jections the lesions were orange-blue, slightly painful to the touch, and looked as though they would become necrotic. The intramuscular injections were then stopped, and the reactions subsided slowly over 2 weeks. A generalized macular eruption also appeared soon after the injections were stopped, most marked over the wrists and ankles, which cleared in 5 days. The local reactions in the thighs appear to have been typical Arthus phenomena, similar to those produced in the rabbits receiving penicillin alone. There is no good reason to believe that oil and beeswax would produce such typically localized reactions.

Discussion. Allergic sensitivity reactions were demonstrated in guinea pigs and rabbits with pure, white, crystalline penicillin G, and with commercial calcium penicillin. These took the form of mild local urticaria after intradermal injections, sometimes without previous known exposure to penicillin, and, more typically, of lesions characteristic of the Arthus phenomenon, some very intense. The reactions with commercial penicillin were no more intense than those with pure penicillin. It is, therefore, apparent that penicillin itself may act, presumably as a haptene in combination with body proteins, as a sensitizing agent, since Chow and McKee have shown that there could be a union between penicillin and serum albumin.[18]

General hypersensitiveness in guinea pigs was not demonstrable with crystalline penicillin, although McClosky and Smith[17] have reported this with less pure penicillin. This discrepancy may depend upon the purity of the preparation, reactivity of the guinea pigs used, or possibly upon differences in technic or dosage. However, it appears that with pure penicillin systemic sensitivity is definitely less important than the local, or contact sensitivity. The skin is an important organ through which penicillin sensitivity is mediated as with some other drugs.

Conclusions. 1. Mild preexisting sensitivity to pure crystalline sodium penicillin G, injected intradermally, was demonstrable occasionally in guinea pigs and rabbits. 2. Typical general sensitivity could not be demonstrated with pure penicillin G applied to guinea pigs by local or parenteral routes. 3. Local sensitization of the Arthus type phenomenon was produced consistently by repeated injections into rabbits of pure sodium penicillin G, or commercial calcium penicillin. These reactions were comparable to those produced by similar injections of horse serum, but somewhat less intense. 4. Similar local sensitization was observed in a patient injected with commercial penicillin in oil and beeswax. 5. Accordingly, the purest obtainable crystalline penicillin can act as a sensitizing agent with manifestations like those of native protein, and the skin is the outstanding organ for the seat of the allergic reaction.

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Comparative Numbers of Fungiform and Foliate Papillae on Tongues of Domestic and Wild Norway Rats.*

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Previous physiological and anatomical studies have revealed marked differences between domestic Norway rats which have lived for many years under laboratory conditions and wild Norway rats which have

* A grant from the International Health Board of the Rockefeller Foundation aided this investigation. The Rodent Control Office of the City of Baltimore supplied the wild Norway rats; Mr. Jack Spencer of the Fish and Wildlife Service in Gainesville, Fla., supplied most of the Alexandrine rats.

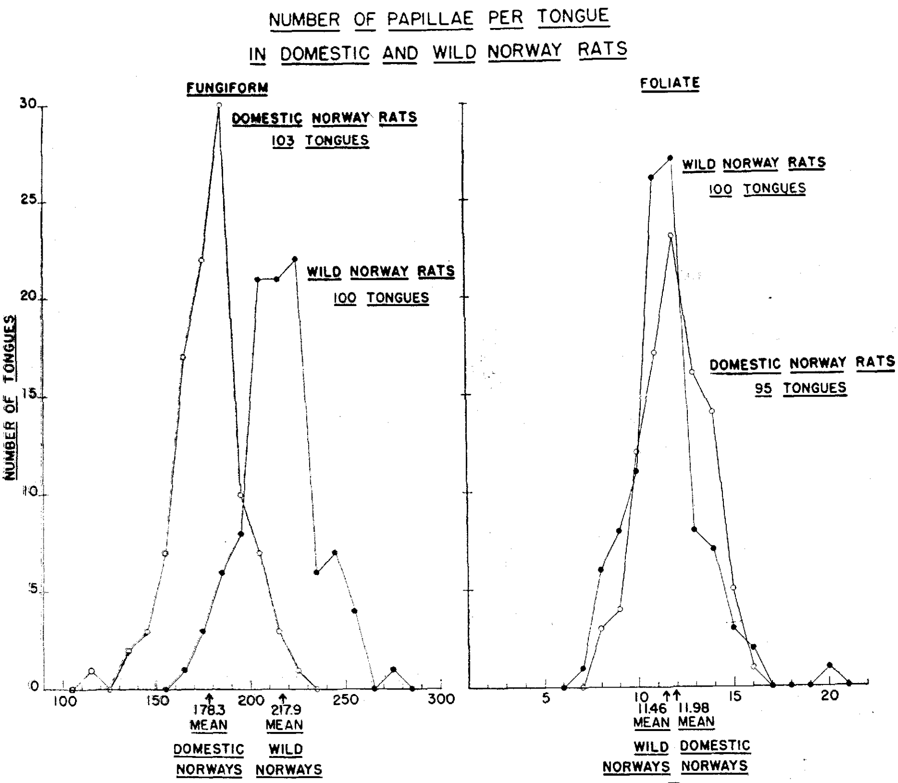

FIG. 1.

just been trapped from the cellars, yards and alleys in a large city. It was found: (1) While wild rats have a high resistance to poisoning with thiourea, as much as 2000 mg per kg body weight being required to kill them, domestic rats show a great sensitivity, succumbing to doses as small as 5 mg per kg body weight.[1] Thus, over a 400-fold difference exists between the 2 strains in the amounts of thiourea needed to kill them. Furthermore, the wild rats killed with thiourea do not show pulmonary edema or pleural effusion, the characteristic symptoms of domestic rats poisoned with thiourea. (2) While wild rats react to sounds of high frequency by furiously attacking the source of the stimulation, a large percentage of domestic rats manifest so-called running fits and convulsions and die in a coma.[2] (3) Owing to a retrogression of their adrenal cortices, domestic rats have much smaller adrenal glands.[3,4]

The present study has revealed that a marked difference exists also between the number and appearance of fungiform papillae on the tongues of these 2 strains of Norway rats.

The gross appearance of the tongues of domestic rats, the number and size of their fungiform and foliate papillae, were described in a previous paper.[5] In the present study a comparison has been made between these previous findings and data obtained with essentially the same technic from recently trapped wild rats. Observations were made also on a few Alexandrine rats *(Rattus rattus alexandrinus)* which, next to the Norways, are the most common and widely distributed rats throughout the world, inhabiting ships and seacoast towns, and building their nests in rafters and upper stories of

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3 Donaldson, J. C., PROC. SOC. EXP. BIOL. AND MED., 1928, **25**, 300.

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buildings rather than burrows or cellars. They are less ferocious than wild Norways and prefer an herbivorous rather than an omnivorous diet.

The 103 domestic rats used in the previous study ranged in age from 8 hours to 466 days and came from a colony of rats of the Wistar strain which had been interbred with rats of the hooded strain from the colony of Dr. E. V. McCollum. No new strain has been added during the past 20 years.

The 100 wild Norway and 20 Alexandrine rats used in the present study ranged in weight between 75 and 487 g and constituted a random sample taken from thousands of rats which were trapped from the yards, alleys and cellars in the residential districts of the city of Baltimore. Most of the Norways were killed and injected within a few days after their capture but most of the Alexandrines were used for various experiments beforehand.

The tongues were injected with methylene blue through the carotid arteries by the same technic as was used previously for the laboratory animal.[5] The fungiform and foliate papillae were observed under a dissecting microscope and plotted on large charts for counting. The papillae were counted usually shortly after the removal of the tongues but, in a few instances, they were placed in formalin and were not counted for 10-20 days.

Results. These observations showed that in gross appearance the tongues of wild Norway rats closely resemble those of domestic rats, but their fungiform papillae are smaller and more uniform in size and are more liberally distributed along the sides of the "intermolar eminence," or large hump near the base of the tongue.

Fig. 1A compares the number of fungiform papillae found on the tongues of 103 domestic Norways and of 100 wild Norways. Calculation leads to mean values and standard deviations of 178.3 ± 15.1 papillae per tongue for the domestic rats and 217.9 ± 19.0 for the wild rats. Thus, there is a statistically significant difference between the number of fungiform papillae in the 2 strains of rats, with the mean for domestic Norways falling 17% lower.

The lowest and highest counts for domestic Norways were 114 and 221 fungiform papillae per tongue, with only one rat having a count above the mean for wild Norways. The wild rat counts ranged from 167 to 271, with only 3 tongues having papillae counts below the mean for domestic rats.

The foliate papillae of wild rats tend to have a more uniform size and shape than do those of laboratory animals. In general the individual papillae are shorter and only occasionally deviate from the typical groove-like structure. The "V," "Y" and "H" forms characteristic of laboratory rats are rare. At both ends of the row of papillae the slits tend to become shorter, and anterior ones appear as small pits.

Fig. 1B shows the number of foliate papillae per tongue for 95 domestic and 100 wild Norways. The range for the domestic rats was from 8 to 16 and for the wild Norways from 7 to 20. The respective means and standard deviations are 11.98 ± 1.72 for domestic and 11.46 ± 1.98 for wild rats. Although there was no essential difference in the average number of foliate papillae, the wild rats showed a definitely wider range of variation.

For the 20 Alexandrines the corresponding values are 191.5 ± 23.8 (range 147 to 231) fungiform papillae per tongue, and 13.5 ± 2.4 (range 9 to 18) foliate papillae. The mean number of fungiform papillae in this smaller series of Alexandrine rats thus falls between the means of the domestic and wild Norways, while the mean number of foliate papillae is somewhat greater than that found for either strain of Norway rat. The character and distribution of the fungiform papillae resemble those of the laboratory rat tongue, while the foliate papillae are more like those of the wild Norway.

Discussion. The results of these observations indicate that in some way the domestic rats of our colony have been selectively bred for a lower number of fungiform papillae. This selective breeding may have taken place before the rats arrived in our colony, or it may have taken place during the last 20 years. In this period the only selective breeding that has been practiced wittingly, and that only to a limited extent, has been for running activity in revolving drums.

The reduced number of fungiform papillae may be an instance of the effect of domestication which results when rats no longer have to forage for their food or to depend on finer taste differentiations in the selection of their food. Before such a conclusion could be drawn, it would be necessary to know whether domestic rats from other colonies show a similar reduction in the number of papillae. Whether or not a direct relation exists between keenness of taste and the total number of fungiform and foliate papillae (and, indirectly, the taste buds contained in them) remains unknown. Taste-threshold tests made before and after sectioning of taste nerves to the various papillae may provide an answer to this question.

Finally, attention may be called again to the opportunity offered by these findings for studies in the field of genetics. An actual count of the papillae makes it possible to express a feature of a strain of rats in numerical rather than in qualitative terms.

Summary. 1. The number of fungiform and foliate papillae were counted on the tongues of 100 recently trapped wild Norway rats and of 20 wild Alexandrine rats, and compared with the number on the tongues of 103 domestic Norway rats. 2. The number of fungiform papillae on the tongues of the domestic Norway rats ranged from 114 to 221, with a mean of 178.3, while for the recently trapped wild Norway ancestors it ranged from 167 to 271, with a mean of 217.9, and for the Alexandrine rats it ranged from 147 to 231, with a mean of 191.5. The mean of the domestic Norway rat thus showed a 17% reduction from that of its wild ancestor. 3. The number of foliate papillae ranged from 8 to 16 for the domestic rats, with a mean of 11.98, and ranged from 7 to 20 for the wild Norways, with a mean of 11.46. The 2 strains thus showed essentially the same number of foliate papillae, but both showed fewer than are found in Alexandrine rats, in which the number of papillae ranged from 9 to 18, and had a mean of 13.5. 4. In general, both types of papillae were more uniform in size, structure and distribution in the wild than in the domestic strains.

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Effect of Riboflavin Deficiency on Endochondral Ossification of Mice.*

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The role of riboflavin in the maintenance of normal body growth has been demonstrated in rats, mice, pigs,[1] and monkeys.[2] Growth is retarded if riboflavin is omitted from the diet, and young rats are born with skeletal abnormalities[3] (especially micromelia) if the mothers are fed a riboflavin-deficient diet during pregnancy. These observations indicate a disturbance of endochondral ossification. The present investigation was undertaken in order to determine which phase of this process is dependent upon the presence of riboflavin, and to compare the find-

* Aided by the Louis M. Monheimer Memorial Fund.

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