

## ALOPECIA IN HYBRID MICE INOCULATED WITH MATERIAL FROM LEPROSY LESIONS<sup>1</sup>

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### ALOPECIA IN LEPROSY

*Alopecia in human leprosy.*—Two types of alopecia in leprosy are recognized, one corresponding to the indeterminate or tuberculoid form, and the other to the lepromatous form. In the former, plaques of alopecia are seen in skin areas that are clinically healthy, or at most show hypochromic or infiltrated erythematous macules. In the latter, on the other hand, the falling of the hairs is observed in thickened, infiltrated, and dry skin areas.

Mitsuda and Nagai (<sup>6</sup>) studied the characteristics of the lepromatous alopecia, and concluded that it results from the changes in the arterioles which supply the papillae. These capillaries are compressed by the lepromatous infiltrate that in the end destroys them, thus provoking serious changes in the nutrition of the skin.

Sometimes the lepromatous infiltrate only depresses and displaces the hair follicles, without ultimately destroying them, and in such cases adequate treatment may melt the infiltrate and the hairs reappear.

The mechanism of the alopecia in the indeterminate form is not well known. It is suspected that it is of nervous origin.

*Alopecia in murine leprosy.*—This is observed in the advanced stage of the infection, sometimes during the year following inoculation. It is accompanied by manifest cutaneous changes, lepromatous infiltrations and ulcerations. The mechanism is similar to that of human lepromatous leprosy.

*Alopecia in animals inoculated with M. leprae.*—Barman (<sup>1</sup>), Chatterjee (<sup>2-4</sup>), Souza-Araujo (<sup>7</sup>) and other workers have described alopecia lesions in rodents inoculated with material from human leprosy. Generally, this alopecia is associated with skin changes, ulcers and infiltrations and is of late occurrence.

### PERSONAL EXPERIMENTS

In 1959, we started a series of experimental attempts to transmit human leprosy to laboratory rodents (<sup>5</sup>). In the course of 4 of these

<sup>1</sup> Investigation carried out in the Center of Dermatologic Investigations, Department of Dermatology, with the aid of a subsidy granted by the World Health Organization.

<sup>2</sup> With the collaboration of Messrs. Osvaldo Garroq and Oscar Furlan, and the assistance of Misses Zulema Lucea and Irma Micheloud.

experiments we observed the appearance of an alopecia "sui generis" which had attracted our attention. The characteristics of this alopecia are described in the present communication, a preliminary report.

The following is a summary description of the experiments in which we observed the alopecia phenomenon.

#### EXPERIMENTS PREVIOUSLY REPORTED

*Experiment 1.*—In this experiment black hybrid mice were inoculated according to Chatterjee's technique.

*Material and method:* Hybrid mice obtained by crossing an Indian house mouse with a Swiss albino female were used.<sup>3</sup> The inoculations were made subcutaneously with a pure bacillus suspension—1,000 millions—obtained from active lepromatous lesions. In April 1959 we inoculated 19 males and 19 females, all below 15 days of age.

*Evolution:* For 6 months after inoculation nothing special was observed. After 12 months, 11 males and 15 females survived. In 4 of the females, partial or total alopecia of the whiskers was noted. After 24 months, among 14 survivors (5 males and 9 females), 4 of the females showed total alopecia of the whiskers.

*Summary:* In 4 females (10.5%) of the total of 38 mice inoculated, there was partial or total alopecia of the whiskers, which began to manifest itself from the 6th month after inoculation.

*Experiment 2.*—This experiment differed from the previous one only in that the hybrid mice used were derived by crossing Swiss albino females with a DBA male (Group A), and a C58 male (Group B). Between June and September 1959, we inoculated 64 animals (34 males and 30 females) of Group A, and 14 animals (5 males and 9

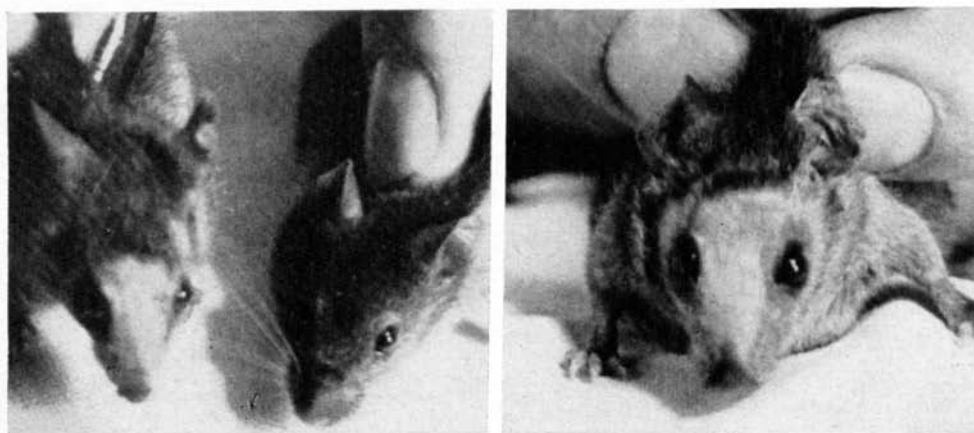


FIG. 1.—Experiment 2. Left: female mouse inoculated 10 months previously. Extensive plaque of alopecia on the head. Right: Control mouse, uninoculated.

FIG. 2.—Experiment 2. Plaque of alopecia of animal in Fig. 1, taken at a shorter distance.

<sup>3</sup> The animals used in this experiment were kindly supplied to us by Dr. K. R. Chatterjee of the School of Tropical Medicine of Calcutta, and by Dr. R. J. W. Rees of the Institute for Medical Research of London.

females) of Group B. All the animals were given the same care with respect to diet and housing.

**Evolution:** In October 1959, between the 4th and the 5th months after inoculation, we observed in the mice of Group A the first symptoms of alopecia. This consisted of partial or total falling of the whiskers in the male, and total loss in the females associated with alopecia plaques on the head.

This phenomenon was not observed in the uninoculated controls of the same lineage which were housed in nearby cages, but on the other hand it was seen in the 2 uninoculated mice which lived in the same cage with the inoculated ones of Group A.

In June 1960, from 9 to 13 months after the inoculation, the alopecia affected 26 mice (40%) of Group A (Figs. 1 and 2), and also the 2 uninoculated mice which lived together with the former in the same cage.

Of the 12 mice of Group B that survived, 6 (50%) showed alopecia of the whiskers.

In December 1960, from 15 to 18 months after the inoculation, 45 animals (27 males and 18 females) of Group A survived. Of the females, 10 showed alopecia of the whiskers. The alopecia plaques of the head had disappeared, due to the regrowth of the hairs except in 2 females.

In Group B, 1 male and 5 females survived. All the females showed alopecia of the whiskers.

**Summary:** From the 4th to the 5th months following the inoculation, alopecia appeared, developing progressively and reaching an advanced stage in about 15 months. The process then subsided in almost all of the animals.

This phenomenon affected 40 per cent of the inoculated hybrids, and the 2 uninoculated animals which lived together with them in the same cage. No alopecia disturbances were seen in the uninoculated controls which were housed in separate cages.

#### FURTHER EXPERIMENTS

*Experiment 3.*—This experiment involved the inoculation of hybrid mice with a pure suspension of *M. leprae* mixed with an extract of fresh lepromas, using the subcutaneous (Group A), intradermal (Group B), intraperitoneal (Group C), and dermal scarification (Group D) routes.

**Material and method:** In August 1960 we inoculated 19 males and 20 females with material from the same patient. The animals were divided into 4 groups, according to the stated routes of inoculation.

**Evolution:** In December 1960, 4 months after the inoculation, alopecia of the whiskers was observed in 9 females.

In May 1961, 9 months after the inoculation, the following was



FIG. 3.—Experiment 3. Extensive alopecia in a female mouse 13 months after inoculation.

FIG. 4.—Experiment 3. Upper: female mouse inoculated 12 months previously. Lower: female mouse, control, uninoculated.

noted: Of the 39 inoculated mice, 35 (18 males and 17 females) were still alive. All of the males were normal. Of the 17 females, 10 showed partial or total alopecia of the whiskers and there were incipient alopecia plaques on the face around the eyes. This phenomenon was noted in 4 animals of Group A, 2 of Group B, 3 of Group C and 1 of Group D.

In August 1961, 12 months after the inoculation, 11 males and 12 females survived. None of the males showed alopecia, while 10 out of the 12 surviving females had alopecia of the whiskers and plaques of alopecia on the face (Figs. 3 and 4).

In November 1961, 14 months after the inoculation, 10 males and 12 females survived. All the males were of normal aspect. Of the 12 females, 2 were normal, 6 exhibited small plaques of alopecia in the periorbital area, and 4 showed large plaques, also periorcular.

In March 1962, 11 females and 9 males survived. The females showed large, confluent plaques of alopecia on the head, accompanied by total falling of the whiskers. Another 6 females showed partial or total falling of the whiskers, and smaller plaques of alopecia almost all situated around the orbit. Only one female was of normal aspect. The males showed nothing in particular except for the decrepit condition attributable to age.

On August 27, 1962, all the males had died and only 10 females survived. Of these, 7 showed characteristic plaques of alopecia.

On October 20, 1962, only 6 females survived. These had been inoculated 23 to 25 months earlier (3 intraperitoneally, 2 subcutaneously, and 1 by scarification) with material of the Vignatti strain.

Except in one female (No. 1002), in which there were no plaques of alopecia, the areas devoid of hairs still persisted, although there were plaques not completely cleared since there were new short hairs on their surface.

On December 15, 1962, 2 decrepit females survived. The hairs covering the plaques were shorter than the normal ones.

Summary: From the 4th month after the inoculation there appeared an alopecia consisting of partial or total falling of the whiskers and plaques of various sizes on the head. With the exception of 2



FIG. 5.—Experiment 4. Left: female mouse inoculated 60 days previously. Note the plaque of initial supereiliary alopecia and the infiltration of the nose; also the dull appearance of the eyes.

FIG. 6.—The female of Fig. 5, 120 days after the inoculation. There is an area of alopecia in the right supraorbital region; also one on the nose, the skin of which is infiltrated.



normal females, the remaining females were affected by this alopecia.

*Experiment 4.*—This experiment consisted in direct and immediate inoculation of leprosy material (serosity of lepromas) to hybrid mice.

Material and method: On June 20, 1962, 11 hybrid mice (from the C58 male), 20 days of age, were inoculated by the subcutaneous route and by scarification. The inoculation material came from an advanced, untreated lepromatous patient. It was obtained by incising a leproma and scraping the borders, thus producing a slightly bloody serosity which was immediately inoculated. Three uninoculated animals of the same origin were placed in the same cage with the inoculated ones as controls.

Evolution: On July 13, 1962, the animals showed no abnormality, but on July 31st one female mouse showed a plaque of alopecia the size of 2 x 2 mm, in the right orbicular area. The other animals showed nothing in particular.

By August 11th the alopecia of one female (No. 16), inoculated intracutaneously, had become more pronounced. There were 2 plaques, one retroorbital and the other interorbital (Fig. 5). The other mice showed nothing special.

On September 18th, 3 months after the inoculation, the alopecia of mouse No. 16 was still persistent. The rest of the animals, inoculated and controls, showed nothing in particular.

On October 16th, 116 days after the inoculation, all of the animals (11 inoculated and 3 controls) of this experiment still survived. Only the No. 16 female (Fig. 6) showed anything in particular on clinical examination. The areas that had been denuded by the scissors during the inoculation had totally recovered.

On December 16th, 11 mice of Experiment 4—not including female No. 16—survived: 9 inoculated 158 days earlier and 2 uninoculated controls. None showed any particular abnormality.

#### FEMALE MOUSE NO. 16

*Condition on October 16, 1962.*—The general condition of this animal as seen on October 16th is worthy of note because of its slow movements and the dullness of its hair. Above the right eye there was a plaque of alopecia and similar other ones a little lower and on the right ear. The whole snout was invaded by a diffuse, elevated infiltration. There were few hairs, and scarcely any whiskers (Fig. 5). Lastly, the hair in the posterior right dorsal area which had been cut for the inoculation *in situ* almost 4 months earlier had not grown again (Fig. 6).

On October 19th, while a biopsy specimen was being taken, the animal died from the anesthetic. For the purpose of carrying out a comparative histopathologic study, female mouse No. 4—also inoculated intracutaneously on the same date and with same material as the female No. 16—was sacrificed, but nothing abnormal was found.

*Subinoculations.*—With material obtained from the alopecia areas of mouse No. 16 (snout and posterior dorsal area) a saline suspension was made and inoculated intracutaneously into 5 female hybrid mice

of the same breed, 30 days old, in the right posterior dorsal area, first shaving off the hairs. Included in the same cage were 3 uninoculated mice as controls.

*Evolution of subinoculations.*—On October 30th, 12 days after the inoculations, all of the animals were of normal appearance. On December 15th, 58 days after the inoculations, one female (No. 108) showed 2 plaques of alopecia on the right retroocular area, with regular borders, of the size a little bigger than a grain of wheat. They had the same appearance as had the alopecic plaques observed in previous experiments. It is also worthy of note that, on the sites of inoculation, the regrowth of the cut hairs was incomplete. The rest of the inoculated animals and the 3 controls exhibited no signs of abnormality.

#### CLINICAL STUDY

*Frequency of the alopecia.*—In Experiment 1, of the 38 animals inoculated, 4 females (10.5%) presented total alopecia of the whiskers. In Experiment 2, of the 78 animals inoculated, 26 (33.3%) exhibited alopecia of the whiskers and/or alopecia of the hairs on the head. In Experiment 3, of the 39 animals inoculated, 11 females (28.2%) showed alopecia of the whiskers and/or falling of the hairs of the head. In Experiment 4, 1 female mouse out of the 11 inoculated (9.0%) showed plaques of alopecia on the head.

In summary, out of the 141 animals inoculated with human material, 42 presented alopecia, a rate of 29.8 per cent.

*General characteristics.*—The outstanding characteristic of these results is that the alopecia was seen only in the females, and only in the whiskers and on the head. The condition seems to have no relation with the route of inoculation of the bacillus.

The alopecia appeared between the 2nd and 4th months following the inoculations. In many animals the hairs grew again after several months. The hairs and the scalp showed no changes on histologic examination.

The alopecia did not affect the uninoculated control mice, except in the 2 animals which were housed in the same cage with the inoculated ones.

*Clinical characteristics.*—The alopecia began in small plaques approximately of the size of 2 x 2 mm., increasing until, by confluence, they covered wide areas (Figs. 2, 3 and 4). They were generally located on the head around the eyes and ears (Figs. 4 and 5), although in exceptional cases they extended down to the neck (Fig. 6). The skin of the area of alopecia was clean, smooth, uninfiltated, and without desquamation or symptoms of inflammation. In cases when the hair regrew, this occurred after several months, and the growth was slow.

With respect to the hairs, we were not able to study them carefully since they fell without presenting previous changes detectable by simple examination.

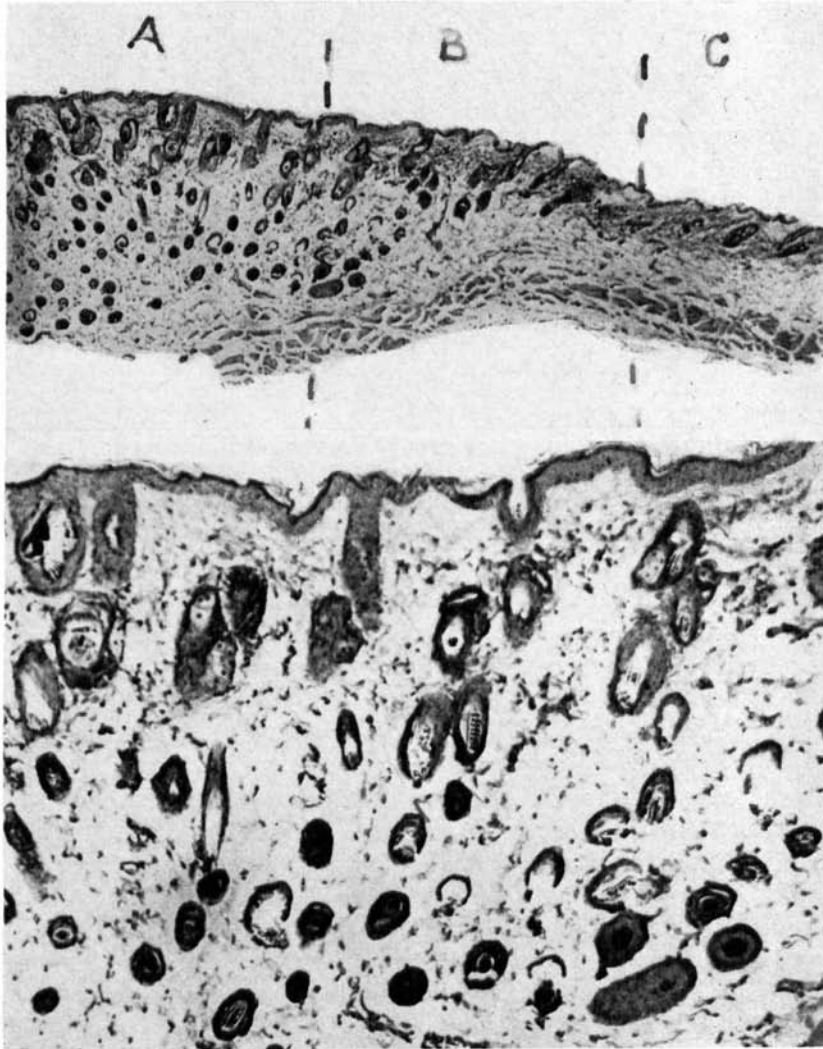


FIG. 7.—Experiment 3. Photomicrograph of an alopecic plaque, 10 months after inoculation. A, area of alopecia; B, area of transition; C, area of normal skin. (25X magnification.)  
 FIG. 8.—Details of area A, Fig. 7. (100X magnification.)

#### ANATOMOPATHOLOGIC STUDY

*Experiment 3.*—In this experiment, a biopsy was made of the area of alopecia on the right side of the head, of female No. 1040, which had been inoculated 10 months earlier. The following changes were found (Figs. 7 and 8): hyperkeratosis, parakeratosis, acanthosis, lack of continuity of the follicle with the surface. The base of the follicle is in contact with the muscular layer over the fatty tissue. The follicles present cells similar to those of the more superficial layer of the stratum of Malpighi. Some of the deep follicles present homogeniza-



tion of all the strata, with difficulty of identification of the cellular images.

Generally, the follicles are larger in diameter than those in the healthy part, and the keratotic substance is more abundant in the normal follicles. Hypertrophied sebaceous glands were observed. The

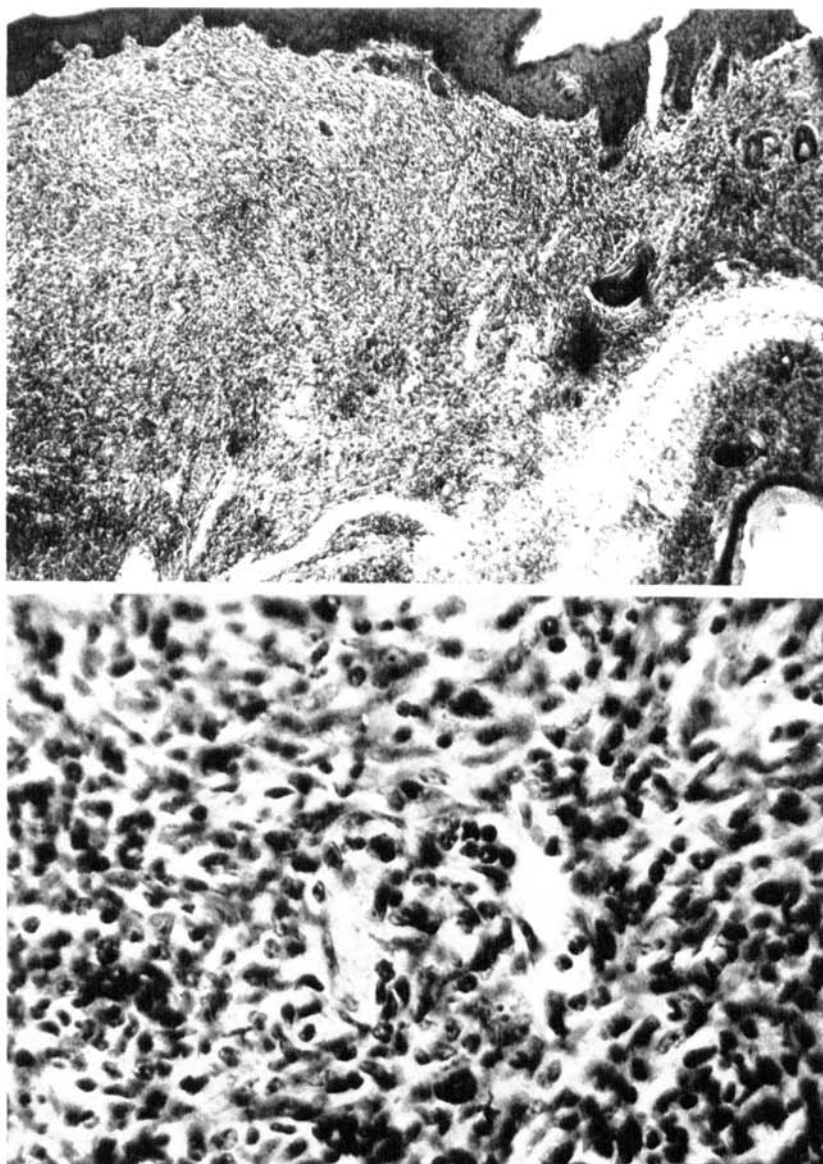


FIG. 9.—Experiment 4. Skin biopsy, right ear of female mouse No. 16. Note the acanthotic epidermis with follicular keratosis. Dense reticulohistiocytic infiltrate, integrated, in addition, by plasmocytes, lymphocytes, and hemosiderin. No changes of the nerve branches. (30X magnification.)

FIG. 10.—A highly magnified detail of the infiltrate shown in Fig. 9. (400X magnification.)

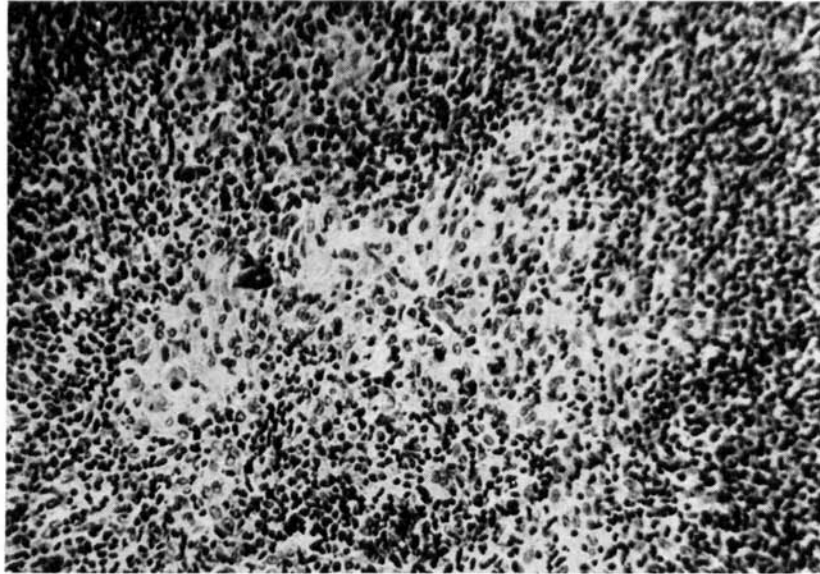


FIG. 11.—Experiment 4. Spleen of female mouse No. 16. Small histiocytic conglomerates of sarcoid aspect. (150X magnification.)

nerve twigs are intact, even the finest ones. The connective-tissue elements are formed by fine collagen fibers, intermixed with a normal number of reticular cells and fibroblasts, to which are added lymphocytes and plasmocytes.

*Experiment 4.*—The examination made in this experiment consisted of tissues removed at autopsy of female mouse No. 16. The microscopic examination showed an enlarged spleen of irregular surface, and lymph nodes of the neck also increased in size. The microscopic examination revealed the following:

Skin of the ear (Figs. 9 and 10): Thickened, acanthotic epidermis, with a few hair follicles and follicular keratosis. There is a very intense reticulohistiocytic infiltrate which contains plasmocytes, lymphocytes, and hemosiderin. There are no changes in the nerve branches.

Skin of the snout: Epidermis of normal aspect. The corium and the adjacent muscular tissue are invaded by a thick reticulohistiocytic infiltrate similar to that of the ear. There are no changes in the nerve branches.

The skin of the dorsum (inoculation site) was also examined, with no special findings.

Liver: Inflammatory infiltrates of a subacute type are found, forming perivascular sleeves, both in the areas of the central vein and in the portal spaces, also surrounding the canaliculi. This infiltrate is of the reticular and lymphocytic type.

Spleen: Besides an abundance of giant cells of the megakaryocytic group, there are encountered some isolated cells of the Langhans'

type. Small histiocytic conglomerates of sarcoid aspect are to be found (Fig. 11).

Lymph nodes: In some of the lymph nodes are noted lymphatic sinuses stuffed by an intense reticuloendothelial hyperplasia, with a few giant cells of the Langhans' type.

#### BACTERIOLOGIC STUDY

The search for acid-fast bacilli, stained by the Ziehl-Neelsen method, was carried out methodically and systematically in all the animals with lesions, both in the skin and in the internal organs of the autopsied animals. The results were always negative.

#### MYCOLOGIC STUDY<sup>4</sup>

This examination was performed in several animals with plaques of alopecia, and at different stages of the evolution of the process. The following is the technique employed and the results obtained.

*Extraction of material.*—The area of alopecia was scraped with a scalpel, and the surrounding hairs were pulled out with forceps, gathering all the material on a sterile surface.

*Direct examination.*—Made with potassium hydroxide and the Gueguen stain. Results negative.

*Cultures.*—Made on media of Sabouraud, with honey or glucose added; also in 1 per cent glucose broth in anaerobiosis. Negative results one month after seeding.

#### DISCUSSION

Is the alopecia here reported attributable to the inoculation of the leprosy material, or was its occurrence due to mere coincidence? Apart from its presumed leprosy etiology, we should bear in mind the possibility that other factors may have intervened, namely: traumatic, dietetic, mycotic, etc. For the purpose of elucidating these questions we have carried out several complementary investigations which we describe here in detail.

In the first place, we examined a total of 255 uninoculated hybrid mice of the same genetic extraction, and placed them under the same diet and care as the inoculated ones. In only 2 animals was a similar alopecia seen (Experiment 1). It happened, however, that these 2 mice were the only ones of the whole group of controls which were living together with the inoculated ones in the same cage. This fact posed the possible hypothesis that the alopecia was due to an infection.

The factor of traumatism is also worth bearing in mind, taking into consideration the localization of the alopecia, which was exclusively on the head. The plastic cages in which the animals were housed were covered with metal netting, through the interstices of

<sup>4</sup>The mycologic study was performed by Dr. Blanca C. de Braealenti, to whom we are thankful for her cooperation.

which they could extend their snouts. But the point of contact does not coincide with the area of alopecia which is, preferentially, retro-orbital, as shown in the photographs. Furthermore there is the fact that, except the 2 mentioned above there was no alopecia in the uninoculated animals which were housed in similar cages.

With respect to the dietary factor, the same objection can be made because of the absence of alopecia in the control animals kept on the same diet. The mycologic study carried out excludes the intervention of any such factor, since all the investigations were negative.

The fact that the alopecia plaques were seen only in female mice is suggestive. It should be investigated in order to find out whether a hormonal factor has anything to do with the matter.

This alopecia of the mice has a certain similarity to that observed in leprosy patients of the indeterminate form. In both cases there is absence of the severe dermal infiltration that is responsible for the alopecia of the lepromatous form. There is simply the falling of the hairs, without pronounced changes of the skin.

We have been unable to find in the available literature any report explaining the mechanism of this type of alopecia.

Dr. F. F. Wilkinson, of Buenos Aires, who also is working on the transmission of human leprosy to rodents, has similarly observed an alopecia in his inoculated mice (<sup>8</sup>), although it was somewhat different in its characteristics from that reported by us.

#### SUMMARY

In the course of a study on transmission of human leprosy to hybrid mice by Chatterjee's method, we failed to observe any development of lesions in a total of 102 animals inoculated. A development of interest, however, was a peculiar alopecia that occurred in 10.5 per cent of mice in the first experiment and 40 per cent in the second. This alopecia consisted of striking alopecia plaques on the head of females, with partial or total falling of the whiskers. Only the whiskers were affected in small proportions of the males (and more recent observations since this report was written have shown that the same condition occurs in normal males). The process in the females reached the most advanced stage in about 15 months, and then subsided in almost all the surviving mice. The alopecia did not occur in uninoculated controls in nearby cages, but it did appear in two uninoculated animals that were housed together with inoculated mice.

This observation led to a further study of the matter with similar results. Plaques of alopecia, especially in the periorbital areas, appeared only in females. Histologic examination showed hyperkeratosis, acanthosis and a dermal infiltrate of histiocytes, plasmocytes and lymphocytes. Search for acid-fast bacilli was negative in all instances.

Possible factors responsible for this alopecia other than the leprosy

inoculations were considered, and traumatic, dietary, and mycotic causes were discarded. The fact that alopecia plaques were seen only in females suggests the action of a hormonal factor still not elucidated.

This type of alopecia is compared to that seen in patients with the indeterminate form of leprosy.

#### SUMARIO

Durante el estudio de la transmisión de la lepra humana a ratones híbridos por el método de Chatterjee, en un total de 102 animales inoculados, no hemos podido observar el desarrollo de ninguna lesión. Sin embargo, una alteración de interés fue una alopecia peculiar que ocurrió en el 10.5 por ciento de los ratones en el primer experimento y 40 por ciento en el segundo. Esta alopecia consistió en llamativas placas alopecias en la cabeza de las hembras, con pérdida parcial o total de los bigotes (mostachos). Solamente en un pequeña proporción de los machos los bigotes fueron afectados (observaciones más recientes desde que este trabajo fue escrito, han demostrado que las mismas condiciones ocurren en machos normales). El proceso en las hembras alcanzan los más avanzados estadios alrededor de los 15 meses, apaciguándose después en la mayoría de los ratones sobrevivientes. La alopecia no ocurre en los controles no inoculados en las jaulas próximas, pero aparecieron en dos animales no inoculados que estaban alojados juntos con los ratones inoculados.

Esta observación condujo a un estudio posterior de esta cuestión, con resultados similares.

Placas de alopecia, especialmente en las áreas periorbitarias aparecieron solamente en las hembras. El examen histológico mostró hiperqueratosis, acantosis y un infiltrado dérmico de histiocitos, plasmocitos y linfocitos. La búsqueda de bacilos ácido-alcohol resistentes fue negativa en todas las instancias.

A más de las inoculaciones leprosas, fueron considerados los posibles factores responsables de esta alopecia, y fueron descartadas las causas traumáticas, dietéticas y micóticas. El hecho de que las placas de alopecia fueran vistas solamente en las hembras, sugiere la acción de un factor hormonal todavía no elucidado.

Este tipo de alopecia es comparado con aquel visto en pacientes con la forma indeterminada (incarácterística) de la lepra.

#### RESUMÉ

Au cours d'une étude sur la transmission de la lèpre humaine à des souris hybrides selon le méthode de Chatterjee, nous n'avons pas réussi à observer l'apparition de lésions parmi 102 animaux qui ont été inoculés au total. Toutefois, un point digne d'intérêt fut l'alopecie particulière qui survint chez 10.5% des souris lors de la première expérience et chez 40% lors de la seconde. Cette alopecie consiste en plaques alopeciques remarquables sur la tête des femelles, accompagnée d'une chute partielle ou totale des moustaches. Chez les mâles, et dans une petite proportion d'entre eux, seules les moustaches furent atteintes (des observations plus récentes, faites depuis que ce rapport a été rédigé, indiquent que la même condition survient chez des mâles normaux). Chez les femelles, le processus atteint son maximum en 15 mois environ, pour regresser alors chez presque toutes les souris survivantes. Aucune alopecie n'est survenue chez des souris non-inoculées placées dans des cages voisines, mais ce type de lésion est apparu chez deux animaux non-inoculés qui partageaient la cage de souris inoculées.

Cette observation a poussé les auteurs à étudier cette question plus avant, et des résultats similaires ont été obtenus. Des plaques d'alopecie, surtout péri-orbitaires, sont apparues, et ceci uniquement chez des femelles. L'examen histopathologique a montré de l'hyperkeratose, de l'acanthose, et une infiltration du derme par des histiocytes, des plasmocytes et des lymphocytes. La recherche des bacilles acido-résistants est restée négative dans tous les cas.



Les facteurs qui pourraient être responsables de cette alopecie ont été passés en revue, et des causes traumatique, diététique ou mycotique ont été écartées. Le fait que les plaques d'alopecie aient été observées uniquement chez des femelles suggère l'intervention d'un facteur hormonal non encore élucidé.

Ce type d'alopecie est comparé à celle observée chez les malades atteints de la forme indéterminée de la lèpre.

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