

## RAT LEPROSY

### A CRITICAL REVIEW OF THE LITERATURE

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#### INTRODUCTION

Leprosy-like diseases have been reported in fish, birds and animals. The one that occurs in the rat is the only one which has attracted much attention. Those that have been found in other animals are discussed only briefly at the end of this review.

It is now more than thirty years since the occurrence of a leprosy-like disease in rats was first reported. Since that time more than one hundred articles have appeared. The subject is of considerable interest in itself, and this interest is enhanced by the fact that, because of the great difficulties attached to research in human leprosy—particularly the difficulties of cultivating the causative organism and the lack of a susceptible laboratory animal—leprosy investigators are turning more and more to rat leprosy as a possible indirect source of light on the problems of the human disease.

Much of the literature of rat leprosy has appeared in journals not easily obtainable and no attempt to survey it thoroughly has been made recently. The purpose of the present review is to summarize the principal publications, though a number of them have not been available or are available only in abstract, the latter applying particularly to reports by Japanese workers. Where

it seems desirable comments on the findings and opinions of various workers are given, and a few hitherto unpublished findings made by myself or communicated to me by others are referred to.<sup>1</sup>

#### NOMENCLATURE

When rat leprosy was first discovered in the brown rat, this animal was known as *Mus decumanus*. The disease was called rat leprosy, murine leprosy, and lepra muris or murium. The organism has been generally called Stefansky's bacillus or *B. lepra muris* or *murium*.

Since that time the brown rat has been renamed *Rattus norvegicus*. The disease, however, is still often called murine leprosy and lepra muris or murium. The bacillus, now classed as a mycobacterium, is often named *Mycobacterium leprae muris* or *murium*. This nomenclature is inconsistent. If the animal is *Rattus*, the names of the disease and the organism should be changed accordingly. In this review, however, I shall use the still current name *M. leprae muris*, and where necessary *M. leprae hominis* for the organism of human leprosy.

#### HISTORY, DISTRIBUTION AND INCIDENCE

*History.*—Two factors combined to bring about the discovery of rat leprosy in the early years of the twentieth century. First, there was great interest in bacteriology in general and in the acid-fast bacteria in particular. The discovery of the organisms of leprosy and tuberculosis had been followed by discovery of other acid-fast germs, including those found in dung, the soil, etc. Second, the development of plague prevention work in many countries had made the examination of great numbers of rats a routine procedure.

Apparently the attention of two independent workers, Stefansky in Odessa and Dean in London, was attracted by a peculiar condition often seen in brown rats. In 1903 Stefansky (110) published an excellent description of the disease and its causative organism. Dean had made similar observations before Stefansky's report appeared, and within a few weeks he published his first paper (26), but he did not dispute the priority of Stefansky's work. A few months later Rabinowitsch (100) reported finding the condition in Berlin, and since then it has been found in many countries.

<sup>1</sup>To minimize the number of reference figures in the text of this review, those figures that apply to authors who have only one article listed in the bibliography are given but once. The same is also done, as a rule, when two articles by the same author are listed of which one is the more important; in such cases references to the lesser articles are given as required.

*Distribution.*—Rat leprosy has been found in Odessa by Stefansky, in England by Dean and by Perrie and McAlister (97), in Germany by Rabinowitsch, in America by A. Walker (125), McCoy (82), and Wherry (136), in Rumania by Mezinescu (84) and Alexandrescu (3), in Japan by Honda (43) and many others, in Korea by Ishawara (45), in Puerto Rico by Ridlong (102), in Australia by Tidswell (114), Bull (17), Priestly (98) and others, in France by Marchoux and Sorel (71), in French Guiana by Theze (113) and Leger (57), in New Caledonia by Leboeuf (56), in Brazil by Azavedo (7), in India by Muir and Henderson (86) and an unnamed writer (4), in Kenya by de Smidt (personal communication), in Batavia by Lampe and de Moor (54). In fact, with a few exceptions it has been found wherever it has been sought. Ehlers, Bourret and With (29) failed to find it in the Danish Antilles, as did Brinckerhoff (15) in Hawaii.

*Rats affected.*—For many years nearly all recorded cases were found in *Rattus norvegicus*. However, the disease was found in India in *Rattus rattus* (4) and in Japan in *Rattus rattus alexandrinus* (47) and *Rattus rattus* (5). It has recently been reported from Batavia in *Rattus rattus diardii* and *Rattus concolor* (54), both of which showed a heavier incidence than *Rattus norvegicus*, and also in *Mus musculus* and *Pachyura murina*.

*Incidence.*—The frequency with which various workers have found the disease is shown in Table 1. The figures vary greatly

TABLE 1.—Frequency with which rat leprosy has been found in different countries.

Author (and reference number)	Place	Incidence (percent)	Number of rats examined
Stefansky (110)	Odessa	45.0	(?)
Cilento and North (23)	Australia	.2	7,504
Bull (17)	Australia	.0005	200,000
Fielding (33)	Australia	1.3	930
Priestly (98)	Australia	5.5	220
Richards (101)	Australia	.6	12,000
Ohtawara and Ichahara (92)	Japan	27.8	1,007
Walker (125)	U. S. A.	.5	2,700
Fidlong (102)	Puerto Rico	.053	5,700
Marchoux and Sorel (71)	Paris	5.0	1,296
Theze (113)	French Guiana	8.6	35
Leger (57)	French Guiana	33.0	49
Asami (5)	Japan	.8	2,157
Kitasato (48)	Japan	.8	5,000
Kawamura (47)	Japan	.05	9,000
Honda (43)	Japan	.83	600
Mezinescu (84)	Rumania	1.0	200
Wherry (136)	U. S. A.	.2	9,361
Leboeuf (56)	New Caledonia	3.0	99
Lampe and de Moor (54)	Batavia	9.0	5,000

for different countries and different parts of the same country; this is even true for different parts of the same city. Marchoux and Sorel for example, reported a general rate of 5 percent, but up to 45 percent in boneyards, slaughter houses, etc.

*Sex incidence.*—Most reports give no data bearing on the sex incidence. The following is all the information that I have been able to collect: Cilento and North (23) found 16 male and 9 female rats infected, a ration of 1.8:1. A. Walker found 10 males and 4 females affected, but Leger found more females affected than males. Ohtawara and Ichihara (92) found the sex incidence approximately equal in 280 leprous rats. Asami (5) found 11 affected males out of 907, and 6 females out of 1,257, respectively 1.2 and 0.5 percent. Lampe and de Moor found 133 males with leprosy out of 1,469 (9 percent), and 317 females out of 2,470 (13 percent).

*Age incidence.*—Asami concluded that the infection is confined to mature animals, and Leger noted that very few young rats showed it. Ohtawara and Ichihara also found the disease most commonly in adults, but stated that rats often contract it when young. Lampe and de Moor found a 9 percent incidence in adult rats and 2 percent in young ones.

#### THE NATURAL DISEASE

Stefansky's original description was excellent. The following is a summary:

The disease occurs in two forms, "glandular" and "musculo-cutaneous." In the former the lymph glands alone are involved. There may be a generalized involvement affecting the inguinal, axillary and cervical groups, or only one gland or group may be affected. The glands are enlarged and hard and occasionally show small areas of softening or caseation. In the musculo-cutaneous form, which is less common, there is cachexia, the skin is strewn with whitish areas of varying sizes covering sometimes the whole neck or chest, from which hairs have been shed, and there are sometimes nodules which may be as large as a pea. At points subject to trauma (the chest and joints) the nodules may ulcerate. On cutting these areas the skin is found to be atrophied, the subcutaneous tissue invisible, and immediately under the skin is seen a grayish-white mass of soft, friable muscle that may be 1 cm. thick. The glands are also affected in this form.

Other descriptions of the disease agree in all essentials with that of Stefansky. Dean described one rat with the musculo-cutaneous form, his description differing from Stefansky's only in that there was more caseation and necrosis. Later he described six more cases (27). He found no distinct line of demarkation between the two forms of the disease. Alopecia was a marked feature. He noted affection of the mammary glands, the cervical lymph glands, and

the submaxillary salivary glands. Visceral lesions were rare, but one rat showed a necrotic area in the liver. One showed loss of toes, but Dean thought this was possibly traumatic.

Descriptions of the disease which call for no special mention include those of Rabinovitsch, Tidswell, A. Walker, Wherry, Mezinescu, Honda, and Iitoyo and Sakai (44). McCoy pointed out that in the glandular form the gland enlargement may be extreme, that in the musculo-cutaneous form ulcers are more frequent than alopecia, and that lesions may be found in the peritoneum and in the liver and spleen. Leger reported finding lesions in the livers of 3 out of 14 leprosy rats in French Guiana.

The description by Marchoux and Sorel mentions the following features:

The glandular form is usually found only postmortem. Besides the superficial gland groups, the mediastinal glands are sometimes affected. Enlargement may be very marked. However, glandular enlargement is not diagnostic; non-leprosy rats often have large glands, and leprosy rats may have comparatively small ones. Only one gland or group may be affected. In the musculo-cutaneous form the animals are cachectic, move with difficulty and can sometimes be captured by hand. They show more or less alopecia. The skin is thin, irregular and adherent. Nodules are often seen, sometimes attaining the size of an almond. Ulceration is common. In the milder forms the inner surface of the skin may be covered with very small projecting nodules; later the skin is detached with difficulty, the fatty tissue having been replaced by connective tissue. The infection is most marked in the posterior part of the body, either dorsally or ventrally. It produces a kind of casing of new-formed tissue terminating symmetrically in points directed towards the anterior part of the body. The cervical lymph glands and submaxillary salivary glands are sometimes affected, but no marked lesions of the internal organs are seen. The glandular and musculo-cutaneous forms are merely early and late stages of the same disease.

A thorough survey of the disease in 500 naturally infected rats has been made recently by Lampe and de Moor. All showed infection of the lymph nodes.

Nearly one-half (213) had both inguinal and both axillary groups involved; about one-quarter (114) showed affection of one or both inguinal groups only; while in but half as many (58) only the axillary groups were involved. The cervical or mesenteric glands showed involvement in 146 of these animals; in 53 only the cervicals were affected, in 10 only the mesenteric glands and in 83 both groups.

These authors in 185 instances found the skin at the root of the tail the commonest place for manifest lesions. Only 14 rats showed outward signs of the disease, and in 9 instances they were slight. The disease was considered probably progressive in 37 percent of the infected animals, contrary to the opinion generally held that it is usually a latent condition.

## TRANSMISSION

## NATURAL TRANSMISSION

The fact that the lesions of rat leprosy are commonly confined to the superficial lymph glands and to the skin and subcutaneous tissue suggests that the disease has a superficial origin, probably in the skin or possibly in the mucous membranes. Numerous experiments have been made to ascertain the mode of transfer and portal of entry of the infection in the natural disease. Most workers have found that actual contact with an infected rat or with infected material is necessary for transmission.

As an example of natural transmissibility may be cited an experiment by Currie and Hollmann (25). Eleven healthy rats were placed in the same cage with several leprosy ones well advanced in the disease. After remaining in the cage several months, they were removed and kept under observation for nearly a year, and then sacrificed. Seven showed leprosy. However, Wayson (134) says that he has observed apparent indirect transmission. Normal rats kept in separate cages several inches distant from the one containing the diseased rats became infected.

## INSECT TRANSMISSION

The possibility that the disease is transmitted by biting insects has been the subject of several investigations, especially with reference to the various animal parasites of the rat.

Wherry (137) found no acid-fast bacilli in pediculae, syphonaptera and tabanidae caught on rats dying of leprosy, but later (138) he reported finding them in lice from leprosy rats but not in those from healthy ones. Flies fed on leprosy material harbored bacilli in the intestines for not more than forty-eight hours, as they were excreted in large numbers. Larvae hatched in leprosy material became infected but the bacilli were soon excreted. Infected larvae could pupate but the pupae did not develop further.

Marchoux and Sorel (72) searched for bacilli in lice (*Haematopinus spinulosus*), fleas (*Ctenocephalus serrabiceps*) and mites (*Laeleps echidninus*). Fleas fed on highly infected rats were negative. In lice they found partially acid-fast bacilli differing from the Stefansky bacillus. They transferred lice from heavily infected rats to young healthy grey ones. Though acid-fast bacilli were later found in the glands of some of these rats, controls gave similar findings and an experiment with white rats was negative, so they concluded that lice do not transmit the infection. Acid-fast bacilli were found in 2 percent of the mites examined. These bacilli were of three kinds: (a) short, thick ones like those found in the lice, (b) a long filamentous form decolorized by alcohol, and (c) numerous forms similar to those of rat leprosy which they considered might possibly be of that nature. However, infected mites were found equally on rats without leprosy. To investigate the possible rôle of sarcoptes in spreading the infection they placed a male rat suffering from both leprosy and itch with four female white rats. All of the females died within four months and all showed itch, but none showed acid-fast bacilli.

Currie and Hollmann found acid-fast bacilli in a mite (*Laeleps echidninus*) which had fed on a rat with ulcerating skin lesions. They transferred 32 mites from a heavily infected rat to three others (*alexandrinus*); twelve months afterward they showed no evidence of infection. One hundred house flies fed on leprosy material were placed in a cage with two rats whose skin had been artificially abraded, but infection did not occur.

Marchoux (67) fed 200 flies on leprosy material and placed them with rats with artificial skin abrasions. The flies fed on the abrasions, and the rats all developed leprosy, but this did not occur if the flies were placed with the rats more than twenty-four hours after feeding. It was concluded that bacilli were carried on the proboscis and feet but did not remain viable more than twenty-four hours. Flies dissected after feeding contained in their intestinal contents bacilli which proved infectious. Bacilli were found in the intestines for four days, but they did not multiply. Marchoux concluded that in nature the transmission of infection by flies, either by excreta or by contamination of sores by bacilli on the proboscis and feet, is possible but extremely rare.

Markianos (75) failed to transmit rat leprosy by the bites of lice fed on infected rats or by feeding such lice to rats, but he produced the disease by grinding up and injecting infected lice.

From this summary it will be seen that up to the present there is very little evidence to show that insects commonly transmit the disease.

#### TRANSMISSION BY FOOD

Rats commonly attack and devour other rats, especially those that are enfeebled by disease or have died naturally, so it is possible that leprosy may be conveyed by eating infected tissue.

Marchoux and Sorel fed eight young rats on heavily infected material. Two of them developed definite signs of leprosy and one other had acid-fast bacilli in the mesenteric and mediastinal glands and the apices of the lungs. The other six died with no signs of the disease.

Muir and Henderson made a similar experiment, giving from three to nine feeds. Of 24 rats examined, 3 showed acid-fast bacilli in the spleen (2 cases), prevertebral glands (2 cases), mesenteric glands (1 case), axillary glands (1 case), and liver (1 case). No mention was made of lesions in the mediastinal glands or the lungs.

It is clear that, while the eating of infected material can produce infection in a small percentage of instances, the lesions produced are not those commonly seen in natural rat leprosy. This mode of infection, therefore, is probably unimportant in nature.

#### INFECTION OF MUCOUS MEMBRANES

Dean (27), having found bacilli in the nasal discharge of infected rats, suggested that this might be the site of the initial lesions. Wherry (137) reported similar findings. Marchoux and Sorel also found bacilli in the nasal discharge, but did not find that the initial lesion was located in the nose.

Marchoux and Sorel swabbed vigorously the noses of twelve young rats with cotton-wool saturated with infected material, with negative results. However, Wayson has recently succeeded in transmitting the infection by placing an inoculum on the nasal mucous membrane of normal rats.

Marchoux and Sorel also placed infective material on the vulva of four female rats, without producing the disease. The four males living in the same cage remained normal, and several litters of healthy rats were born. Infected material was inserted under the prepuce of two male rats, which were kept in the same cage with four females. At the end of a year the females were found normal but both males showed large inguinal glands with many bacilli.

#### INFECTION THROUGH THE SKIN

Several workers have investigated the skin as the possible portal of entry of the infection, with more positive results than in the other fields.

Marchoux and Sorel washed with infected material eight very young rats, still bald but with healed umbilicus. None subsequently showed any sign of leprosy. With six young rats they scarified slightly areas of skin from which the hairs had been pulled and rubbed these areas with infected material. In all of these animals leprosy developed later in the glands, and in some cases at the point of inoculation. Muir and Henderson reported a similar experiment with nine rats, with positive results in three only.

From these and other similar experiments it seems fairly certain (a) that the infection is conveyed through the skin, (b) that the intact skin is unaffected, but (c) that the slightest abrasion makes infection possible. There is in rats an obvious cause of frequent abrasions. Rats are great fighters and bites are very common. If, as has been reported by Dean and by Marchoux and Sorel, the salivary glands are infected, it is possible that a bite made by an infected rat may be infected by saliva. It is probably more common for a bite by a healthy rat to be infected later, probably by direct contact with leprosy material. Bites probably act in two ways: one in a leprosy rat may provide a means of exit for the bacilli, while one in a healthy rat may provide a portal of entry for them.

Walker and Sweeney (126, 127, 128) consider that leprosy is a soil infection and is contracted by rats through contamination of wounds by the soil. Ohtawara and Ichihara (92) considered that the disease is most likely transmitted through grain or vegetables or from the earth. There is very little evidence in support of these views.

#### CONGENITAL TRANSMISSION

Only two citations can be made with reference to this interesting question.

Marchoux (68) holds that rat leprosy is never congenital. Rats born of leprosy female rats are healthy, and if they are separated from the mothers they



do not develop leprosy later. When the disease is advanced the genital organs are affected so as to produce sterility; in the milder forms they are not affected.

Le Guyon (58) found that all rats born of leprosy female rats died within five weeks, but on autopsy showed no sign of the infection. Death was apparently due to malnutrition from suckling by the diseased mothers, of which the mammary glands were often affected by the disease. Emulsions made from the organs of the young rats produced no disease in others. Le Guyon changed the litters of a healthy and a leprosy rat and found that the rats suckled by the leprosy mother all died in five weeks, while those suckled by the healthy rat remained healthy, though born of a leprosy one.

#### EXPERIMENTAL TRANSMISSION

Several instances of experimental transmission have been given in the foregoing section, and others will appear in the one to follow. Here are summarized the experiments of some of the earlier students of this disease.

Stefansky tried to infect other rats with material taken from rats found infected in nature. He reported that 5 cc. of an emulsion rich in bacilli injected subcutaneously into white rats was absorbed in three or four days, and one or two months later no bacilli or lesions were found. Similar results followed intraperitoneal injections of large doses except that in several isolated cases examined forty-four days after inoculation the omentum was found to be swollen and hard, with purulent cavities containing many bacilli; a few bacilli were also found in the spleen and the inguinal and mesenteric glands. Stefansky concluded that he had failed to transmit the disease, but apparently he kept the experimental animals under observation for only two months.

Dean reported that he found no evidence of disease two months after pocketing a fragment of leprosy tissue in the abdominal skin of healthy rats. Later, however, he reported that injection of emulsions of infected tissue was followed by the development of marked lesions in many rats, and that the infection could be carried on in series. He attributed his own and Stefansky's previous negative results to the fact that the experimental animals had not been kept under observation for a sufficiently long time, six months at least being usually necessary for marked lesions to develop.

Dean's findings were soon confirmed by McCoy and by Alexandrescu, and since that time experimental transmission has been found to be very easy, every experimental animal becoming infected after the injection of even small doses of bacilli. Subcutaneous, intradermal, intravenous, intracardiac, intraperitoneal and intraocular injections have all been used for the purpose.

#### THE EXPERIMENTALLY INDUCED DISEASE

The following is a summary of the results reported by different workers using various methods of inducing the infection.

*Subcutaneous inoculation.*—Dean obtained skin lesions at the site of injection, usually with a local and sometimes general glandular

involvement. Marchoux and Sorel reported similar results except that the local skin lesion was rarely seen. Henderson (41) and Fukamachi (37) reported results similar to those of Dean. Lowe (62) verified these results and found that if the infected animals were kept under observation long enough a generalized condition developed, with involvement of the internal organs.

*Intraperitoneal inoculation.*—Dean reported lesions in the omentum, the parietal and visceral peritoneum, and sometimes the liver and spleen. The mediastinal glands were involved and the infection spread to the pericardium. The lungs were affected only late, when lesions in the peribronchial lymphatics were found. McCoy, Alexandrescu, Marchoux and Sorel, Fukamachi, and Lowe have reported similar findings. Muir, Henderson and Landeman reported the occurrence of large, tumor-like growths in the omentum, which Muir later concluded to be due to secondary infection.

*Inoculation of the scarified epidermis.*—Marchoux and Sorel produced local skin lesions as well as glandular lesions by this method, those of the skin being much more marked than when produced by subcutaneous injection.

*Intradermal inoculation.*—Lowe produced marked skin lesions and glandular involvement by this method. A year after the inoculation, the infection was found to be generalized.

*Intracardiac inoculation.*—Lowe obtained rapid general infection of the viscera by this method, the most marked lesions being in the liver, spleen and bone marrow.

*Intravenous inoculation.*—Bernard (11) produced a generalized infection by intravenous injections into the tail vein.

*Intraocular inoculation.*—Guilliny and Montestruc (40) produced lesions in the ciliary body by inoculating the anterior chamber of the eye. Chorine, Guilliny and Montestruc (22) observed later a marked invasion of the eye and the surrounding tissues.

*Secondary infection of the inoculum.*—Marchoux (66) reported that the injection of an uncontaminated inoculum caused the glandular form of the disease, while the injection of a contaminated inoculum gave rise to the musculo-cutaneous form. This seems to conflict with the statement of Marchoux and Sorel, already quoted, that the two forms are merely early and late stages of the disease, which is in accordance with the general experience.

#### PATHOLOGY

Most workers have found that the distribution of the path-

ological changes in the natural disease is somewhat different from that seen in animals infected experimentally. In nature the organs principally affected are the lymph glands and the skin and underlying muscles, while the internal organs show little involvement. In laboratory animals the skin affection is usually much less, the gland affection is about the same, and the visceral involvement is very much greater than in the natural disease. Nevertheless, the essential pathological changes appear to be identical and the difference is probably due to the comparatively large number of bacilli introduced in experimental infections.

#### LYMPHATIC GLANDS

Stefansky described changes in the axillary, inguinal, submaxillary and cervical lymph glands.

The glands are large and hard, sometimes with small areas of softening. Microscopically there is seen thickening of the capsule and trabeculae. The sinuses contain large masses of endothelial cells with much protoplasm and a large nucleus, most of which contain enormous numbers of bacilli. Multinucleate giant cells full of bacilli are often seen. The connective tissue cells of the capsule also contain bacilli. There are none in the lymphocytes and very few in the follicles.

Dean and Marchoux and Sorel have given similar descriptions. Marchoux and Sorel and several other workers observed frequent involvement of the mediastinal glands.

#### SKIN AND SUBCUTANEOUS TISSUE

Stefansky's description of the naked-eye changes in the skin has already been quoted. The microscopic appearances he described as follows:

In the epidermis there is little change, but a few bacilli may be found. The dermis is atrophied, edematous and infiltrated by inflammatory cells, with many such cells around the vessels. The subcutaneous tissue is infiltrated with cells full of bacilli; they are grouped in little lobules or elongated bundles so dense that the masses of bacilli are confluent from one cell to the other, and one can see nothing except the cell nuclei and the bacilli. Separated by layers of cells, these lobules appear to correspond to fatty lobules that are no longer detectable. There are numerous large cells with abundant protoplasm and many bacilli that resemble the lepra cells of Virchow except that they show no vacuolation. A few bacilli are seen in lymphatic spaces. The blood vessels show little change, but their endothelial cells sometimes contain bacilli.

Marchoux and Sorel's description is summarized as follows:

In the dermis the infection starts in the loose perivascular tissue. The vessels are enclosed in a sheath of heavily infected cells. The sebaceous glands are surrounded by leprosy nodes and they are finally atrophied; the glands themselves contain no bacilli. The hair follicles are also compressed and destroyed, and this causes the alopecia so often seen. Infected cells invade the papillary

zone and spread out under the germinative layer of the epidermis; some invade the Malpighian layer. Sometimes most of the cells of the epidermis contain bacilli, but those of the Malpighian layer are principally affected and are destroyed, and it is due to this that ulceration often occurs. In the subcutaneous tissue are large masses of bacilli; the lymphatic spaces of the connective tissue are destroyed and the tissue itself is altered, becoming fibrotic and cicatricial, filled with infected leucocytes. The infection spreads until finally it forms a casing from which all fatty tissue has disappeared.

Henderson made a careful study of the development of lesions in the skin at the site of inoculation.

Between one and eight days after inoculation there was infiltration of the corium and the superficial layer of the subcutaneous tissue with lymphocytes and lepra cells containing a few bacilli. In the period from two to eleven weeks the bacilli and cellular infiltration steadily increased. Some of the lepra cells assumed a fibroblast-like form. There were foci of heavy infection with cells of indistinct outline full of bacilli massed together; no giant cells were seen. The nuclei of heavily infected cells underwent karyorrhexis, but the cells contained enormous numbers of bacilli without disintegrating. After the third month the infection spread up towards the epithelium. Lepra cells and lymphocytes were found around the sebaceous glands and hair follicles. After the twentieth week, in densely infected areas, foci of necrosis appeared and the whole of the corium and most of the subcutaneous tissue was converted into a lepromatous mass full of bacilli, the mass extending up to the epithelium in which, however, few or no bacilli were found. Necrotic foci were numerous but no liquefaction occurred. Finally the epithelium broke down, with ulcer formation and secondary infection. There was increase of the "mast" cells containing acid-fast granules; those are also found in healthy animals and have to be differentiated from cells containing granular acid-fast bacilli.

Lowe noted that in experimental animals the skin lesions are confined to the area round the point of inoculation until the advanced stage of the disease, when perivascular lesions can be found in the skin of most parts of the body. These lesions sometimes ulcerate.

#### MUSCLES

Stefansky described the lesions in the superficial muscles in the musculo-cutaneous form of the disease.

These lesions begin in the skin whence they may spread deeply into the skeletal muscles, which may be markedly affected. Microscopically some muscle fibers may show little change, but bacilli are seen near their nuclei. They lose their transverse striation, later disintegrating to leave nothing but the nuclei and the bacilli. Here and there are masses of leucocytes containing bacilli; these masses may be as big as a pea and constitute a muscle abscess.

Dean and Alexandrescu both gave similar descriptions, but Marchoux and Sorel found that the muscle fibers are compressed and atrophied as a result of the development of the infected tissue between the bundles, and that the fibers themselves are not infected. The findings of Henderson and of Lowe are in agreement with this. Lowe reported involvement of the heart muscle after intracardiac injection.

## ABDOMINAL VISCERA

Stefansky observed no visceral lesions in natural rat leprosy, but Dean found that intraperitoneal inoculation produced marked lesions in the omentum, peritoneum and sometimes in the liver and spleen. McCoy found lesions in the spleen of leprosy rats, and Leger observed lesions of the liver in three out of fourteen leprosy rats caught in French Guiana. Marchoux and Sorel rarely found marked lesions of the internal organs in the natural disease or after subcutaneous inoculation. They and Muir, Henderson and Landeman verified Dean's findings of marked lesions in the viscera after intraperitoneal inoculation. Lowe always found such lesions in animals inoculated by any route, even with small numbers of bacilli given intradermally, provided they could be kept living for a sufficient period. The necessary period was from three months to a year or more, depending upon the method of inoculation and the number of bacilli given. Development was rapid after intracardiac injection, slower after intraperitoneal injection, and still slower after subcutaneous or intradermal injection.

*Liver.*—Neither Dean, nor Marchoux and Sorel, nor Leger gave any detailed description of the liver lesions. Muir, Henderson and Landeman described infection of the liver from the portal vein, which produced proliferation of Kupffer cells and formed nodules which broke down and affected the liver tissue by pressure. Lowe found bacilli inside Kupffer cells in a few minutes after intracardiac inoculation; those cells had multiplied in a few days, there was marked increase of the cells and bacilli in a few weeks, and in three months there had appeared definite macroscopic lesions consisting of round or oval masses of proliferated endothelial cells crammed with acid-fast bacilli. These lesions, gray in color contrasting with the liver substance, increased in size and number, often undergoing caseation, until the liver was enormously enlarged, when the animal died. The actual liver tissue was affected only by pressure. Bernard (11) also described finding bacilli in the liver a few minutes after intravenous inoculation, and Afanador and Bernard (2) described the subsequent development of marked lesions.

*Spleen.*—Dean mentioned superficial involvement of the spleen after intraperitoneal inoculation, and Currie and Hollmann reported the frequent and early finding of bacilli in that organ. Marchoux and Sorel found occasional lesions in the spleen in the natural disease, and heavy infection after intraperitoneal inoculation, which Muir, Henderson and Landeman also saw in one instance.

McCoy reported cases with marked involvement. Lowe found the spleen always involved if the animal was kept alive long enough. The lesions were produced most rapidly after intracardiac injection; within a few minutes bacilli were found in the reticulum cells, within one month there was marked proliferation of cells and bacilli, and later large masses of lepra cells full of bacilli were visible, first microscopically and later macroscopically, the spleen finally becoming very large and studded throughout with these masses. The Malpighian corpuscles were rarely affected, the bacilli being found in the interstitial tissue and the sinuses. Bernard reported finding many bacilli in the splenic sinuses within a few minutes of intravenous injection, and Afanador and Bernard reported the subsequent development of slight lesions at the edge of the Malpighian corpuscle.

*Peritoneum and omentum.*—Dean obtained marked lesions of the peritoneum and omentum after intraperitoneal inoculation. McCoy, Alexandrescu, Marchoux and Sorel, Muir, Henderson and Landeman, Lowe and others have confirmed this finding. Eight or ten months after inoculation the omentum often has become a large solid mass several grams in weight, consisting of an accumulation of cells crammed with bacilli. This fact makes intraperitoneal injection a useful method of obtaining material rich in bacilli for experimental purposes.

#### RESPIRATORY SYSTEM

*Nasal mucous membrane.*—This tissue has been found to be affected in natural rat leprosy by Dean, Wherry (137) and Marchoux and Sorel.

*Lungs.*—Stefansky observed no lesions in the lungs, but Dean found that after intraperitoneal injection lesions sometimes occurred in the peribronchial lymphatics. Marchoux and Sorel concluded that the lungs act as a filter, and that bacilli so removed from the blood are transferred to the mediastinal glands, where marked lesions were often found; lesions of the lungs themselves are rare, bacilli in them are never numerous and nodules are never seen. Currie and Hollmann reported quite different findings; they stated that leprosy pneumonia was the earliest and most constant of the visceral lesions. Lowe found that lung lesions are common only in a late stage; they take the form of nodes arising in the peribronchial lymphatics but, as Marchoux and Sorel reported, the mediastinal glands frequently show marked involvement.

## DIGESTIVE SYSTEM

*Gastro-intestinal tract.*—This tract is apparently unaffected, for lesions of it have not been reported. Since the disease can occasionally be acquired from infected food, it must be that the mucous membranes are traversed by the bacilli without injury.

*Salivary glands.*—Leprous lesions spreading from the submaxillary lymph glands to the submaxillary salivary glands have been reported by Dean, Marchoux and Sorel, and Chorine, Guillyny and Montestruc. Lowe (unpublished) has failed to verify this, finding only a few bacilli in salivary glands in the last stage of a generalized infection.

*Liver.*—The lesions in the liver have already been described.

*Pancreas.*—No lesions of this gland have been reported, and Lowe (unpublished) has made many examinations without finding any.

## GENITO-URINARY SYSTEM

*Kidneys and bladder.*—Dean found that only the capsules of the kidneys were affected, while Marchoux and Sorel very occasionally found lesions in the kidneys themselves and in the bladder. Lowe did not see lesions of the kidney, though in very advanced stages the glomeruli frequently contained bacilli apparently filtered from the circulating blood; masses of bacilli were also found under the epithelium of the pelvis, of the kidneys and of the bladder. Afanador (1) found that five minutes after intravenous injection bacilli were present in the renal vein and the capillaries, some in the glomeruli, and a few in the tubules. Many were found in the urine for two days, and excretion continued for twelve days. Berny (13) found no spontaneous bacilluria, or bacilluria after the administration of potassium iodide. However, novarsenobenzol injected into heavily infected rats produced a bacilluria starting in twenty-four hours and lasting for five or six days.

*Sexual organs.*—The testes and seminal vesicles are infected in the last stages of the disease, according to Lowe, and the ovaries, fallopian tubes and uterus also show massive infection then. The same is true of the mammary glands, according to Marchoux and Sorel. On the whole the female sex organs are more affected than those of the male.

## OTHER ORGANS

*Nervous system.*—Dean found one leprous rat with a deformity of the foot that may have been either trophic or traumatic.

Marchoux and Sorel stated that lesions in the nervous system are rare, and the findings of Fukamachi were in agreement with that view. On the other hand, Takeuchi (112) reported that the nerves are affected as in human leprosy; this is the only published statement of this nature. Lowe found the nervous system unaffected, though (unpublished) he has found a few bacilli in the brain, spinal cord, meninges, and peripheral nerves of rats dying of a massive generalized infection. Chorine, Guilliny and Montestruc found that the infection did not spread to the optic nerve, brain or meninges after intra-ocular inoculation.

*Glands of internal secretion.*—Lowe (unpublished) has found slight but definite lesions in the thyroid gland and marked infection of the parathyroid and suprarenal glands in advanced cases.

*Bone marrow.*—The bone marrow was reported by Dean to be affected. Most workers have not studied this matter. Lowe found that it was affected comparatively early, and that ultimately it became little more than a mass of bacilli.

*Eyes.*—Uchida (121) found that 10 percent of naturally infected rats showed eye affections, consisting of infiltration of the eye-lids encroaching onto the conjunctiva and spreading backwards around the eyeball to form a focus about the optic nerve. The lachrymal gland showed moderate involvement. The cornea and optic nerve were little affected, and there were no lesions inside the eyeball. Lowe (unpublished) has confirmed these findings experimentally. Guilliny and Montestruc found slight lesions in the ciliary body of one rat, and conjunctival lesions in another. Intraocular inoculation of small numbers of bacilli produced infection of the ciliary body, with rapid multiplication of bacilli in the anterior part of the eye, but the posterior part was little affected.

#### CYTOLOGY

*Lepra cells.*—Stefansky described the characteristic cells of rat leprosy as endothelial cells with much protoplasm and a large nucleus, often containing many bacilli. Henderson noted that they sometimes assume a fibroblast-like form. Lowe described them as large round or oval cells having a large vesicular nucleus staining rather faintly, and abundant protoplasm sometimes showing vacuolation.

Marchoux and Sorel described the lepra cells as of mesodermic origin. Friedheim (36), investigating their origin and nature in cultures, concluded that they were either monocytes or lymphocytes



which had increased in size. Previously Oliver (94), by vital staining with trypan blue, had shown that they are really fixed-tissue histiocytes. Henderson and Lowe have confirmed this, the latter concluding that rat leprosy is essentially an infection of the reticulo-endothelial system.

*Giant cells.*—Multinucleate giant cells full of bacilli were seen in the lymph glands by both Stefansky and Dean, and Lowe found them frequently in other organs as well. These cells, which may be 70 or 80 microns in diameter, Marchoux and Sorel believed to be formed by fusion of swollen lepra cells.

*Relation of cells to bacilli.*—Stefansky observed that the bacilli were nearly always intracellular, a fact confirmed by later workers. Marchoux and Sorel believed that because of their waxy coating they resist destruction and multiply, in spite of their location; the distended cell finally bursts and other cells engulf the liberated bacilli. Lowe agreed with this opinion that the lepra cell forms a culture medium for the bacilli.

#### BIOCHEMICAL CHANGES IN TISSUES

Emerson, Anderson and Leake (30) studied the lipolytic activity of rat leprosy tissues in order to investigate the suggestion made by Walker and Sweeney that the action of chaulmoogra oil in leprosy might be due to stimulation of that activity. They found the lipase content of leprosy tissues to be significantly and constantly lower than in nonleprosy tissues in the same animal, or the same tissues of a healthy rat. They also found (31) that injections of chaulmoogra preparations did not increase lipolytic activity.

#### BACTERIOLOGY

##### MORPHOLOGY AND STAINING

Stefansky described the bacillus as a rod 3-5 microns in length with slightly rounded ends and often showing, when stained, a granular appearance. It stained well by Gram's method and with cold carbol-fuchsin, resisting decolorization with 5 percent sulphuric acid and 90 percent alcohol. Rabinowitsch considered that it was clearly distinguishable from other, cultivable, acid-fast bacilli, but had a very close affinity to that of human leprosy.

Marchoux and Sorel stated that it resisted decolorization as well as or better than Hansen's bacillus; 10 percent nitric acid, 25 percent sulphuric acid, and 3 percent hydrochloric acid in alcohol did not decolorize it quickly. They found that the bacilli are

sometimes distinguishable from Hansen's bacilli by their grouping; they do not show the same parallel arrangement, are not being surrounded by gloea, and do not form globi. They noted that the bacilli were not uniform, some being short and some long, some showing terminal swellings and some a coccothrix form. They thought that the coccothrix-like organisms were degenerated forms, but Marchoux (68) later changed his opinion on that matter.

#### VIABILITY

Marchoux and Sorel found that bacilli desiccated over sulphuric acid were no longer infectious, apparently were killed, a conclusion indicated by Marchoux's experiments on transmission by flies, already quoted. They found that the bacilli resisted a temperature of 60°C. for five, but not for fifteen minutes; Muir and Henderson found them killed after twenty-five minutes at that temperature. Chorine (21) reported that the bacilli kept in 4 percent glycerin-saline remained pathogenic for 39 months but were dead after 51 months. Lowe kept them alive for several weeks in a moist condition at a temperature a little above freezing. Marchoux and Chorine (69) found that they resisted 5 percent sulphuric acid and 15 percent antiformin (time not stated). Tisseuil and Chorine (118) mixed an emulsion of leprosy material with basic fuchsin in alcohol, which stained the bacilli but did not kill them. Lowe (unpublished) confirmed this, and also found that the stained bacilli survived 1 percent hydrochloric acid for ten minutes. He (63) found that leprosy material treated with 1 percent sodium hydncarpate for twenty hours had not lost its pathogenicity.

*(To be concluded)*