SUSCEPTIBILITY OF WILD RODENTS TO THE MURINE LEPROSY BACILLUS

SHINJI NISHIMURA

Department of Leprosy, Research Institute for Microbial Diseases, Osaka University
Osaka, Japan

Attempts to infect animals of the murine family other than the natural host (the rat) with the murine leprosy bacillus are of interest because of the role they may play in clarifying the problem of transmitting human leprosy bacilli to animals. I have reported previously on the infection of hamsters with the murine bacillus ([3]), and preliminary reports have been published recently on the susceptibility of several wild mice to it ([5, 6]).

In the present communication the findings in later studies are summarized. The susceptibility of wild rodents to the murine leprosy bacillus is discussed; the histopathologic findings of the lesions in the already known species, i.e., Rattus, Mus and Mesocricetus (hamster), and in the recently tested species of Apodemus, Meriones and Microtus, are compared; and suggestions are advanced regarding the problem of transmission of lepra bacilli to animals.

MATERIAL AND METHODS

Rodents used.—The four species of wild mice used were *Apodemus speciosus speciosus, Apodemus geisha geisha, Meriones unguiculatus,* and *Microtus montebelli montebelli.* The Apodemus and Microtus animals are native to the mountainous areas of Kamikochi, Nagano prefecture, and Kyoto city. The specimens of Meriones and some of Microtus were obtained from the Tokyo Central Experimental Animal Laboratory where they are bred.[1]

Apo. speciosus closely resembles the house mouse in form, but is slightly smaller. The length of the head and body is less than 120 mm., and the tail is less than 120 mm.; the average weight 30-40 gm. The color of the fur of the back is yellowish brown, and the belly is white.

Apo. geisha also resembles the house mouse but is even smaller in size than the speciosus variety. The head-body length is 77-90 mm., the tail 86-100 mm., and the weight about 30 gm. The color of the back is yellow-brown, and the belly is grey. This animal is peculiar to Japan.

Mer. unguiculatus is a small animal weighing 40-50 gm., with a long tail and long hind legs like a kangaroo. The head-body length is less than 125 mm., and the tail less than 98 mm. The hair of the back is light yellow-brown, and the belly is white. It is native to the plains of central and western Manchuria.

Mic. montebelli is a species of short-tailed field mouse. The head-body length is less than 132 mm., and the tail is short and less than 49 mm. The hair of the back is blackish-brown, and the belly is grey. It is found in the central and northern parts of Honshu, Japan.

Inocula and inoculations.—For the initial inoculations, the Kumamoto strain of murine leprosy bacillus maintained in the rat was used. The leproma was suspended in saline and 10^{-2}, 10^{-3} and 10^{-4} dilutions prepared. *Apo. speciosus, Apo. geisha,* and

[1] To simplify the use of the names of these animals as they appeared in the manuscript, the generic names will where permissible be abbreviated: Apodemus to Apo., Meriones to Mer. and Microtus to Mic. There being no apparent reason, in the present connection, for using the reduplicated species names, the repetition is avoided hereafter.—EDITOR.

Mic. montebelli were inoculated subcutaneously, and the *Mer. unguiculatus* animals were inoculated by three routes, subcutaneously, intraperitoneally and intratesticularly. The first lepromas in the speciosus, geisha and unguiculatus mice were made into suspensions and back-passed.

Observation of results.—The responses of the animals to the inoculations are rated in terms of (*a*) the time required for lepromas to appear following the injection of the different infecting doses; (*b*) of the enlargement, persistence or healing of lesions; (*c*) of the histologic picture; (*d*) of the number of bacilli found in the lesions; and (*e*) of the transmissibility of the induced infection to rats, mice or the homologous species of wild rodent. Histologic specimens for the rat, mouse and hamster were selected from material collected in previous experiments. In all instances the tissues were fixed in formalin, and paraffin sections were stained by the hematoxylin-eosin, van Gieson, or Ziehl-Neelsen methods, and occasionally the Bielschowsky silver method.

RESULTS

The results which are most important for comparative purposes are summarized in Table 1.

Apo. speciosus: Subcutaneous inoculation of a 0.2-0.25 $\times$ 10^{-2} suspension resulted in the local formation of a pea-sized nodule after 2-3 months. This nodule gradually increased in size and developed into a typical leproma. There was massive proliferation of bacilli within the lesion cells, and transfer inoculations into animals of the same species resulted in a similar infection. Back-passage in rats and mice also resulted in infection. The organs in general were macroscopically normal, although bacilli were present in the more severely infected animals after 26-29 months. The lymph nodes, however, showed moderately severe changes and contained numerous bacilli.

Apo. geisha: A pea-sized granuloma with a necrotizing center developed at the site of inoculation after 3 months in this animal, too. A massive quantity of bacilli was present in the necrotic focus, but there were relatively few in the surrounding granulomatous tissue. Differing from the typical rat leproma, this lesion did not enlarge. Although a small number of bacilli was found in the inguinal lymph node, there were no changes or bacilli in the other organs. A second passage in the same species resulted in the formation of small pea-sized lesions after 3 months, but there was no further development. However, the back-passage of the bacilli recovered from the lesion after 6 months into the mouse resulted in infection. In other words, a typical leproma is not formed in this animal, but the bacilli in the lesions remain viable over a long period of time.

Mer. unguiculatus: Intraperitoneal inoculations with either heavy or light doses produced only small nodules in the omentum which did not develop progressively, and lesions were not produced elsewhere. Although the nodules contained a few bacilli, there were no signs that they had proliferated. Lesions appeared relatively early after subcutaneous inoculations of heavy doses (10^{-1} and 10^{-2}, but not 10^{-3}) and then formed abscesses containing many bacilli, but these lesions were gradually absorbed with the passage of time. Passage of bacilli from the

TABLE 1.—*Results of inoculation of wild mice with the murine leprosy bacillus.*

Species	Inoculation				Local lesion			Fate		Bacilli					Passage inoculation (months)		
	Source of inoculum[a]	Number of animals	Route[b]	Suspension	Produced after (months)	Leproma or granuloma[c]	Progress	Killed (months)	Died (months)	Local lesion	Lymph nodes	Lung	Liver	Spleen	Same species	Rat	Mouse
Apodemus speciosus	Orig.	3		0.2×10^{-2}	2-3	L.	Enlarge	6-15		8	2+	1+	1+	1+		1+	1+
		2	S.C.	0.25×10^{-2}	2-3	L.	Enlarge		26-29	8	2+	1+	1+	1+	1+	(3)	(6)
	Pass.	3		0.4×10^{-2}	3	L.	Enlarge	21		8	2+	1+	1+	1+	(3)−		
Apodemus geisha	Orig.	2	S.C.	0.25×10^{-2}	3	G.	Persist		6	3+	1+	—	—	—	— (3)	1+ (6)	
	Pass.	2		0.5×10^{-2}	3	G.	Persist / Healed		18-23	3+	1+	—	—	—			
	Orig.	3	I.P.	0.25×10^{-1}	2		Nodule omentum	2-6		1+	—	—	—	—			
		4		0.5×10^{-2}	6		Nodule omentum	6-12		1+	—	—	—	—			
		3		0.5×10^{-3}			None	6-12		—	—	—	—	—			
Meriones unguiculatus		5		0.25×10^{-1}	2-3	G.	Healed	2-12		2+	1+	—	—	—	—		1+
		6	S.C.	0.5×10^{-2}	2-3	G.	Healed	2-12		2+	1+	—	—	—	(3)		(9)
		4		0.5×10^{-3}			None	6-12		—	—	—	—	—			1+ (2)
	Pass.	2	S.C.	0.5×10^{-2}			None	6		—	—	—	—	—			
		3		0.1×10^{-1}	2-3	G.	Persist	6-9		2+	1+	—	—	—			1+ (6)
	Orig.	3	I.T.	0.2×10^{-2}	2-3	G.	Persist	6-12		2+	1+	—	—	—			1+ (6)
		4		0.1×10^{-3}	3	L.	Persist	6-12		3+	1+	—	—	1+			1+ (6-12)
Microtus montebelli		6		0.25×10^{-2}	2-3	G.	Healed	6-12		—	—	—	—	—			1+
					28	L.	Enlarge		31	8	1+	—	—	—			(31)
	Orig.	4	S.C.	0.25×10^{-3}	2-3	G.	Healed	12		—	—	—	—	—			
		2		0.25×10^{-4}			None	6-13		—	—	—	—	—			

[a] Original, the original suspension of rat leproma; Pass., passage transfer to other mice of the same wild species from an infected one.
[b] S.C., subcutaneous; T.P., intraperitoneal; I.T., intratesticular.
[c] L, typical leproma; G, granuloma not characteristic of leproma.

3-months lesion failed to infect other animals of the same species. Material recovered after 9 months, however, infected mice.

The most successful route in this species was intratesticular inoculation. Injections of heavy doses resulted in rapid response, but there was only destruction of the testicular tissue by the granuloma and there was no proliferation of bacilli; atrophy took place later. With the 10^{-3} inoculum, intracellular proliferation of bacilli was found only after 12 months in the lymph node (bronchial glands) and spleen. Mice inoculated with these bacilli all became infected. The results suggested that in this species infection is possible only with intratesticular injection of small doses.

Mic. montebelli: In this animal subcutaneous injection of heavy doses resulted in the formation of small nodules after 2-3 months, but these were gradually absorbed. No local response was seen to the 10^{-3} dose after 13 months, and it was believed that this animal was not susceptible. However, examination of an animal injected subcutaneously with the 0.25×10^{-2} inoculum which died after 31 months with swelling of the joints, showed pathologic changes characteristic of murine leprosy and many bacilli. Back-passage of the bacilli in mice resulted in infection of all the animals. In this animal leproma formation at the site of inoculation, characteristic of murine leprosy, was not seen, but lesions were produced at far-distant points. This suggests that infection in a species of low susceptibility may take place after the lapse of a long period of time.

HISTOLOGIC FINDINGS

The histologic picture—i.e., cellular morphology, presence of giant cells, proliferation of connective tissue, number of migratory cells, necrotic foci, and numbers of bacilli—in these four species, and in the Rattus, Mus and *Mesocricetus auratus* (golden hamster) are compared in Table 2.

Rattus: The rat is readily infected by all routes. The lepra cells appearing in the lesion are epithelioid cells with swollen cytoplasm, the nucleus pushed to one side. At times spindle-shaped connective tissue cells are filled with bacilli and form lepra cells. Proliferation of connective tissue is the more marked the older the lesion, and the boundaries of lesions are sharply defined, especially in the liver (Figs. 1 and 2). Migratory cells are not found in the leproma, but a slight infiltration is seen in the periphery of necrotic foci or in the vessels surrounding very new lesions. Bacilli are present in large numbers. Central necrosis is a characteristic of old lesions. The most favorable site of lesion formation is the lymph node, where many Langhans' giant cells are found (Fig. 15), followed in order by the spleen, liver (Fig. 16), and lung.

Mus: In the mouse, also, infection occurs readily. In general, there

is less connective tissue in the lesions than in those of the rat, giving the lesion a soft appearance. The lepra cells are rounder than in the rat, and resemble large monocytes in shape (Figs. 3 and 4). Typical Langhans' giant cells are seldom seen, but atypical giant cells are observed at times. Bacilli fill the cells, giving the appearance of red balls on acid-fast staining. The findings in the organs are similar to those in the rat.

Mesocricetus: Again in the hamster, infection takes place readily. As in the mouse, the quantity of connective tissue in the lesion is small and its appearance is consequently soft. The lepra cells are round epithelioid cells with the nucleus pushed to one side by the proliferation of the bacilli. (Figs. 5, 6 and 17.) Typical Langhans' giant cells are not found, but atypical giant cells—presumably formed by grouping of large monocytes—are observed, especially in the liver. Many bacilli are present. In severe infections, diffuse lesions are found in the spleen, liver and lungs. Necrotic foci are few, however, and the changes in the lymph nodes are less than in the rat.

TABLE 2.—*Comparison of histologic findings in lesions of the rat family.*

Species	Lesion cell	Connective tissue proliferation	Giant cells	Bacilli	Necrosis	Viscera[a]			
						Lymph nodes	Spleen	Liver	Lung
Rattus norvegicus	Typical epithelioid	Marked	Many, Langhans	Many	Marked	4+	3+	2+	2+
Mus molosimus	Rounder epithelioid	Slight	Few, different	Many	Slight	4+	3+	2+	2+
Mesocricetus auratus	Rounder epithelioid	Slight	Few, different	Many	Very slight	1+	3+	2+	1+
Apodemus speciosus	Monocyte-like round epithelioid	Slight	None	Many	Slight	2+	1+	1+	—
Apodemus geisha	Large round epithelioid	Marked	None	Many, later few	Slight	1+	1+	—	—
Meriones unguiculatus	Spindle-form epithelioid	Marked	None	Many, later few	Heavy	1+	1+	—	—
Microtus montebelli	Typical epithelioid	Slight	None	Many, later few; one case many	Slight	1+	(Joint 3+)		

[a] Degree of visceral involvement, 1+ to 4+.

Apo. speciosus: Typical lepromas resembling those in the mouse are produced. Lepra cells have the appearance of large monocyte-like cells, and they are filled with bacilli. The lesions are poor in connective tissue, and giant cells are not seen. (Figs. 7 and 8.) Slight necrosis is observed. The changes in the lymph nodes are moderately severe, but those in the spleen, liver and lung are slight and bacilli there are few.

Apo. geisha: The leproma at the site of injection is not made up of

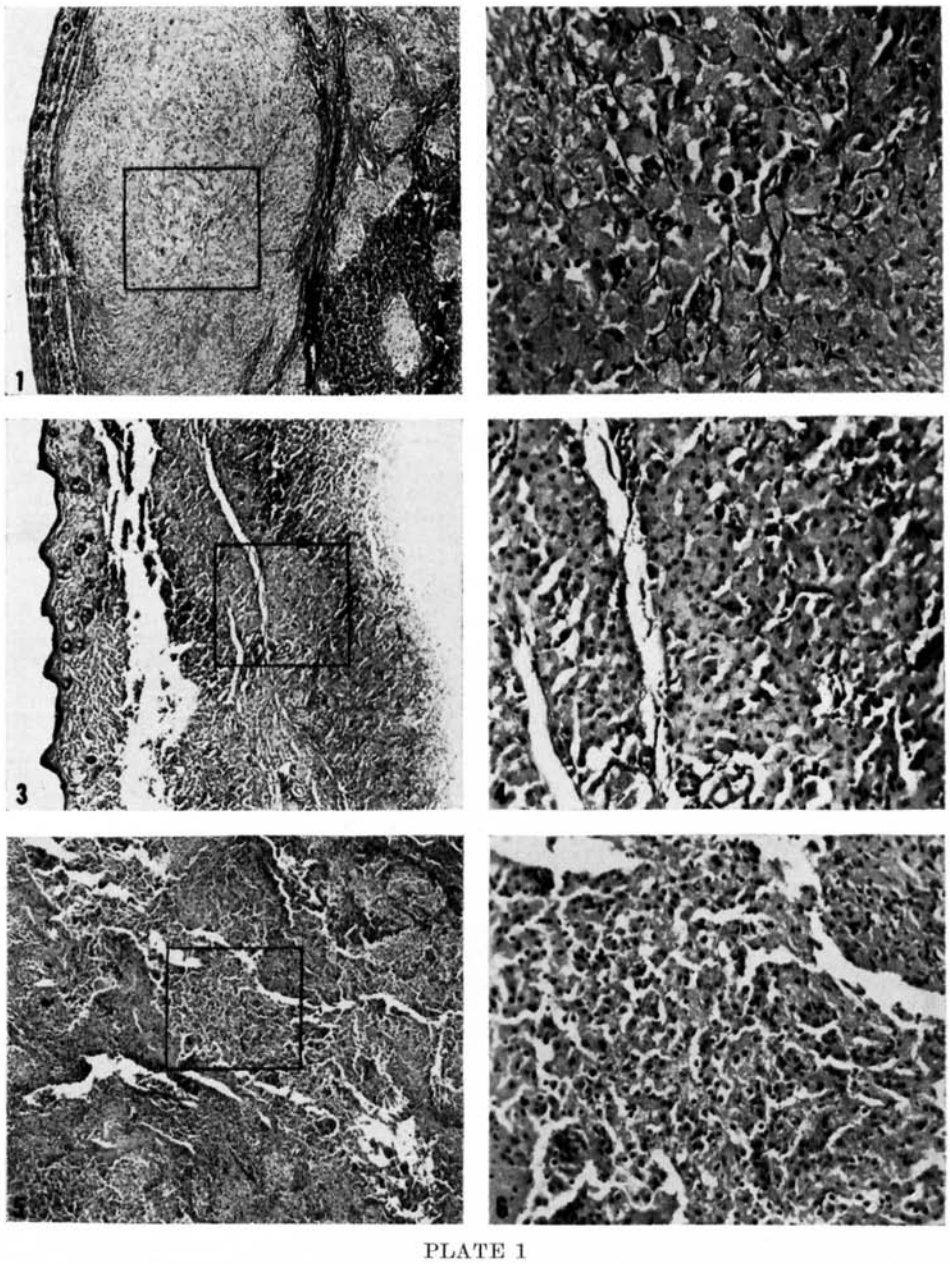

PLATE 1

FIG. 1. Somewhat old subcutaneous leproma in the rat, surrounded by connective tissue. 50×.

FIG. 2. A field of Fig. 1 at higher magnification, 200×. Typical epithelioid rat leprosy cells.

FIG. 3. Subcutaneous leproma in the mouse. Slight round-cell infiltration present in the periphery, but only a small quantity of connective tissue. 50×.

FIG. 4. A field of Fig. 3 at higher magnification, 200×.

FIG. 5. Somewhat old subcutaneous lesion in the hamster. Diffuse lepra cell infiltration. 50×.

FIG. 6. A field of Fig. 5 at higher magnification, 200×.

typical lepra cells. It consists of spindle-form cells containing many bacilli, and round epithelioid cells with their nuclei pushed to one side but containing only a few bacilli in the central part. (Figs. 9 and 10.) The center is necrotic. Giant cells are not found. Of the organs, nodules are produced only in the lymph nodes, and bacilli are found here.

Mer. unguiculatus: The lesion produced locally is not a typical leproma. It is similar to the granulation tissue which develops when nonpathogenic bacteria are injected into the rat, and there is no formation of epithelioid cells due to bacterial proliferation. After intratesticular injection there is strong interstitial reaction and the seminal tubules are destroyed, but typical lepra cells are not found. (Figs. 11, 12 and 18.) In an animal injected with a dilute inoculum, proliferation was observed in smear specimens after 1 year, but unfortunately this specimen was lost.

Mic. montebelli: The subcutaneous inoculation lesion was a localized atypical leproma containing a few bacilli, and it disappeared after one year. The lesion in the joints was a leproma formed of typical epithelioid lepra cells, with necrosis in places, and the perimeter was composed of spindle-shaped cells. (Figs. 13 and 14.) Bacilli were found in all the tissues except bone, ligament and skin, and on staining with Ziehl-Neelsen the whole took on a red color, because of the proliferation of the bacilli. Giant cells were not seen. Although nodular lesions formed of epithelioid cells and many bacilli were found in the lymph nodes, no marked changes were observed in other organs.

A comparison of the histologic changes shows that those in the mouse, hamster and *Apo. speciosus* were close to those in the rat, and the lesion produced in the joints of one of the Microtus animals shows a close similarity. In the *Apo. geisha* mice, bacillus proliferation was not marked and suggested phagocytic granuloma cells rather than lepra cells. In the Meriones mice, injection with heavy doses resulted in a severe granuloma, but typical lepra cells and bacillary proliferation were not found.

DISCUSSION

On the basis of the findings in the experimental infections of four species of wild mice with the murine leprosy bacillus and the pathologic changes occurring in these animals, the following points are discussed.

Relationship between endogenous characteristics, susceptibility to murine leprosy and zoologic classification.—The mouse, the hamster, and *Apo. speciosus* as well as the natural host, the rat, are highly susceptible, while *Apo. geisha, Mer. unguiculatus* and *Mic. montebelli* show little susceptibility. It can therefore be said that, within the range of the present investigation, susceptibility and morphology are related.

Most favorable route of infection.—The murine leprosy bacillus proliferates within mesenchymal cells, so in highly susceptible animals sub-

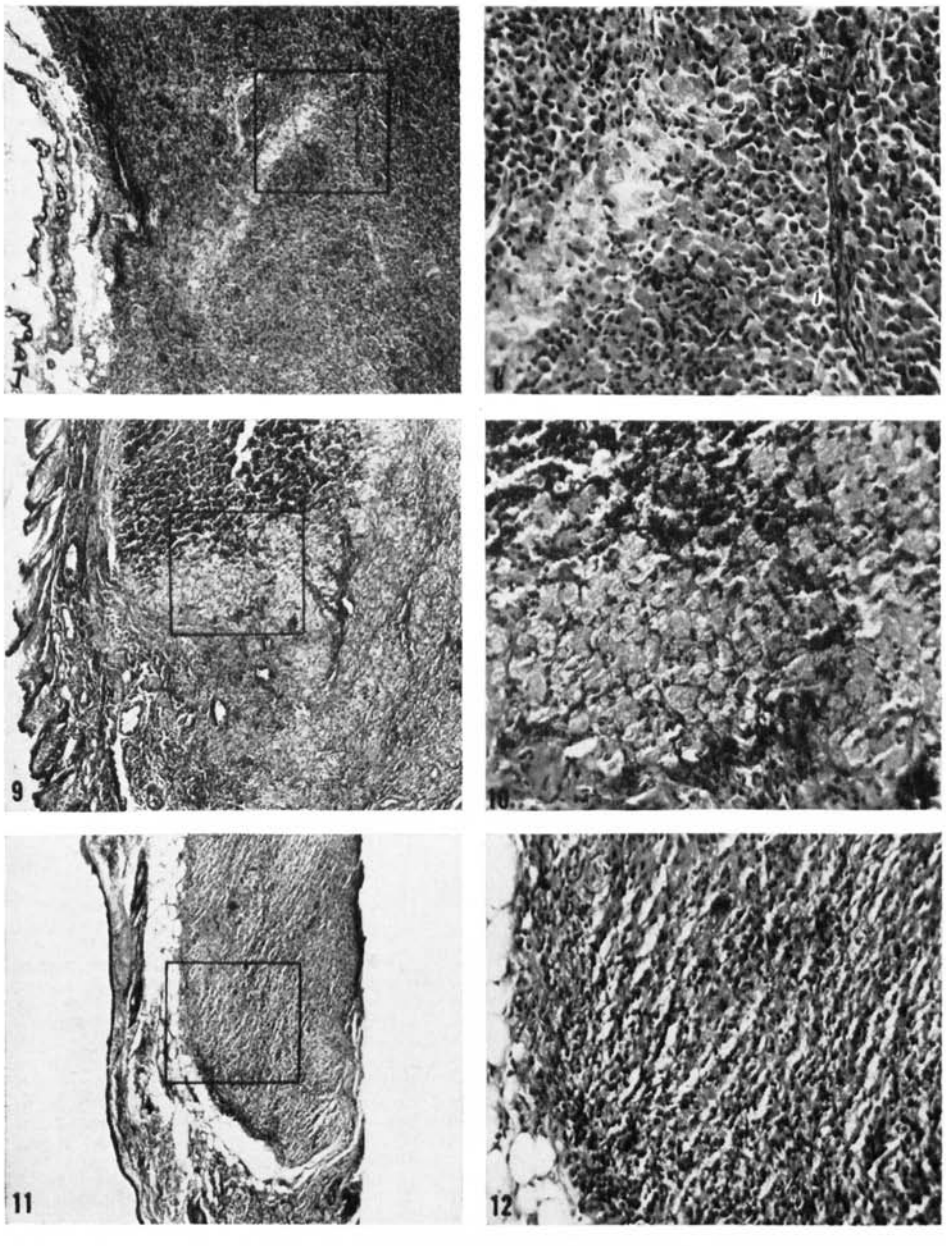

PLATE 2

FIG. 7. Subcutaneous lesion in *Apodemus speciosus*. 50×.

FIG. 8. A field of Fig. 7 at higher magnification, 200×. Filled with large monocyte-like lepra cells, some undergoing mitosis.

FIG. 9. Localized subcutaneous lesion in *Apo. geisha*. 50×.

FIG. 10. A field of Fig. 9 at higher magnification, 200×. Epithelioid cells losing the nucleus. Round cell infiltration is marked.

FIG. 11. Localized subcutaneous granuloma in *Meriones unguiculatus*. 50×.

FIG. 12. A field of Fig. 11 at higher magnification, 200×. Similar to ordinary granuloma; epithelioid lepra cells absent.

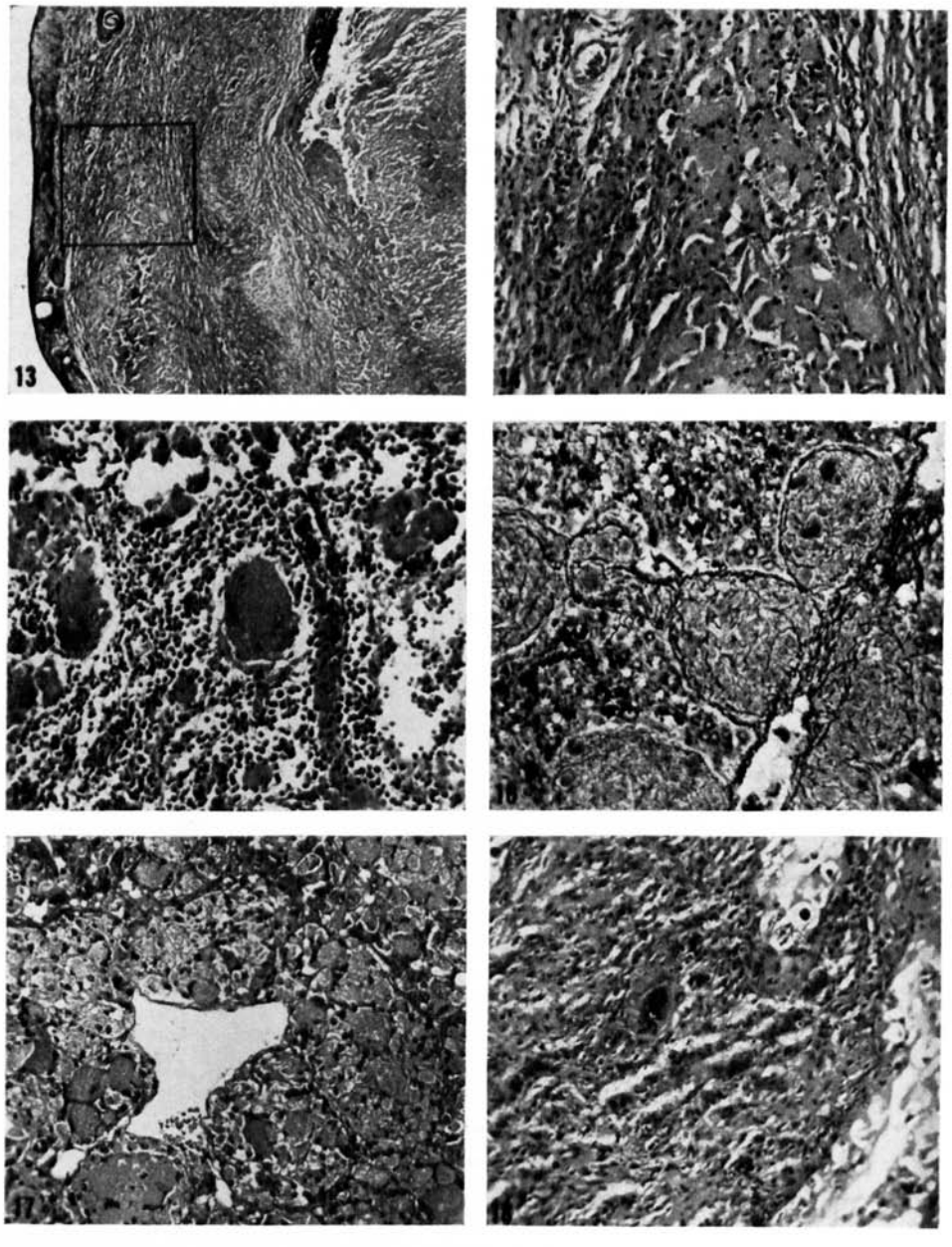

PLATE 3

FIG. 13. Leproma in the joint of *Microtus montebelli*. 50×. Necrosis in places.

FIG. 14. A field of Fig. 13 at higher magnification, 200×. Note typical lepra cells.

FIG. 15. Langhans' giant cells in the lymph node of the rat. 200×.

FIG. 16. Formation of connective tissue within a murine leprosy nodule in the rat liver. 125×. (Bielschowsky's method.)

FIG. 17. Giant murine lepra cells with the nuclei pushed to one side, in the liver of the hamster. 200×.

FIG. 18. Proliferation of connective tissue and damage of seminal tubules in the testis of *Mer. unguiculatus*. Note absence of lepra cells. 200× H.E.

cutaneous injections will result in the formation of typical lepromas. In animals of low susceptibility, as Meriones, intratesticular injection gives better results. This has already been reported by Takayama ([8]) in the Meriones and, by Hanks ([2]) in the rat.

Quantity of inoculum.—In animals of high susceptibility, a small dose (0.2×10^{-3}) suffices. When the inoculum is too concentrated, it contains much of the tissue components and tissue reaction is severe, and bacillary proliferation is suppressed by the production of immune antibodies. A good example is the successful infection intratesticularly of *Mer. unguiculatus* by injecting a small dose. Hanks and Backerman ([3]) have presented data on the suppression of development of lesions in the rat by the injection of heavy doses.

Period of observation.—In highly susceptible animals, infection can be successfuly back-passed within a period of one year, but this length of time is believed to be insufficient with animals of low susceptibility. In Meriones, proliferation is observed with intratesticular injection after 12 months, and lesions occurred in the joints of one of the Microtus animals after 31 months. Careful observation for a long period is therefore required in determining susceptibility.

Viability of bacilli in animals of low susceptibility.—In animals of low susceptibility infection takes place according to individual differences, and in other than special organs (e.g., the testes) infection will not take place. The period of viability of the injected bacilli when typical lesions are not formed is an important problem. In *Apo. geisha*, bacilli were viable in the subcutaneous granuloma for more than 6 months, while in *Mer. unguiculatus* viable bacilli were found after more than 9 months. This finding differs greatly from the fact that murine leprosy bacilli disappear within 8 weeks from the site of injection in a hetero-host such as the guinea-pig. It is believed that this is due to a difference in resistance of the animals.

Characteristics of the pathologic changes. — Comparison of the pathologic picture with the findings in the rat used as the standard shows that in the mouse, hamster and *Apo. speciosus* there is less connective tissue, Langhans' giant cells are absent, bacillary proliferation is very marked, and the rat leprosy cells are always swollen and take a round monocyte-like shape. The occurrence of necrotic foci is more tardy and of less severity, The findings that bacilli proliferate specifically in cells of mesodermal origin and that there is no affinity toward peripheral nervous tissues are basically similar. The degree of resistance is somewhat slighter. The subcutaneoues lesion in *Apo. geisha* and *Mer. unguiculatus* does not show the characteristic picture of murine leprosy, but appears to be a transient granuloma. The lesions in the joints of one Microtus mouse were similar to the picture in the rat except for the absence of giant cells.

Factors related to susceptibility of animals to leprosy bacilli.—In order for leprosy bacilli successfully to invade the host, proliferating and producing a lesion, the host cells must furnish nutrients for their growth on the one hand, and the host also must be in a state of low resistance, either congenital or acquired, on the other hand. In the rat, mouse, hamster and *Apo. speciosus,* the growth factor predominates over resistance, while in the other wild species used the intracellular growth factor is inadequate although resistance is low. Recently, we attempted to enhance proliferation of the murine bacillus in *Mer. unguiculatus* by administering adrenocortical hormone to suppress the defensive action, but were unsuccessful ([7]). Similar attempts have been made previously by many investigators. Yasuda ([11]) inoculated mice with human leprosy bacilli after pretreatment with "habu" toxin, and obtained findings of interest in the first generation but further passage was reported unsuccessful. Cochrane and Ramanujam ([1]) inoculated splenectomized monkeys with the human bacillus but did not obtain satisfactory results. They believed that "success will be attained only if this tissue defense reaction can be abolished, allowing free multiplication of the bacilli in the corium of the skin." Kató ([4]) has treated guinea-pigs with antihistaminics and then injected murine leprosy bacilli, this too apparently done in an attempt to suppress resistance. From the findings, however, I believe that the presence or absence of the growth factor in the host cells rather than the strength of the resistance is of the greater importance in determining suscepibility of the animal.

Several years ago Tanimura and Nishimura ([10]) suggested that in order to infect animals with leprosy bacilli successfully, a substance perhaps a growth factor must be present in the host cells which is able symbiotically to accept the bacilli. There is no need to reverse this suggestion at the present time. It is therefore believed that in conducting animal experiments with leprosy bacilli the most important point is to find species or strains of animals which inherently possess this property.

SUMMARY

Four species of wild mice have been inoculated with the murine leprosy bacillus, and the following observations were made.

(1) *Apodemus speciosus* is the most susceptible of them. *Apo. geisha, Meriones unguiculatus,* and *Microtus montebelli* are susceptible although in low degree.

(2) The inherent characteristic of susceptibility is closely related to zoologic classification.

(3) In animals of high susceptibility the subcutaneous route of infection was satisfactory, but in animals of low susceptibility, as *Mer. unguiculatus,* intratesticular inoculation is more effective.

(4) The quantity of inoculum should be as small as possible, in order to minimize irritation by the tissue elements of the leproma suspension.

(5) The lower the susceptibility of the animal, the longer should be the period of observation.

(6) Bacilli remain viable for a long time, even in animals of low susceptibility which do not show active infection.

(7) The pathologic changes in the mouse, hamster and *Apo. speciosus* are similar to those in the rat, which is taken as the standard, although slightly less resistance is seen. The changes in *Apo. geisha* and *Mer. unguiculatus* are not typical, but those found late in the lesions of the joints of one *Mic. montebelli* animal were close to those seen in the rat.

(8) It is concluded that the most important factor in determining susceptibility of animals to human or murine leprosy bacilli is the natural presence of an intracellular growth factor required by the bacilli, rather than the strength of resistance possessed by the animal.

RESUMEN

A cuatro especies de ratones campestres se les ha inoculado el bacilo de la lepra murina, llevándose a cabo las siguientes observaciones.

(1) El *Apodemus speciosus* es el más susceptible de estos animales. El *Apo. geisha,* el *Mariones unguiculatus* y el *Microtus montebelli* son también susceptibles, pero en menor escala.

(2) La característica inherente de susceptibilidad se relaciona íntimamente con la clasificación zoológico.

(3) En los animales de elevada susceptibilidad, la vía subcutánea de infección resultó satisfactoria, pero en los de baja suceptibilidad, como el *Mer. unguiculatus,* la inoculación intratesticular es más eficaz.

(4) La cantidad de inócilo debe ser lo más pequeña posible, a fin de reducir al mínimo la irritación producida por los elementos histológicos de la suspensión de leproma.

(5) Mientras menor sea la susceptibilidad del animal, más largo debe ser el período de observación.

(6) Los bacilos permanecen viables por mucho tiempo, hasta en los animales de poca susceptibilidad que no revelan infección activa.

(7) Las alteraciones patológicas en el ratón, el *Cricetus* y el *Apo. speciosus* son semejantes a las observadas en la rata, que se toma como pauta, aunque se nota una resistencia ligeramente menor. Las alteraciones en el *Apo, geisha* y el *Mer. unguiculatus* no son típicas, pero las notadas tardíamente en las lesiones de las articulaciones de un *Mic. montebelli* son parecidas a las observadas en la rata.

(8) Dedúcese que el factor más importante en determinar la susceptibilidad de los animales a los bacilos de la lepra humana o murina es la

presencia natural de un factor intracelular del crecimiento requerido por los bacilos, más bien que la fuerza de resistencia poseída por el animal.

REFERENCES

1. Cochrane, R. G. and Ramanujam, K. Inoculation of monkeys with human leprosy material. Internat. J. Leprosy **13** (1945) 98-100.
2. Hanks, J. H. Three factors which may influence the experimental transmission of leprosy. Internat. J. Leprosy **18** (1950) 33-47.
3. Hanks, J. H. and Backerman, T. The tissue sites most favorable for the development of murine leprosy in rats and mice. Internat. J. Leprosy **18** (1950) 185-207.
4. Kató, L. Experimental transmission of murine leprosy to the guinea-pig by means of induced macrophage exudate and suppression of natural defence mechanism. Internat. J. Leprosy **25** (1957) 193-206.
5. Nishimura, S., Nakao, M. and Iwasa, K. Susceptibility of *Meriones unguiculatus* to murine leprosy bacilli. Bull. Exp. Animals **4** (1955) 42-43.
6. Nishimura, S., Nakao, M. and Kosaka, K. Susceptibility of *Apodemus speciosus speciosus* and *Microtus montebelli montebelli* to rat leprosy bacilli. Bull. Exp. Animals **5** (1956) 43-44.
7. Nishimura, S., Nakao, M. and Kosaka, K. Sensitivity of wild mice to murine leprosy. La Lepro **28** (1959) 192-200.
8. Takayama, Y. Studies on the hetero-host transmission of leprosy bacilli. Report V. Susceptibility of *Meriones unguiculatus* to rat leprosy bacilli. Hiroshima Med. J. **4** (1956) 1337-1344.
9. Tanimura, T., Nishimura, S. and Ogita, K. On the sensitivity of hamster to the human and murine leprosy bacillus. La Lepro **21** (1952) 181-186.
10. Tanimura, T. and Nishimura, S. A review of recent animal inoculation studies with human and murine leprosy bacilli. Internat. J. Leprosy **21** (1053) 335-346.
11. Yasuda, T. Experimental studies of onset mechanism in animal inoculation with leprosy bacilli. La Lepro **15** (1944) 169-186 (in Japanese).