Social Interaction and Wounding in the Genesis of "Spontaneous" Murine Amyloidosis

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Seven strains of mice were closely observed during the development of amyloidosis in the absence of experimental manipulation except for alteration in group and cage sizes. Amyloid development was greatest in the strains showing the most evident effects of wounding from fighting activity. In groups fighting extensively, up to a 100% incidence of generalized amyloidosis was reached in submissive mice. Groups of female mice did not fight and only developed amyloidosis in association with infection. The occurrence of amyloidosis correlates with the chronic anemia and splenomegaly long known to attend submissive social standing within groups of male mice. Dominant mice were uniformly spared wounding, anemia, splenomegaly and amyloidosis as were singly caged mice. Amyloidosis appearing in the absence of experimental manipulation is a sequel of social submissiveness and consequent wounds (Am J Pathol 67:555–570, 1972).

THE MOUSE has been a favorite subject for amyloid studies since Davidsohn [1] found a higher incidence of induced amyloidosis in mice than in other animals studied. Laboratory mice also frequently develop amyloidosis in the absence of experimental manipulation; because this phenomenon is age dependent, it has been suggested as a valid model for human senile amyloidosis.[2] During our recent studies on the chemical characterization of both induced and spontaneous murine amyloid,[3] we noted an extensive degree of wounding in the high "spontaneous" amyloid strains of mice. This finding stimulated further investigation into the social and physical correlates of spontaneous amyloidosis. It is the purpose of this paper to report the relationship of spontaneous murine amyloidosis to social patterns and resultant wounding of submissive animals.

Materials and Methods

All mice except the SJL J strain were obtained from the National Institutes of Health Animal Production Section where they had been sex-segregated in groups of 25 to 50 animals at time of weaning (age 3 weeks) until received at

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our animal care facility at age 6 weeks. The SJL/J mice were obtained from the Texas Inbred Mice Co, Houston, Texas. All groups, from the time of receipt until sacrifice, were maintained in stable (unchanged) cage groupings on a standard laboratory diet consisting of Purina Laboratory Chow and tap water *ad libitum*. A mixture of pine and hardwood sawdust with cedar shavings was used for bedding in plastic cages and changed twice weekly. Two sizes of plastic cages were used: small, 6¼ by 10½ inches; and large, 18 by 10½ inches. A large number of mice were also caged singly in wire bottomed cages, 4 × 7 inches and 5 inches high. Most of the observations were made on general purpose Swiss albino mice (GP) from a noninbred colony. The NGP/N strain was derived from the GP strain and during this study was in the nineteenth through twenty-fifth generations of brother–sister matings. The remainder of the strains studied were inbred with the exception of the CFW strain which was on a restricted random mating system.

Tissues from mice sacrificed or found dead in a state suitable for autopsy were fixed for 24 to 48 hours in 10% neutral formalin, embedded in paraffin, sectioned at 6 μ and stained with hematoxylin and eosin as well as alkaline Congo red.[4] The spleen, liver, heart and kidney were systematically examined histologically with polarized light to identify amyloid by its green birefringence and to grade the amount of amyloid present in these organs. Microscopic examination was also made of the penis, preputial glands, scrotum and skin at the base of the tail. Also examined in the majority of mice were: brain, thyroid, eye, larynx, trachea, lung, thymus, pancreas, testis, adrenal, bladder and mesenteric lymph node.

Dominant or submissive status of each mouse was determined primarily by the presence of wounding and/or scarring (submissive) or its absence (dominant) at time of sacrifice. These observations were further verified by histologic examination of scarred areas. Each group was also observed during life and the dominant mice were not only unscarred, but showed a dominant behavior pattern.[5,6]

Sterile dissection of the periurethral glands was performed on one group of mice; pus was collected on sterile swabs and placed in thioglycollate broth. Standard bacteriologic methods of identification were performed on these specimens courtesy of Dr. James MacLowry of the NIH Clinical Center Clinical Pathology Department.

Splenic weights were determined on a Roller-Smith Precision Balance, model LG at time of sacrifice. Mice under ether anesthesia were exsanguinated by cutting the axillary artery and vein. Hematocrits were determined on paired samples of blood collected in heparinized microhematocrit tubes from the axillary pocket during exsanguination.

Results

Table 1 and Text-figure 1 present the relation of amyloidosis to social subordinate status. Dominant mice were easily recognized during life by their successful aggressive encounters with other mice and by the absence of wounds. The dominant mice were uniformly spared involvement by amyloidosis, while subordinate mice attained up to a 100% incidence of the disease. We initially attempted to quantitate wounding and relate this to distribution or quantity of amyloid, but found this impossible as wounds varied in depth and area as well as in temporal sequence. The presence or absence of healing or active

Table 1—Relation of Submissive (Wounded) Status to Amyloid Development in Male Sex-Segregated Mice.

Mouse strain	Age at sacrifice (mon)	Mice begun/ cage	Amyloidotic total wounded	Dominant
GP*†	4.5	6	1/5	1
GP*‡	5.5	6	2/5	1
GP*‡	8	5	1/2	2
GP	8.5	3	1/2	1
GP	9	6	3/5	1
GP‡	5.5	10	4/9	1
GP‡	7	10	5/8	1
GP‡	8	10	5/8	2
GP	6	10	6/6	1
GP	8	10	8/8	1
NGP/N	9	10	8/8	1
SJL/J	6	20	15/15	0
AL/N†	14	20	2/6	—
Balb/C†	8	10	0/0	—
C_3H/Hen†	12	25	0/0	—

* Maintained in small cages (65 sq in); the remainder were maintained in large cages (190 sq in).

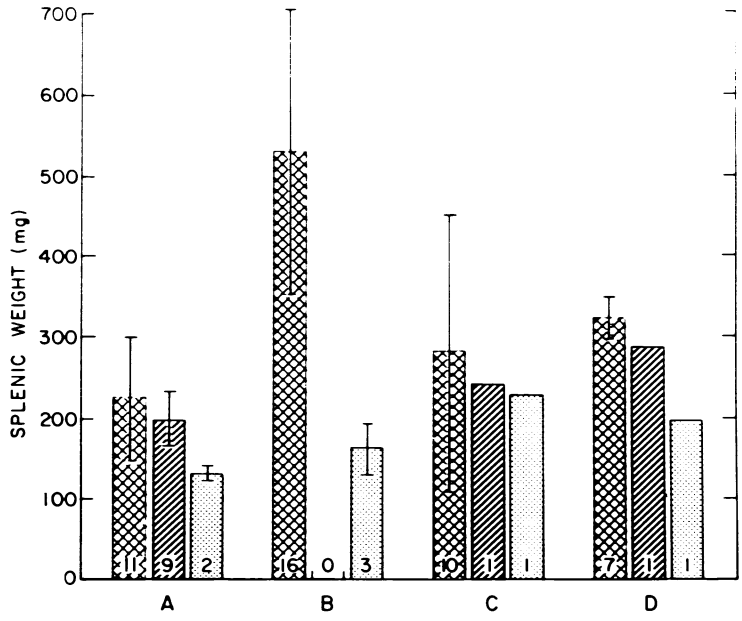
† No deaths prior to sacrifice in these groups. All other mice found dead were wounded and had extensive amyloidosis or acute pyogenic infection.

‡ Groups begun simultaneously.

abscesses in the scrotum and preputial glands did not correlate with the extent of cutaneous wounds. More importantly, the animals most severely wounded at the onset of fighting usually were not involved in subsequent fighting behavior and were found to have only healed wounds at time of sacrifice. There was a definite tendency for mice having only acute wounds at sacrifice to be without amyloid deposits.

Observations During Life

Within 4 to 6 weeks after receipt in our animal care facility, acute scarring associated with fighting wounds and attempted mounting became evident in the groups of GP male mice studied and blood was usually present on the sides of the cage. Although 1 or 2 animals in each cage had no evident scarring (Figure 1), all the remaining animals had scars and/or wounds of the scrotal area, base of tail and, frequently, of the entire back (Figure 2). In a single cage there were 3 unscarred mice, but one of these had an unexplained neurologic disorder with unsteadiness of gait and did not display dominant behavior patterns. He was neither submissive nor dominant, although he was operationally defined as dominant because of the absence of wounding.



TEXT-FIG 1—Splenic weights in wounded and amyloidotic mice (cross-hatched columns), wounded mice without amyloid (hatched columns) and dominant mice (dotted columns). Groups A, B and C represent, respectively, GP male mice in large cages sacrificed at 5, 7 and 9 months of age. Group D represents a group of CFW/N male mice sacrificed at 8 months of age. Twenty-five mice were begun in Groups A and B; 15 in Group C and 10 in Group D. Numbers of mice are noted at the bottoms of the columns. Line segments show standard deviations. All mice found dead had extensive amyloid and were wounded.

Fighting ceased at the approximate age of 7 months, and after this time many of the mice in the cage appeared sickly, with ruffled fur and greatly decreased activity. No ectoparasites were found in many observations made under the dissecting microscope. Wounds healed, blood was no longer seen on the sides of the cage and hair again appeared over the regions of wounding. At the approximate age of 9 months the only remaining sign of the former wounded status of the mice was the sparseness of hair over the wounded regions, particularly the scrotum and lower back. The patterns of aggressive behavior and scarring (summarized in Table 1 and Text-figure 1) were the same for the NGP/N mice as for the GP mice. The CFW mice had scars strictly confined to the region of the base of the tail and the posterior scrotum. The AL/N mice had few lesions, confined to superficial areas of the tail and focal areas of the snout. Observations during life were unable to establish dominant members of this group. Balb/C and C_3H/Hen mice produced no recognizable scarring and very little aggressive behavior. The SJL/J mice fought almost inces-

santly; there was extensive wounding of all mice, confined mostly to the back, but extending from the tail to the neck in all 15 survivors. In this group, no dominant members could be determined either by behavior or from pattern of scars. All of these mice had amyloidosis.

Anatomic Findings

Histologic observations in amyloidotic mice (Table 1 and Text-figure 1) revealed the most massive amyloid deposits in the spleen and liver. Deposits in the spleen circled the follicles and commonly filled the spleen, sparing only the follicles. Amyloid was deposited in portal and hepatic vein walls and was present in local, nodular deposits in the hepatic sinusoids. Mice with massive amounts of amyloid in liver and spleen also had extensive renal amyloid with involvement of the glomeruli, but most mice had amyloid only in the medulla of the kidney and in some foci in the lower cortical interstitium. The densest renal amyloid deposits were in the papilla and about 50% of the amyloidotic mice had papillary necrosis as previously described.[7] No amyloid was found in skin, including regions of wounding and scarring where dense dermal fibrosis and mixed inflammatory cell infiltrates were present (Figure 3) without any evidence of parasitic infestation. Preputial glands did not show amyloid, but had significant morphologic changes: the large ducts were often dilated with squamous metaplasia of the lining cells, and both active and healing localized abscesses in which bacteria were commonly demonstrated were frequently noted (Figure 4). There was a consistent amyloid distribution—*ie*, after establishing the amount of amyloid present in liver, spleen or kidney, the extent and distribution of amyloid could be accurately predicted in other organs and followed the pattern seen in late stages of induced murine amyloidosis.[8–10]

No amyloid deposits were found in the lung, but the submucosa of the larynx and trachea commonly contained amyloid. In mice with massive liver and splenic amyloid, the submucosa of the ureter and bladder had amyloid. The interstitium of the adrenal between the cortex and the medulla commonly contained amyloid and amyloid was frequently found in the thyroid interstitium. On only one occasion was amyloid found in the testis, as a small deposit adjacent to the basement membrane of a seminiferous tubule. Focal collections of amyloid were occasionally found in lymph nodes, usually ringing a medullary cord. The heart usually contained amyloid deposits, most commonly in the subendocardium of the atria, in the aortic or mitral valve and occasionally in the myocardial interstitium. Amyloid was commonly

found in the tongue, but was not found associated with skeletal muscle elsewhere, nor was it found in the brain or peripheral nerves. The submucosa of the distal small bowel consistently contained amyloid, but this was often minimal; occasionally, small deposits of amyloid were seen in the duodenum. Amyloid deposits were found around small vessels in the salivary glands and the pancreas.

Dominant mice shared some histologic findings with their submissive and amyloidotic cage mates. All of the older mice had focal lymphocytic and plasmacellular infiltrates of the renal interstitium and hepatic portal areas. Hepatic parenchymal cellular (particularly nuclear) variation in size and form was seen in all older mice.

Splenic weights of dominant mice were consistently lower than splenic weights of submissive mice (Text-figure 1). The differences between the splenic weights of dominant mice and those of the wounded groups are each significant by the Student's t test at a level of less than .01 for Groups A, B and D. The anemia of subordinate and amyloidotic mice is documented in Table 2. These values are also significant at a P value less than .01.

Cultures for bacteria were taken from 5 subordinate mice in Groups B (Text-figure 1) with grossly visible periurethral gland abscesses at autopsy (0.1 to 0.3 cm in diameter). Two of these grew *Proteus mirabilis* and *Staphyloccus aureus*, one grew *S aureus* alone and the last two revealed *P mirabilis* only.

Control Observations on Female Mice, and Males Housed in Small Groups

Thirteen groups of 2 to 3 male GP mice were placed into the small wire cages at 6 weeks of age. Within 1 month 50% of the cages had only 1 live mouse and within 10 weeks of receipt of the animals, all cages had only 1 live mouse. Most of those dying had wounds, but many did not and the cause of death was not apparent at autopsy.

Table 2—Representative Mean Hematocrit Values (in percent) of Submissive and Dominant Mice

	Wounded with amyloid	Wounded without amyloid	Dominant
Group A	37.7	37.5	44
	(29–38)	(24–41)	(43–45)
Group B	31.5	—	44
	(25–37)		(43–45)

Range of values in parenthesis.
Group designations refer to those of Text-figure 1.

Active fighting behaviour did take place in each cage. The survivors of these encounters lived up to 10 months of age. None of these animals had amyloidosis.

Twenty-three male GP mice were housed singly in small wire-bottom cages, and none had developed amyloid deposits at sacrifice or death at 10 to 12 months of age. A group of 20 GP female mice housed in a large cage evidenced no fighting and at sacrifice of 18 months, 2 had amyloid and both of these had severe pyogenic infection involving the kidneys. Twenty SJL/J female mice were housed in a large cage and neither fought nor had amyloid deposits at sacrifice at 7 months of age.

Fourteen retired male and a similar number of retired female breeders of the NGP/N colony were received at 5 to 6 months of age and caged singly. The males survived to an average age of 10.4 months; they either died from inapparent causes in the cages or were sacrificed. The longest survivors (4 mice to 12.5 months) were sacrificed. The females survived an average of 11.1 months, and were free of amyloid as were the males. As a further control to guarantee that these animals received as retired breeders were still active fighters, a group of 6 males were caged together after being caged singly for 1 to 2 months. Within 1 month 3 were dead from fighting and after 2 months together in a large cage only 1 mouse was left alive. None of these six had amyloidosis. At the same time 5 female mice were caged together. At sacrifice at 11 months of age, they had no scars and no amyloid.

Discussion

Since dominant mice never had amyloidosis, this study demonstrates a clear relationship between social subordinate status and the development of amyloidosis. The relationship is further strengthened by the finding that splenomegaly and anemia, long known to be associated with submissive social standing [11-13] are also demonstrated in wounded and amyloidotic mice. Submissive status preceded amyloid development and was not a result of this condition as social status was constant from onset of fighting (at an age when no amyloid was present) to sacrifice. The data from paired cages of GP mice summarized in Text-figure 1 and Table 1 also demonstrate that wounding, splenomegaly and anemia temporally precede amyloid development. It seems most probable that previous studies have not documented this relationship because observations were not directed to physical and social correlates of amyloid development in individual mice and

because the scars of submission are often subtle and have usually healed by the time of sacrifice. Tucker and Baker,[14] highlighted fighting as the prime cause of death in sex-segregated males from an outbred albino mouse colony. Amyloidosis was present in 45% of the mice found dead with lesions attributed to fighting. Perineal and preputial gland abscesses caused by *S aureus* were often present in their study as well as in the present study.

Splenomegaly in the submissive and/or amyloidotic mice undoubtedly reflects cellular proliferation related to amyloid formation,[9,10] as well as splenic hematopoiesis related to anemia in subordinate mice.[12,13] Reduction in spleen size at 9 months (Group C, Text-figure 1), has a direct parallel in reduced spleen size late in induced murine amyloidosis.[15]

The organ distribution of amyloid in our mice differs only slightly, and probably insignificantly, from that previously reported in "spontaneous" murine amyloidosis [16–18] as well as the induced disease model.[8–10] Indeed, Thung theorized from histopathologic data that induced murine amyloidosis and the senile amyloidosis of untreated mice were basically similar conditions.[19] Dunn has written that the "primary" and induced forms differ in the decreased prevalence of splenic amyloid in the primary form.[20] However, these differences can be resolved by considering the demonstration that patterns of organ distribution are not constant. Differential amyloid resorption from various tissues is known to take place after the experimental induction of the condition wherein amyloid deposits decrease in liver and spleen while renal deposits increase in amount.[15,21] A parallel example is evident in the Tucker and Baker report [14] of spontaneous amyloidosis in which a different pattern of amyloid deposition from that in mice dying early, was seen in mice over two years of age with amyloid found in only one organ, usually the kidney. If patterns can change after amyloid deposition, it seems equally likely that the chronicity of the amyloidogenic stimulus and the rate of amyloid deposition would affect organ distribution. This concept is also supported by a recent study in which spontaneous amyloidosis in caged wild mice showed extensive splenic amyloid deposition.[22]

The design of the present study does not allow the separate evaluation of the two prime variables—*ie*, a) the stress of the state of submissiveness and b) the state of having wounds, as both conditions are present in amyloidotic animals. There are good indications from previous studies that wounds are not necessary for the elevation of adrenocortical activity found in submissive mice.[23,24] It has also been

demonstrated that exogenous administration of adrenocorticoids can increase the amount of amyloid deposition in induced experimental amyloidosis.[25–28] Therefore, the stress resulting from the state of submissiveness may affect the degree and/or rate of amyloid development in addition to the effect of wounding. Another parallel between spontaneous murine amyloidosis and the pathophysiologic consequences of crowding is the example of reserpine administration which reduced spontaneous amyloid deposits [29] and reduced adrenomegaly and fighting behavior.[30] Recent studies in the white Pekin duck [31] have demonstrated a relation of amyloidosis to experimental social grouping, with a higher incidence of amyloidosis associated with larger numbers of ducks caged together.

It is most enticing, however, to relate spontaneous amyloidogenesis to the physical insults of chronic inflammation and/or infection as this is a long established relationship in the development of "secondary" amyloidosis in humans and animals.[32] Infection was not demonstrable in most mice in our study and seems unlikely in animals with little scarring, however, *P mirabilis* and/or *S aureus* were cultured from periurethral gland abscesses in 1 group of mice. The importance of chronicity of the wounding is demonstrated by the lack of amyloid in animals with only acute wounds. The importance of wounding in the genesis of amyloidosis is demonstrated by the single mouse that for reasons of some underlying neurologic condition stood outside the social hierarchy, and was neither wounded nor dominant. He did not develop amyloidosis.

Not only did fighting within a group of mice correlate with amyloidogenesis, but strain differences in aggressive behavior were directly related to amyloid development. Thus the Balb/C and C_3H/Hen mice had no scars and no amyloid (Table 1); the AL/N strain had little scarring and little amyloid development; the SJL/J strain had 100% incidence of scarring and amyloidosis; and the remaining three strains had up to 100% incidence of amyloid in scarred mice with uniform sparing of wounding and amyloid development in dominant mice. It is evident, however, that there are other important strain-related variables the nature of which are presently unknown. This is most forcefully demonstrated by the finding of no amyloid in 12 Balb/C male mice of 1 to 2 years of age which were extensively wounded.[33] The rarity of amyloid development in Balb/C mice has been commented upon by Dunn.[20]

It has been theorized that spontaneous murine amyloidosis is the result of an autoimmune process,[34] however, this seems unlikely as

the lymphocytoid infiltrates cited as evidence for this theory[35] are also found in dominant mice. Also, through the courtesy of Dr. Norman Talal of the National Institute of Arthritis and Metabolic Diseases, sera from dominant and amyloidotic mouse were tested for antibody activity to DNA and RNA with negative results. In addition, sera from many sex-segregated aged GP mice have been tested by Dr. L. R. Barker, formerly of the National Institute of Allergy and Infectious Diseases, for antinuclear antibodies by an indirect fluorescent antibody test. Positive results were found only in rare females.

Crowding does not seem to be a factor in the development of spontaneous amyloid at the range of densities studied. There is good evidence that aggressive behavior is found in the defense of territory at low population densities, but that this behavior is utilized in the establishment of a social hierarchy at higher population densities.[36,37] Review of Table 1 reveals that cages with the largest numbers of mice, irrespective of density, developed the highest incidence of amyloidosis. It would seem that in any caging arrangement in the present study, the mice were already at a density in which their aggressive behavior patterns are utilized to establish a social hierarchy. This study underlines the great importance of social interaction as well as sex and strain differences in the outcome of long-term experiments with mice.

Our findings demonstrate that some murine amyloidosis previously considered unrelated to any predisposing factors, except for genetic differences[33,38,39] or, possibly psychologic stress,[40] is the result of discernable predisposing conditions. This conclusion emphasizes the necessity of investigating all cases of so-called "idiopathic" or "primary" amyloidosis in humans or animals in order to determine if an underlying inflammatory process or metabolic derangement is a predisposing factor for the development of this disease. Such investigations are of particular relevance since the association of amyloidosis with the immune system has recently been strengthened by the identification of some human amyloid fibril proteins as homogeneous fragments of immunoglobulin light chains.[41,42]

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Acknowledgments

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[*Illustrations follow*]

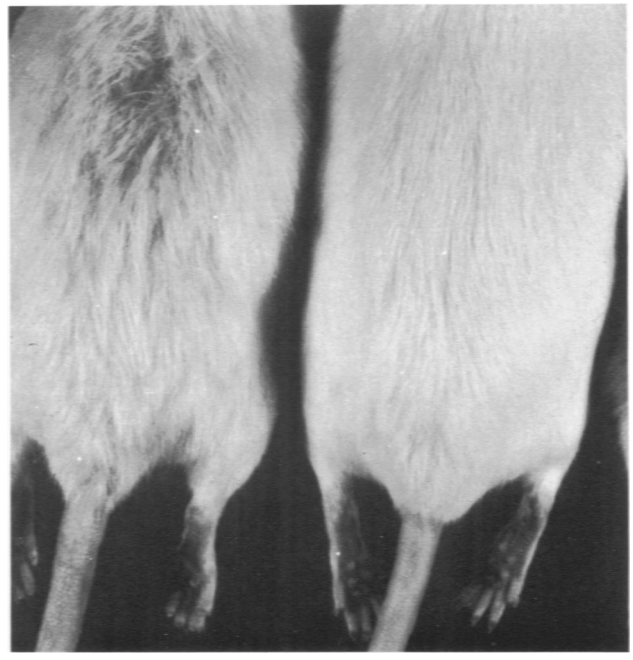

Fig 1—Both mice are 7-month-old GP males. The one on the left is one of two dominant males from the same cage as the mice in Figure 2. The former had no amyloidosis, but there was dermal scarring at the tail base, and a dishevelled appearance to his coat is evident when compared to the mouse, a retired breeder, on the right.

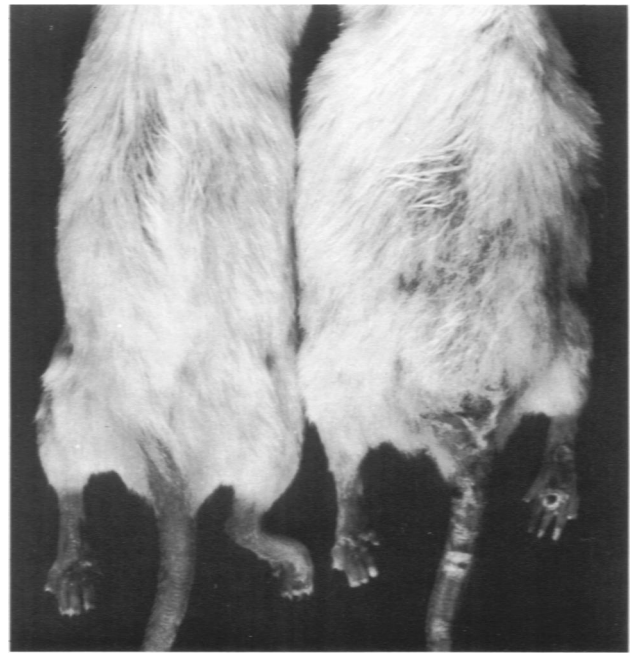

Fig 2—Two submissive, 7-month-old GP male mice from a cage with 25 mice initially present. The mouse at the right had unhealed wounds of the tail base and right leg. The mouse at the left had sparseness of hair at the tail base with dermal scarring. Both mice had amyloidosis.

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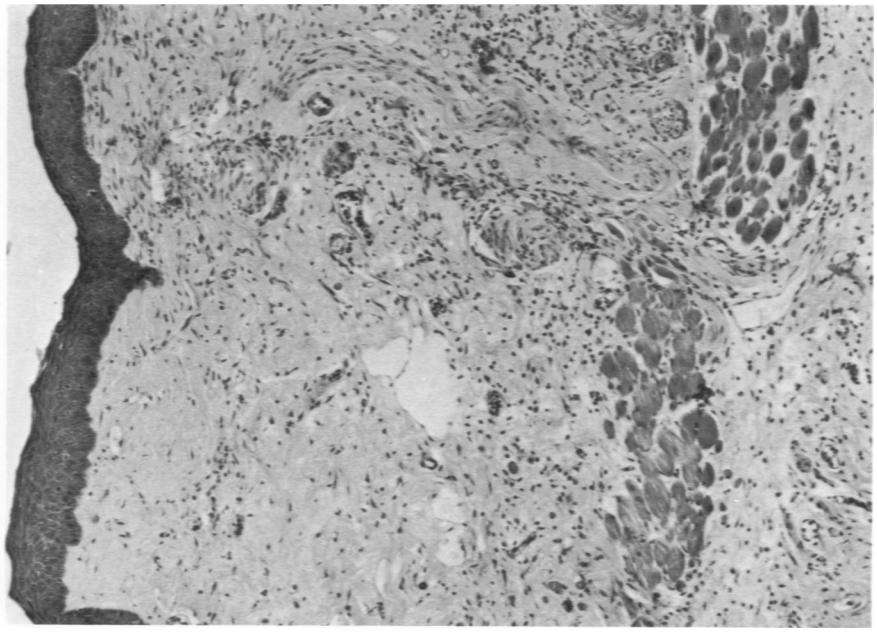

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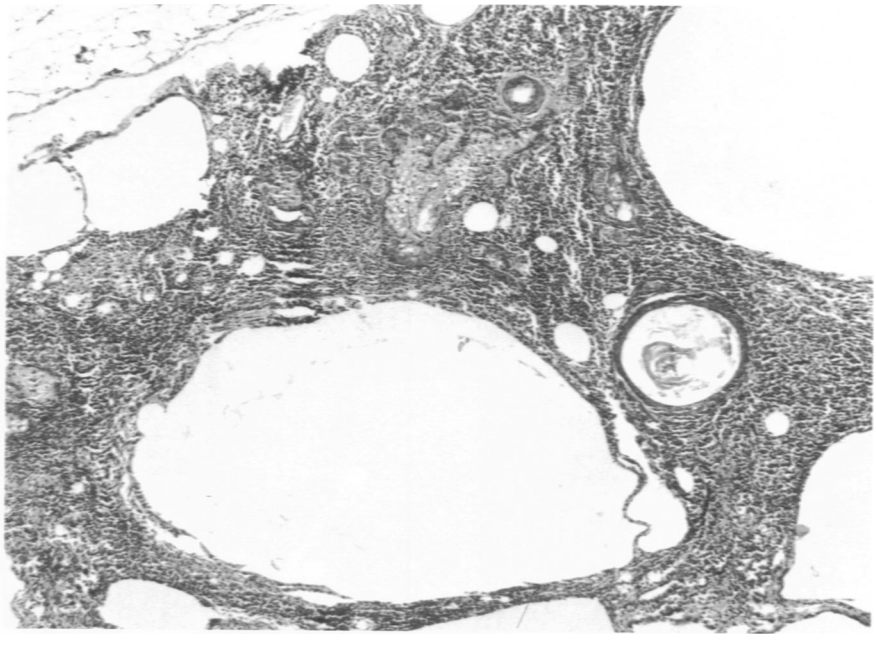

Fig 3—Skin of the tail base in a 7-month-old submissive GP male mouse with amyloidosis. There is dense scarring of the dermis and subcutis with sparse scattering of chronic inflammatory cells (H&E, × 100). **Fig 4**—Preputial gland from a 7-month-old submissive male mouse with amyloidosis. Huge, dilated ducts and a dense chronic inflammatory infiltrate have replaced most of the gland. Squamous metaplasia of two ducts is present (H&E, × 65).