocytes and consisted exclusively of macrophages. These were all heavily loaded with bacilli. The vast majority of bacilli encountered in this strain was morphologically intact and presumably viable. Lipid-like bodies similar to those observed in infected C57BL macrophages were not encountered in C3H mice. It is concluded that unless the infected macrophages become immunologically activated they are unable to cause bacterial damage or to inhibit the growth of MLM.—Authors' Summary

Howells, R. E., Carvalho, A. D. V., Mello, M. N. and Rangel, N. M. Morphologic and histochemical observations on *Sarcocystis* from the nine-banded armadillo, *Dasypus novemcinctus*. Ann. Trop. Med. Parasitol. **69** (1975) 463-474.

Sarcocysts have been found in tongue and skeletal muscle, but not esophageal or car-

diac muscle, of the nine-banded armadillo, *Dasypus novemcinctus.* Histological and histochemical observations have been made and two distinct types of *Sarcocystis* have been recognized. These are each given specific rank although attempts to complete the life cycle experimentally were unsuccessful, using cats and dogs. In both species the cyst walls contained no demonstrable mucosubstances but stained for elastin, being also PAS-negative and low in tryptophan and arginine.—Authors' Summary

Kirchheimer, Waldemar F. Experimental leprosy in the nine-banded armadillo. Public Health Rep. **90** (1975) 483-485.

This is a nice review of the by now well-known characteristics of *M. leprae* infection in the armadillo and presents the general hopes and goals formulated for work with this disease model.—Olaf K. Skinsnes

Royce, G. J., Martin, G. F. and Dom, R. M. Functional localization and cortical architecture in the nine-banded armadillo *(Dasypus novemcinctus mexicanus).* J. Comp. Neurol. **164** (1975) 495-522.

A functional map of the armadillo neocortex was produced by cortical stimulation and recording evoked potentials following somatic, auditory and visual stimuli. The results obtained were then correlated with the cortical architecture as revealed by Nissl, Golgi and myelin stained sections. Cortex rostral to the supraorbital sulcus has a wide layer IV and is mostly silent, except for a motor eye field and a part of the tongue sensory region in its caudal part. Two types of motor sensory cortex are present caudal to the supraorbital sulcus. Postsupraorbital I is mostly motor and has prominent pyramidal layers. Layer V is particularly well developed and in rostral sections its superficial zone is broken up into clusters similar to the solid "barrels" seen in layer IV of other species. Postsupraorbital II has less prominent pyramidal layers and layers II and III are organized into clusters. This region corresponds to the sensory area for the limbs and trunk and the partially overlapping (surface recordings) sensory and motor areas for head, snout and tongue. Digits and limbs are rostral to the trunk representation in both the sensory and motor "homunculi." Even though surface recording was employed, potentials evoked by visual stimuli could only be recorded from a small caudal area with a very thin layer IV. Although striate and peristriate areas appear similar in Nissl stained preparations, they can be readily differentiated in Weil stained sections. The stellate character of neurons in layer IV of the visual cortex is particularly apparent in Golgi material. Auditory evoked surface potentials were recorded from a broad oval region in the caudal lateral cortex which has a wide layer IV and aggregates of neurons in layers II and III. A Weil stain demonstrates inner and outer bands of Baillarger in this same region. The presumptive insular cortex is electrically silent to sensory stimulation and presents as a narrow band just dorsal to the rhinal fissure with indefinite cell lamination and little myelin.—Authors' Abstract

Silva, C., Andrade, L. M. C. de, Damasco, M. H., Viana, S. M. and Gama, P. C. C. Experiência do Instituto de Leprologia na transmissão experimental do *Mycobacterium leprae.* [Experiences of the Institute of Leprology with experimental transmission of *Mycobacterium leprae.*] Bol. Div. Nac. Dermatol. Sanit. **34** (1975) 55-59. (In Portuguese)

Inoculations of *Mycobacterium leprae* into various species of wild animals have been carried out for more than ten years by the research workers at the Institute of Leprology. Observations included the following species from the Amazon area: *Kinosternum scorpioides, Geoemyda punctularia, Typhlonectes Kaupii;* and from Rio de Janeiro: *Bufo marinus, Thaumastus Taunayi, Strophocheilus oblongos, Carollia perspicillata, Akodon arviculoides* e *Oryzomus nigripes, Didelphis marsupialis.*

The successful transmission of *M. leprae* to the armadillo and previously to the mouse foot pad encouraged more attempts to discover other adequate species for this infection. Presently the following species are under observation: *Euphractus sexcymctus flavimanus, Bradipus infuscatus, Testudo tabulata* e *Nectomys squamipes.* Facilities to maintain other species, particularly the armadillo, in sufficient numbers to do research work and to produce lepromin are ready.—(*Adapted from* authors' English abstract)

Storrs, E. E., Walsh, G. P. and Burchfield, H. P. Development of leprosy in another species of armadillo *Dasypus hybridus* (L.): genetic and immunologic implications. J. Trop. Med. Hyg. **78** (1975) 216-218.

The development of severe disseminated leprosy in one of a pair of seven-banded armadillos *(Dasypus hybridus)* after inoculation with *M. leprae* is reported. This is a smaller animal than the nine-banded armadillo, but is of interest in that it regularly produces 8-16 monozygous young, compared with 4 in the case of its larger relative. This feature gives *Dasypus hybridus* a potential importance in studying the relationship of susceptibility in leprosy to genetic factors.—T. F. Davey (*From* Trop Dis. Bull.)

Epidemiology and Prevention

Aquino, U. M. de, Callado, E. A., Santos, C. dos and Aragao, O. Hanseníase na Amazônia: resultados do I Inquérito sobre Dermatoses Tropicais no Alto Solimões. [Hanseniasis in the Amazon: results from first inquiries on tropical skin diseases in Upper Solimoes river, Brazil.] Bol. Div. Nac. Dermatol. Sanit. **34** (1975) 49-53. (In Portuguese)

After examining a sample of 722 persons from military, civil and Indian communities, the authors concluded:

1. Hanseniasis is not a public health problem in that region. Only one case of Virchowian type leprosy was found in the civil community, and one tuberculoid type in the military community. Both of them were under sanitary control.

2. Very high rates of negative Mitsuda test were found. While the difference between the military and civilians is highly significant, significant differentiations were not observed between the civilians and Indians. Neither the civilians nor the Indians are subject to conditions conducive to developing delayed hypersensitivity against *Mycobacterium leprae.*

3. The Indian community responded to the Mitsuda test in the same manner as the children from the civilian community.—(*Adapted from* authors' English summary)

Browne, Stanley G. The training and deployment of medical auxiliaries in the leprosy campaign. Ann. Trop. Med. Parasitol. **69** (1975) 413-416.

After describing the different types of medical auxiliary carrying out essential work in the antileprosy campaigns in the tropics and subtropics, the author draws on his experience in the former Belgian Congo in the training and deployment of the most valuable of them all, the polycompetent auxiliary, and gives a detailed account of the curriculum and the type of service such a qualified auxiliary can render.—W. H. Jopling (*From* Trop. Dis. Bull.)

Chatterjee, B. R. Are children the most susceptible to leprosy? Lepr. India **46** (1975) 197-200.

In the area monitored by the Jhalda leprosy control unit in West Bengal the incidence of leprosy in children is three times lower than in adults. The incidence in children reported by other workers is reviewed. —C. S. Goodwin (*From* Trop. Dis. Bull.)

Nyunt, T., Gallego Garbajosa, P., Matejka, M., Tamondong, C. T., Gyi, M. M. and Guld, J. Sensitivity to tuberculin and to a nonmammalian sensitin in Mandalay District, Burma. Bull. WHO **52** (1975) 63-67.

Delayed hypersensitivity that can be demonstrated with either a strong dose of tuberculin or a conventional dose of a sensitin prepared from certain nonmammalian mycobacteria (mycobacteria of Runyon Groups II and III, e.g., *Mycobacterium avium*), is known to be highly prevalent in most tropical and many subtropical areas and rare in many temperate zones. Whether such sensitivity interacts significantly with tuberculosis or with leprosy is not known.

A study of reactions to tuberculin (PPD-S) and to a sensitin prepared from *M. intracellulare* (PPD-B) was carried out in villages close to an area in which a clinical trial of the preventive effect of BCG against leprosy was being conducted. The population had not been vaccinated with BCG. Some of the villages were in river valleys that became flooded every year for a long period during the rainy season; others were on slopes

above the area subject to floods. The findings showed that sensitivity to the nonmammalian sensitin was prevalent in the area, and thus confirmed previous findings of low-grade tuberculin sensitivity in Burma and neighboring countries. No difference in this prevalence was found between flooded and nonflooded villages.—Authors' Abstract

Pattyn, Stefaan R. Imported leprosy in Belgium 1960-1974. Acta Clin. Belg. **30** (1975) 511-517.

Seventeen new and one relapsed case of leprosy were diagnosed in Belgium between 1960 and 1974: all were imported cases, nine lepromatous and eight tuberculoid.

A survey is presented concerning the origin of the infections, their diagnosis, evolution and therapy, and the changes the latter underwent during the years. As in most non-endemic regions no secondary infections are known in our country.—Author's Summary

Russell, D. A., Worth, R. M., Jano, B., Fasal, P. and Shepard, C. C. Prevention of leprosy by acedapsone. Lancet **2** (1975) 771. (Letter to Editor)

Sir: Treatment with acedapsone injections five times a year was offered during 1967-1970 to about 1,600 people in three villages in which leprosy was common in the Ponape District of Micronesia. The object of this trial was to prevent new cases of leprosy in this highly inbred, highly susceptible population, which has been completely reexamined for new cases of leprosy each year since the autumn of 1967. The design and execution of the trial and the two year post-treatment incidence of leprosy have been reported elsewhere. Acedapsone treatment was continued in all cases (except two who are sulfone resistant), with multibacillary (bacillary index 2+ or greater) cases receiving, in addition, a 90 day course of rifampin during 1974-1975. Clinical and bacteriologic results have been good whenever treatment has been regular, and no ill effects have been encountered.

The fourth annual round of post-treatment leprosy examinations was completed in February 1975. Of the 2,103 people eligible for examination (1,597 potential acedapsone recipients born 1968 or earlier, plus 506 born later and not offered acedapsone), all but 91 were examined (a 95.7% reexamination rate). The people who were not examined were almost all adults who were out of the villages at the time. Another 71 on the original examination roster have died since 1968, none of them having developed leprosy by the time of death.

A different pattern of subsequent leprosy incidence is now evident in the populations of the two Pingelapese villages on Ponape island compared with their relatives on Pingelap. In the two villages on Ponape this "epidemic" of leprosy which started in 1918, seems to be coming to an end even though there was less than full compliance with treatment during the acedapsone campaign. Two new cases of tuberculoid leprosy in Mant occurred in the children of an old sulfone-resistant lepromatous case in which leprosy was active in 1968 but is now under control. These two children are the only new cases in Mant in the past six and a half years. Fourteen new cases would have been expected from the previous five years' experience. There are two potentially troublesome cases in Sokes, so a few more years of observation are necessary before it can be stated with confidence that transmission has ceased in that village. The total load of active leprosy cases needing continuing close medical supervision in these two villages has been reduced from about 30 in 1967 to 5 at the end of 1974.

On Pingelap atoll until the end of 1973 no new cases had appeared among those who had received the full course of acedapsone, except for one case in which the strain was sulfone resistant. Beginning in 1974, however, there was a burst of five new cases, three of which occurred in previously untreated children born after the acedapsone campaign, and the other two were older children (one treated and one untreated). These three younger children provide clear evidence of secondary spread of new infection from multibacillary cases known to have been inadequately controlled during and shortly after the acedapsone campaign. Therefore, the Pingelap atoll population can no longer serve as an indicator of the preventive effectiveness of the acedapsone campaign, since we cannot distinguish new cases which are acedapsone failures from those which are the result of new postacedapsone exposure. The load of active cases on Pingelap, has, however, been reduced from about 40 in 1967 to 13 at the end of 1974.

In Sokes village two active multibacillary cases in 1972 (one new case in a man without previous acedapsone treatment and one reactivation) were potential sources of new infection. Both were given a 90 day course of rifampin during 1974-1975. On Pingelap atoll, moreover, there were several such sources (three new multibacillary cases among those who did not comply with treatment during the acedapsone campaign, one new sulfone resistant case among those who did comply, and two reactivations of old cases). All of these potentially dangerous Pingelap cases (except one absent on Kusai) have now been given a 90 day course of rifampin.

Our results show that the considerable risk of leprosy developing in highly susceptible individuals exposed to multibacillary leprosy cases can be reduced to zero by 15 acedapsone injections given over three years, except during the first six months of acedapsone injections and in those patients who are infected with a sulfone resistant strain of *M. leprae*.

It is also apparent that eradication of leprosy in a population (breaking the chain of transmission) by the use of acedapsone for preventive treatment of exposed people cannot be effective without the simultaneous and continuing control by adequate treatment of all multibacillary cases in that population.—(*Adapted from* authors' letter)

Social Reaction and Rehabilitation

Ramu, G., Dwivedi, M. P. and Iyer, C. G. S. Social reaction to leprosy in a rural population in Chingleput District (Tamil Nadu). Lepr. India **47** (1975) 156-169.

1. Social reaction to leprosy was studied with respect to 40 patients, and from the responses to questions from 25 normal subjects in a rural area in Tamil Nadu.

2. No social disability is faced by patients who do not have obvious deformities or stigmata of the disease.

3. Most patients are emotionally adjusted. The factors which provoke anxiety, depression, withdrawal or other adverse psychological states in the patient are: a) uncertainty about the course of the disease; b) painful complications and physical disabilities and stigmatizing signs; c) fission in family life; and d) economic deterioration. Reassurance regarding the curability of the disease, through drugs and correction of deformities through physiotherapy and surgery are likely to allay the mental state. Education of the family will lead to improvement of the relationship within the family.

4. Studies on the limitations of the health education media, determinants of social acceptability of the patient in his work and social environment, and the factors responsible for the patient's attitude toward his various relationships are necessary in order to reorient the approach to the social problem in keeping with the vastness of the national effort of leprosy control. A coordinated approach between the public health agencies and social welfare agencies is of great importance.

5. The loss of manpower resulting from disabilities in patients may result in a significant loss of productivity in hyperendemic areas. The question of "human values" should far outweigh the returns from the investment in the prevention and treatment of the disease.

6. Proper intensive education of the public on the scientific facts about the disease would serve to break down the leprosy complex, which is based on the concepts that leprosy is highly infectious, incurable, invariably associated with deformities and is an irrevocable retribution for sins.—(*Adapted from* authors' summary and conclusions)

Other Mycobacterial Diseases and Related Entities

Morrison, Norman E. and Collins, Frank M. Immunogenicity of an aerogenic BCG vaccine in T-cell-depleted and normal mice. Infect. Immun. **11** (1975) 1110-1121.

Aerogenic infection of adult thymectomized, lethally irradiated, bone marrow-reconstituted (THXB) C57B1 × C3H F_1 hybrid mice with 1 to 3,000 viable BCG Montreal was followed by an extended period of logarithmic growth to a maximum population of 5×10^6 bacilli by day 35. The infection

spread to the liver, spleen, and bone marrow with extensive multiplication in all test organs before the growth curves abruptly entered a stationary phase. Up to 30% of the THXB mice eventually died as a result of the ongoing BCG infection. There was no sign of an antimicrobial immune response in the THXB mice analogous to that seen in the control animals beginning about day 30. The THXB mice developed considerable immediate but no delayed hypersensitivity to PPD. Intravenous challenge of the BCG-vaccinated THXB mice with 10^5 virulent *Mycobacterium tuberculosis* Erdman indicated that they were as susceptible to the tuberculous challenge as a group of unvaccinated controls. Visible surface lesions developed on the lung 90 days postinfection in the T-cell-depleted host with a sharp rise in counts to 175 per lobe on day 120 followed by a plateau for the remainder of the study. Control mice developed visible lesions about day 50, with 225 lesions per lobe by day 70 and a sharp decline to undetectable levels by day 90. The histopathology of these changes was examined carefully, together with the rate of cellular proliferation (tritiated thymidine uptake) by lung and spleen cells as the BCG infection progressed in the THXB mice. Peak uptake by both organs was depressed during the early stages of the BCG infection in the T-cell-depleted mice, but later the incorporation rates were significantly elevated above control values as the infection progressed.—Authors' Abstract