Estudios en honor de
Gustavo Hoecker
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ON THE ORIGIN OF MICE

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DEDICATION

The mouse, in particular its tame variety, the laboratory mouse, has probably brought more people together than many a Lonely Hearts Club. At first it was the "mouse fanciers" who sought each other out to talk about their common interest. Then pet dealers made many contacts through the mouse. These days, however, it is mainly the scientists who use mice as a means of making overtures. They get together, and what do they talk about? Not about the weather, not about politics, but about mice. Hundreds, perhaps thousands of scientists have made acquaintances, struck up friendships, and yes, even found mates through mice.

It was through mice that we got to know Gustavo Hoecker. We knew about him long before we met him*: his paper on the serological similarity between *H-2* and *Rh* (Hoecker *et al.*, 1954) was a classic and anybody who was seriously interested in the *H-2* complex had to read *all* his papers. [Footnote: *One of us (F.F.) worked as a student in Professor Hoecker's laboratory]. Therefore, when our paths finally crossed, there were no awkward moments of choosing the right topic for discourse. It was as if we had known him for ages and the meeting was just an opportunity to continue an interrupted conversation. For we had a subject that interested us all — mice. We think it therefore befitting that we are able to contribute to this volume of *Anales de la Universidad de Chile*, which is

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published in his honor, with and essay on the origin of the animal that brought us together.

MOUSE POLITICS

There are two forms of the house mouse, western and eastern, and they have divided the world between themselves (no Third World mouse has emerged as yet). They differ in color (no, neither variety is red, nor even pink), but so very slightly that a layman has difficulty distinguishing them. They also differ in the tail lenght and, most importantly, in their genes. If given no other choice, they interbreed but the progeny is often sterile. These facts leave plenty of room for an argument as to whether the two forms are different species or two subspecies of the same species. We are not interested in that argument and will call the forms "species" because their names are then shorter. The western form is *Mus domesticus*, the eastern form *Mus musculus*.

In Europe, they meet in a narrow zone that runs across the Jutland peninsula (a line Tarm-Billund-Fredericia) and then across Holstein, south to the Elbe, and follows a line Dessau — the river Zwickauer Mulde — Nürnberg — Regensburg — München — and the river Isar (Zimmermann, 1950; Reichstein, 1978). In Austria the zone reaches the Vorarlberg, north Tyrol, and south Salzburg (Fig. 1). This border between the species is not very far from the political border between Western and Eastern Europe. In contrast to the political border, however, there are no walls, no minefields, and no visa requirements to keep the two mouse species to their respective sides. In fact, where the two species meet, they mix in a narrow hybrid zone (Zimmermann, 1950; Sage *et al.*, 1986). There is no natural physical barrier separating the two species, no mountain range, no river, yet they still respect the border between them.

Outside Europe, *M. domesticus* has colonized all of America, all of Australia, and at least some parts of Africa. *M. musculus*, on the other hand, is distributed over entire northern Asia (Soviet Union and China; Fig. 3).

The first question we must therefore ask is: How have the two species attained their present-day distribution? Before we attempt to answr it, however, let us mention some of the other species of *Mus*, and also discuss some of the genetic differences between *M. domesticus* and *M. musculus*.

MOUSE ALLIES

The members of the genus *Mus* can be divided, rather artificially, into two groups, the mice of the *musculus-domesticus* complex and all the others. In

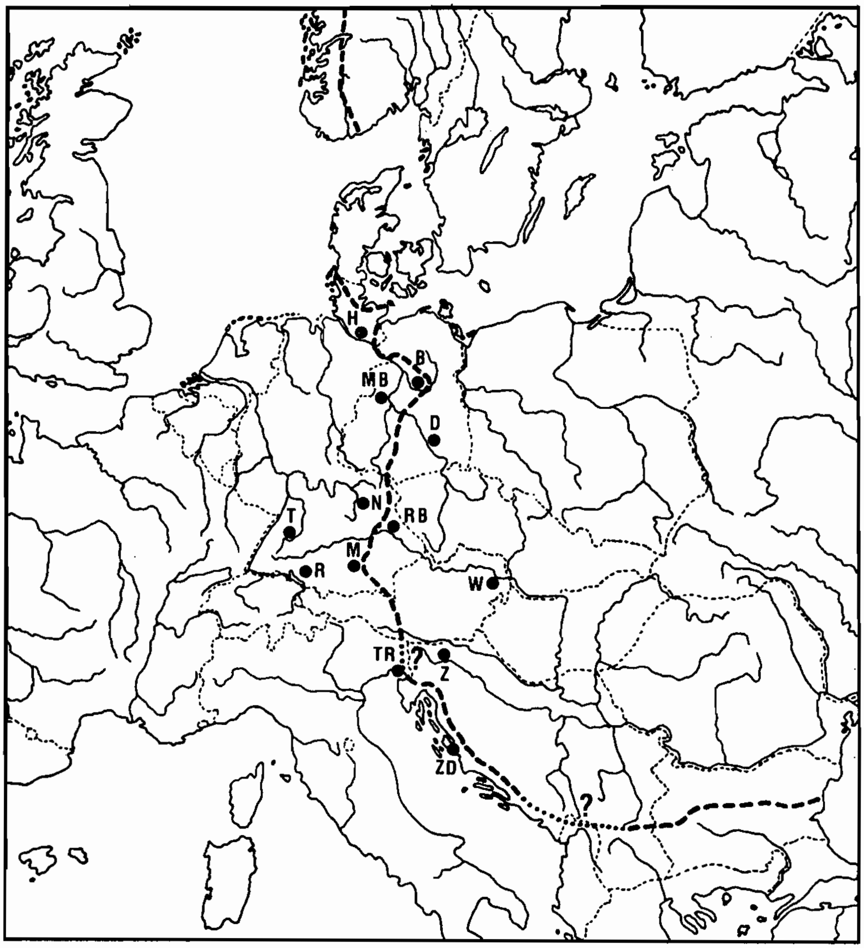


Fig. 1. The hybrid zone between *Mus domesticus* (west) and *Mus musculus* (east) in Europe. Dashed line indicates the firmly established border, the dotted line with question mark indicates a tentatively established border.
B, Berlin; D, Dresden; H, Hamburg; M, München; MB, Magdeburg; N, Nürnberg; R, Ravensburg; RB, Regenburg; T, Tübingen; TR, Trieste; W, Wien; Z, Zagreb; ZD, Zdar.

the former group (Table 1) are mice that interbreed with *M. musculus* and/or *M. domesticus*, both in the wild and in the laboratory (e.g., *M. musculus* interbreeds with *M. domesticus* in the hybrid zone in central Europe) or only in the laboratory (e.g., *M. domesticus* interbreeds with *M. spretus* under laboratory conditions but not in the wild). In the latter group

TABLE 1

THE HOUSE MOUSE, ITS CLOSE RELATIVES AND THEIR DISTRIBUTION. (BASED PRIMARILY ON MARSHALL 1977, 1981)

Species	Subspecies	Status	Distribution
Mus domesticus	*domesticus*	C	See Figure 2
	poschiavinus	C	Valle di Poschiavo in Switzerland
	brevirostris	C	From Yugoslavia to Greece; Aegean and Ionian Islands; Mediterranean Islands to the Iberian peninsula; central and southern France
	praetextus	F	Northern Africa; eastern Mediterranea area to Arabia; Cyprus; Crete; Lampedusa
	bactrianus	F	Deserts of Afghanistan and Pakistan
	homourus		Higher altitudes of Himalayas
	gentilulus		Southern and eastern edges of the Arabian peninsula
Mus musculus	*musculus*	C, F	See Figure 2
	wagneri	F	Turkestan; China; Mongolia
Mus castaneus	*castaneus*	C	Southern Asia from at least Central India and Sri Lanka to Taiwan; Indonesia; and the Philippines
	tytleri	C	Cities of north-central India
Mus molossinus		C	Japan; Manchuria; Korea
Mus spretus		F	Iberian peninsula; southern coast of France; north Africa
Mus hortulanus		F	Austria; Czechoslovakia; Hungary; Yugoslavia; Greece; Rumania; Bulgaria
Mus abbotti		F	Greece; Yugoslavia; Turkey; southern Iran to the southern coast of the Caspian Sea

C, commensal; F, free-living.

(Table 2) are mice that either do not interbreed with *M. musculus* and *M. domesticus* at all, or interbreed only under special conditions such as by artificial insemination (e.g., *M. domesticus* with *M. caroli*). Even in the former group, however, the interbreeding of forms is often accompanied by sterility of the resulting progeny.

The taxonomy of the *musculus-domesticus* complex is extremely difficult. Ellerman listed in 1941 some 170 forms described in the literature; since that time a few more have been added to this list so that the number is now around 200. The first attempt to bring some order into a very confusing situation was made by Schwarz and Schwarz in 1943. Although the classification these two authors proposed is now looked down upon by contemporary mouse taxonomists, the truth is that it has served as the foundation on which modern taxonomists have based their classifications. It has therefore fulfilled an extremely useful purpose and it is petty to try and deny it.

The system used in Tables 1 and 2 (and Fig. 2) is principally that of Marshall (1977, 1981). In it, the *musculus-domesticus* complex is divided into seven species, some living in close association with man (the commensal forms) and others living more or less independently of man. Some of the species are then subdivided into subspecies. The main pitfall of this system is that it completely ignores the forms described in the Soviet Union and China, of which there are many (Argiropulo, 1940). But even as far as western Europe is concerned, the system is biased because it includes forms such as *M. poschiavinus*, which may no longer exist in the wild, and ignores others such as *M. helgolandicus*, which are well-defined. The main difficulty with any classification system of the *musculus-domesticus* complex is that the forms are often extremely hard to distinguish from one another. Often the best identifying characteristic is the place of origin of the specimen. We are convinced that not even Joe Marshall would be able to correctly identify ten specimens representing the different subspecies if he did not know where the specimens came from. Most of the subspecies are, therefore, best thought of as geographical variants that are clearly distinct from neighboring variants but are difficult to evaluate in the context of all the forms in the *musculus-domesticus* complex. To someone interested in speciation, the complex provides extremely interesting material to study but to a taxonomist, the complex is a nightmare.

The situation is somewhat better ouside the *musculus-domesticus* complex but only as far as the Asian species of the genus *Mus* are concerned, mainly because of the efforts of Marshall and his colleagues. The African species are awaiting another Joe Marshall to put them in order. At least

TABLE 2.
THE MORE DISTANT RELATIVES OF THE HOUSE MOUSE.
(BASED ON CORBET AND HILL 1986)

Species	Distribution
	AFRICA
M. baoulei	Ivory Coast
M. bufo	E. Zaire
M. callewaerti	S. Zairte, Angola
M. goundae	N. Central African Republic
M. gratus	W. Uganda
M. haussa	Senegal-Niger; steppe
M. indutus	S. Africa, Bostwana
M. mahomet	Ethiopia
M. mattheyi	Senegal-Ghana; savanna
M. minutoides	All of Africa south of the Sahara
M. oubanguii	Central African Republic; savanna
M. proconodon	Somalia, Ethiopia, Zaire
M. setulosus	Guinea-Gaboni; Ethiopia
M. setzeri	Botswana, Zambia
M. sorella	Uganda, Kenya - Zambia
M. tenellus	East Africa
M. triton	E. Zaire - Kenya
	ASIA
M. booduga	Central and south India, Sri Lanka
M. caroli	Ryukyu Island, Taiwan, Indochina - Sumatra, Java; cultivation
M. cervicolor	Nepal - Indochina, Sumatra, Java; cultivation, forest
M. cooki	Assam - Indochina
M. crociduroides	Sumatra; montane forest
M. dunni	India
M. famulus	South India; montane forest
M. fernandoni	Sri Lanka
M. pahari	Sikkim - Indochina
M. phillipsi	India
M. platythrix	India
M. saxicola	India, Pakistan, Nepal
M. shortridgei	Burma, Indochina
M. terricolor	Nepal, Pakistan
M. vulcani	Java; montane forest

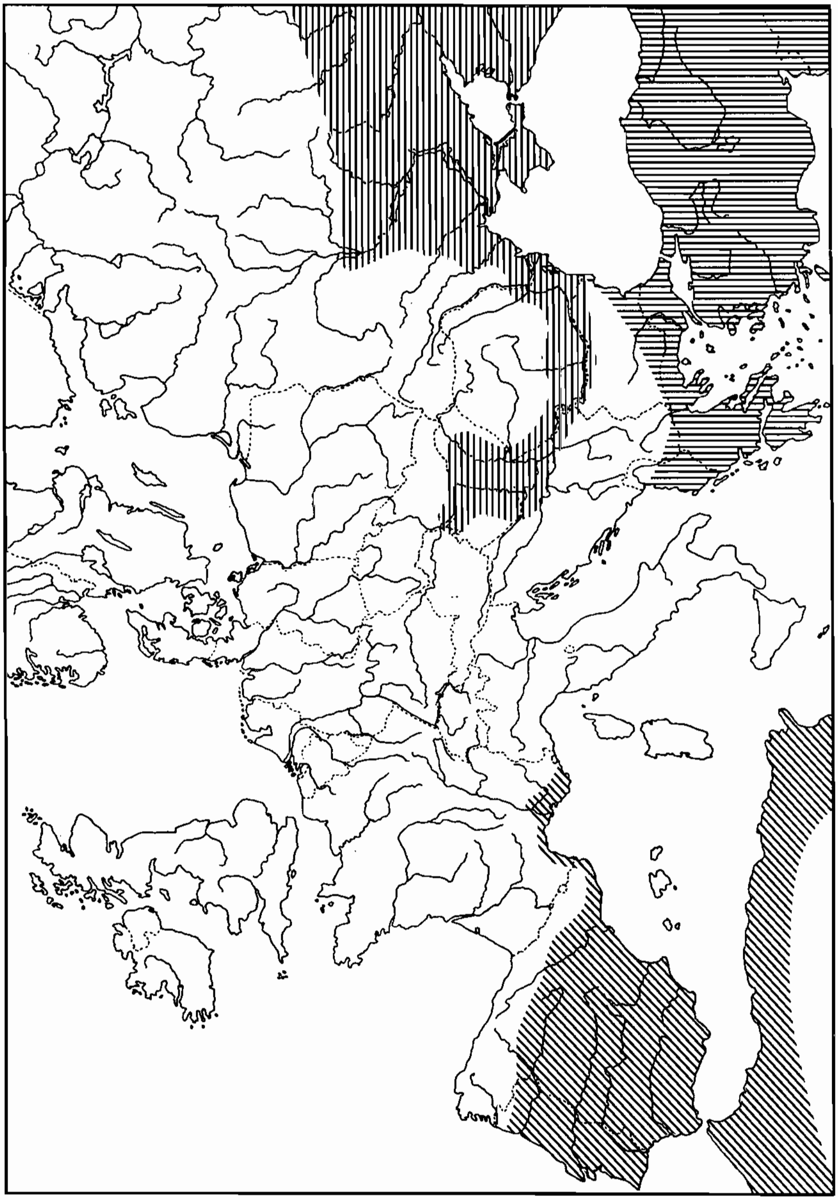


Fig. 2. Distribution of *Mus spretus* (///), *M. hortulanus* (≡), and *M. abbotti* (||||) in Europe.

some of the forms that are currently listed as separate species (Table 2, see Corbet and Hill, 1986) will probably turn out to be subspecies and the number of "proper" species may eventually be reduced to possibly no more than four or five (Kingdon, 1974). The most widely distributed African mouse is *M. minutoides*, which is found everywhere south of the Sahara. It was once thought to belong to a separate genus (*Leggada*) but was later reunited with the genus *Mus*.

DISTRIBUTION

The subject of this essay is the origin of mice but such a topic cannot be dealt with without considering the distribution and variation of the species. Mice are rodents and hence members of a very large group that constitutes some 40% of all mammals. Mouse-like species, in turn, constitute some two-thirds of rodents. Traditionally, the rodent order was divided into three suborders — Sciuromorpha or squirrel-like rodents, Caviomorpha (Hystricomorpha) or cavy-like rodents, and Myomorpha or mouse-like rodents (Simpson, 1945) — based on skull modifications related to jaw musculature. When it turned out, however, that similar modifications occurred independently in different evolutionary rodent lines, this division was dropped, although the terms are still used to describe certain evolutionary trends within individual rodent families. There is no accepted modern classification of rodents. The one that we shall use here is adapted from Eisenberg (1981). In this scheme, mice belong to the superfamily of Muroidea (the muroids), which contains two major and two minor families (Table 3). The two major families are Muridae (the murids) and Cricetidae (the cricetids).

Indigenous muroids are found in all continents except Antarctica (Misonne, 1969). The only muroids in South America belong to the tribe Hesperomyini, which is believed to have invaded this subcontinent from North America some 6 million years (MYR) ago* [Footnote: *This estimate is based on paleontological data. Sarich and his colleagues (reviewed by Sarich, 1985) have arrived, in what must be one of the largest discrepancies between paleontological and molecular data, at a drastically different date of the invasion — some 60 to 40 MYR! — based on immunological comparisons of protein molecules. This molecular estimate must be well off-target, possibly by an order of magnitude. The reason is probably to be found in the method: the immunological comparison is rather an arcane way of estimating evolutionary distances, subject to all kinds of vagaries and uncertainties, as taxonomists realized early in this century]. Since that time, they have managed to differentiate

TABLE 3

CLASSIFICATION OF MURIDS. (ACCORDING TO EISENBERG 1981.)

Superfamily	Family	Subfamily	Tribe	N° Species	Distribution
Muroidea (muroids)	Rhizomyidae	Rhyzomyinae		6	E. Africa, S.E. Asia
	Muridae (Muride)	Hydromurinae		20	Philippines, New Guinea Australia
		Rhynchomyinae		1	Luzon (Philip.)
		Phloeomyinae			Indonesia, New Guinea, Philippines
		Conilurinae		38	Australia, Tasmania
		Murinae			Eurasia, Africa, Australasia
	Cricetidae	Petromyscinae		2	Africa
		Microtinae	Lemmini		
			Microtini	121	N. America, N. Eurasia
			Ellobiini		
		? Otomyinae		13	Africa, S. of Sahara
		Cricetinae	Hesperomyini	359	N; C; S. America
			Cricetini	23	Europe, N. Asia
		Gerbillinae		95	C; W. Asia, Africa
		Dendromurinae		22	Africa, S. of Sahara
		Cricetomyinae		5	Africa, S. of Sahara
		Lophiomyinae		1	E. Africa
		? Myospalacinae		8	Altai - China
		? Nesomyinae		11	Madagascar, S. Africa
	Spalacidae	Spalacinae		8	E. Medit., S. Soviet Union

into 38 genera and 185 living species. (The rest of the 359 Hesperomyini lives in Central and North America; they are not found on any other continent). South America is, however, also inhabited by another group of rodents, the Caviomorpha, which are restricted to this subcontinent. The ancestors of the cavy-like rodents entered South America presumably from North America long before the ancestral Hesperomyini did, some 38 MYR ago, during the "great exchange".

There are no native murids in North America, only cricetids. The ancestors of the latter probably entered the subcontinent from Asia some 42 to 38 MYR ago. The absence of murids has been explained by the fact that these animals generally dislike chilly climates and because of their preferential distribution in Old World subtropical or tropical regions (Martin, 1980). To reach North America, the murid ancestors would have had to pass through the northern, rather harsh zones of Eurasia. The two groups of cricetids present in North America are the Hesperomyini, which have already been mentioned (71 species), and the Microtinae, which are otherwise also present in northern Eurasia (altogether 121 species).

In Australia, we have the opposite situation to that in North America. Here, there are no cricetids, only murids, which are also the only rodents present on this continent. In addition, the native murids of Australia are not found anywhere else except New Guinea, the Philippines, and Tasmania. The families Hydromurinae, Rhynchomyinae, Phloeomyinae, and Conilurinae are present only in Australasia; only the Murinae are also represented in other parts of the world. The murids are believed to have invaded Australia in three waves; they probably came from Malaysia on floating vegetation mats and debris (Hand, 1984). The first wave which entered Australia some 5 MYR ago was probably made up of conilurine rodents related to those living in this continent today; the second wave contained the ancestors of the Hydromurinae; and the third wave, which may have reached Australia as recently as 40,000 years ago, consisted of at least two species of rats.

In Africa, both murids and cricetids are present. Some cricetid subfamilies (i.e., Petromyscinae, Otomyinae, Dendromurinae, Cricetomyinae, Lophiomyinae, and Nesomyinae) are limited to sub-Saharan Africa and are not found anywhere else. Other muroids (i.e., Murinae, Rhyzomyinae, and Gerbillinae) are represented not only in Africa, but also in Europe and Asia. (There are no muroids shared between Africa and the Americas). There are no native *species* shared between sub-Saharan Africa and Europe or Asia, but there are species distributed from North Africa over the Middle East into Asia. Muroids may have invaded Africa 5 to 3 MYR ago, coming from Asia.

In Euroasia, most of the muroids live in the tropical or subtropical regions, particularly in Southeast Asia. Northern parts of Europe and Asia have a very low number of muroids, particularly murids. The overall distribution of muroids is as follows: 417 species (37.2%) are found in Eurasia, 233 species (19.9%) in Africa, and 480 species (42.8%) in the Americas. Of the Murinae, some 318 species live in Eurasia and 108 species live in Africa. Of the genus *Mus* 22 species live in Eurasia and 17 species in Africa. All except three (*M. minutoides, M. musculus,* and *M. domesticus*) have rather restricted distributions. *M. minutoides* is widely distributed all over sub-Saharan Africa (Kingdon 1974). *M. musculus* is found in north-east Europe, most of the Soviet Union, Mongolia, and China (Fig. 3). *M. domesticus* is present on al continents, including Antarctica, although it has a rather limited distribution in Asia and Africa (Fig. 3). We shall return to the distribution of these two species later.

GENETIC VARIATION

Space does not permit us to review all that is known about the genetic variation in the *musculus-domesticus* complex, but we would like to point out one particular feature which we believe to be important for the interpretation of the origin of this complex. We wish to argue that the *M. musculus* population is genetically more homogeneous than the *M. domesticus* populations, and we shall support this argument by data obtained in the study of chromosome variation, *t* haplotypes, and restriction site polymorphisms in noncoding DNA segments.

CHROMOSOMAL VARIATION

All the species and subspecies of *musculus-domesticus* have 20 pairs of acrocentric chromosomes and do not, with one exception, show any variation in this number. The one exception is *M. domesticus*, in which Robertsonian-type fusions were first demonstrated by Gropp and his coworkers (1970) in the subspecies *M. d. poschiavinus*. Later, Robertsonian variation could be demonstrated as occurring throughout most of Western Europe occupied by *M. domesticus* [reviewed by Winking (1986) and by Capanna (1985); for the most recent data, see Tichy and Vucak (1987); Fig. 4]. The principle of this variation is that two acrocentric chromosomes fuse at their centromeres, thus forming a single metacentric or submetacentric chromosome. The Robertsonian fusions thus reduce the number of chromosomes in the karyotype and change their morphology.

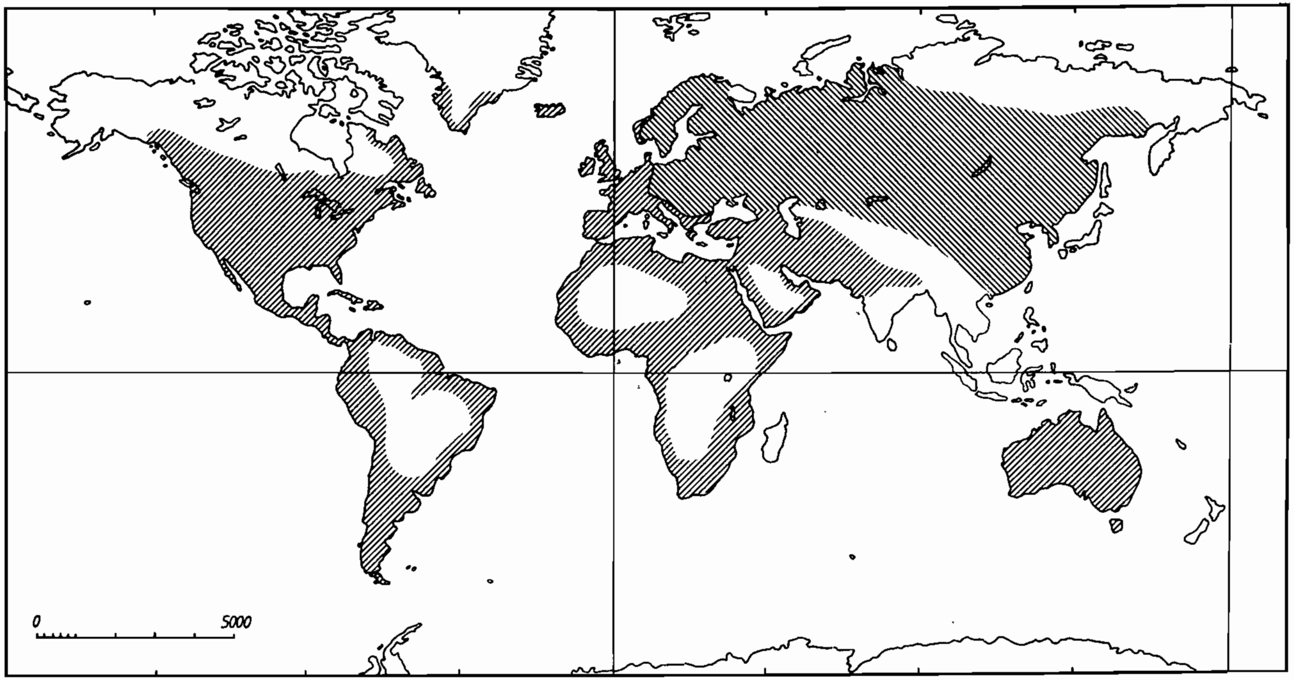


Fig. 3. The worldwide distribution of *Mus domesticus* (///) and *M. musculus* (\\\\).

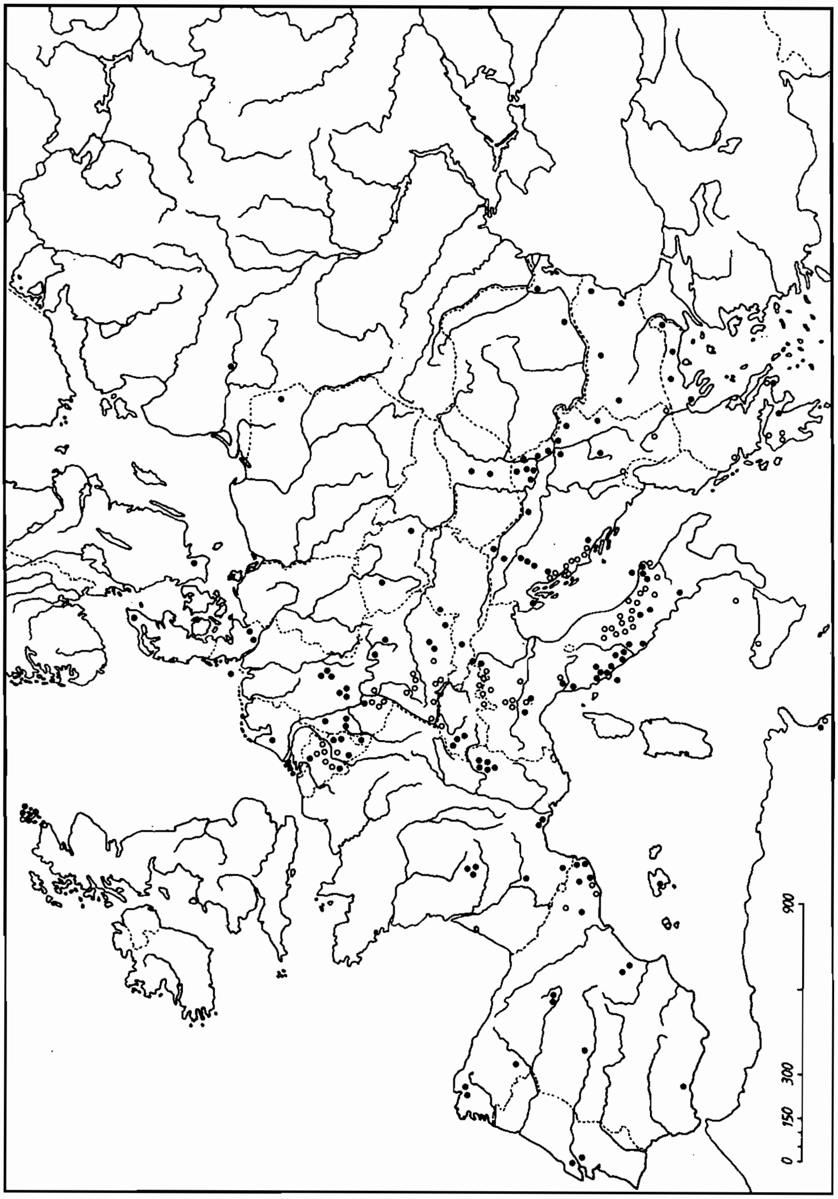


Fig. 4. Distribution in Europe of mouse populations with (○) or without (●) metacentric chromosomes.

The selection of chromosomes for participation in the Robertsonian fusions seems to be random in that any autosome can apparently fuse with any other autosome. All autosomes have been implicated in at least one fusion, and several autosomes have participated in several fusions. The metacentrics occur in wild *M. domesticus* populations in homo— or heterozygous states, singly or in various combinations, depending on the population. Different populations have different numbers and also different combinations of metacentric chromosomes. No clear trends in terms of number or combinations could be discovered as yet which would tie different populations together. Also, the populations have a patchy distribution because they are intermingled with all-acrocentric populations. The only two indications of a trend seem to be first, that a high number of metacentrics are found in a terrain that is physically fragmented into small, relatively isolated areas; and second, that the Robertsonian translocation seems to be more frequent in coastal regions than inland. The fragmented habitats could be series of valleys separated by high mountain ranges (as in the case of the original population of *M. poschiavinus* in the Alpine valleys; see Groop *et al.*, 1970), spread-out villages on a plateau (such as in the area of the Schwäbische Alb in southern Germany; see Adolph and Klein, 1983), or groups of small islands in the coastal regions (such as the Orkney Islands off north-east Scotland (see Adolph and Klein 1981; Nash *et al.*, 1983). Such habitats seem to support the accumulation of metacentric chromosomes.

While there are no trends in the composition of the karyotypes in different populations, trends in the distribution of individual metacentric chromosomes are beginning to emerge. For example, the Rb(4.12) translocation is distributed from central Italy, across the Alps into southern Germany, all the way to the Rhine river in the north and to Belgium in the west (Adolph and Klein, 1981; Tichy and Vucak, 1987 and unpublished data; Hübner *et al.*, 1985, Bauchan, personal communication). In southern Germany, this translocation is so widely distributed that one has a hard time finding any mice without it in this region (Adolph and Klein, 1983). Another example is the Rb (1.11) translocation, which is distributed along the Miditerranean coast (Gropp and Winking, 1983; Said *et al.*, 1986; Tichy and Vucak, 1987). In no instance, however, is the distribution known to be contiguous in any reasonably large geographical region. The individual populations with the particular metacentric chromosome may be separated by populations in which this translocation is absent, but which are not necessarily all-acrocentric populations.

In populations with a high number of metacentric chromosomes one often finds odd metacentrics with combinations of arms that are not found anywhere else. For example, the Schwäbische Alb in southern Germany is occupied by four different populations of mice differentiated by the number and composition of the metacentric chromosomes. Some od the metacentrics are shared by some of these populations; others are shared with populations found elsewhere in Europe. However, each population has, in addition, a "private" metacentric chromosome, which is absent in the other populations and also absent, or very rare, elsewhere in Europe [e.g., Rb (13.14) in one of the populations; see Adolph and Klein, 1983].

The genetic distances among the different populations are not significantly different from those between populations with and without metacentric chromosomes (Britton-Davidian *et al.*, 1980; 1987; Nash *et al.*, 1983). At least some of the populations, however, are differentiated in terms of the *H-2* polymorphism: the populations in the Schwäbische Alb each have a characteristic and unique profile of their *H-2* alleles (Figueroa *et al.*, 1983). Such differentiation can apparently occur rather rapidly whenever the migration rates drop.

We interpret the Robertsonian variation in *M. domesticus* as the result of constant intermingling of mouse populations. The translocations are probably very rare events: *M. domesticus* in the Americas and in Australia has no metacentric chromosomes (J. Klein and H. Tichy, unpublished data), although it must have had plenty of opportunity to acquire some, if they did arise with a high frequency. Similarly, metacentric chromosomes rarely appear in laboratory mice (Evans *et al.*, 1964; and others). It is therefore very unlikely that the presence of identical translocations in different populations is the result of independent *de novo* formations. It is more likely that all identical translocations present in different populations have a common origin and have been introduced into these populations by migrant mice. If so, the existence of different combinations of metacentric chromosomes in different populations must mean that mice come together from different parts of Europe and form a transient population which eventually breaks up; the migrants then mingle with migrants elsewhere to form other populations. The point we wish to emphasize, however, is that no population with metacentric chromosomes have been found in *M. musculus*.

T HAPLOTYPES

Both *M. domesticus* and *M. musculus* carry special forms of chromosome 17 in which genes effecting high transmission ratios of the mutant chromosomes through males have been locked up in a more or less permanent assembly by inversions. These *t* haplotypes, which are ubiquitous and occur at high frequencies, are often associated with lethal genes. The different lethal genes can be distinguished by a complementation test in which genes that do not complement each other are considered to carry identical mutations. Some 16 noncomplementing genes, all located in the inverted region on chromosome 17, have been identified (reviewed by Klein, 1986). Fifteen of these genes occur in *M. domesticus* [(3 in N. America, the rest in Western Europe), whereas only 2 or 3 occur in *M. musculus* (Klein *et al.*, 1984)]. Even more striking is the observation that all the *t* haplotypes extracted from *M. musculus* populations thus far have one gene (t^{w73}) in common (Fig. 5). This gene is not found in *M. domesticus* but

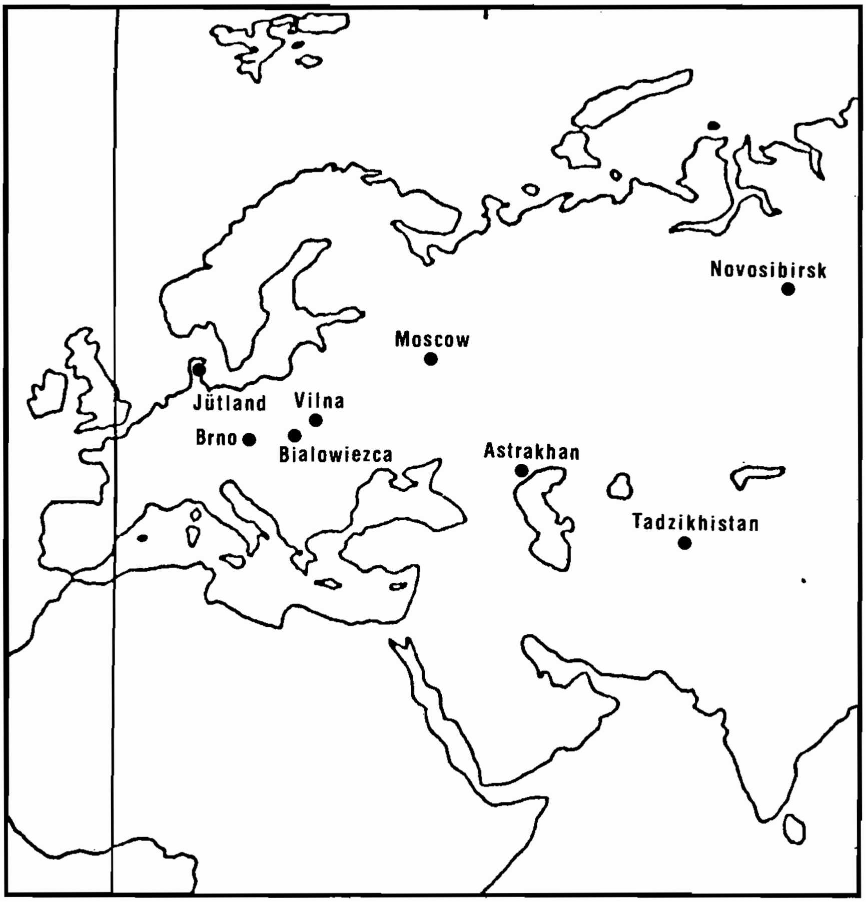


Fig. 5. Distribution in Europe of the t^{w73} haplotype (full circles).

all *t* haplotypes of *M. musculus* have it. (Some of the *M. musculus t* haplotypes may, in addition, possess other lethal genes which are also present in *M. domesticus*). This very biased distribution of t^{w73} is not a sampling error, because a wide range of localities in the *M. musculus* area has already been covered to rule out such a trivial explanation. The contrast between *M. domesticus* and *M. musculus* is very striking indeed. While in the former many different *t*-associated lethal genes are found even in a small area and often in the same population, in *M. musculus* a very large geographical region is dominated by a single gene. *M. domesticus* is quite heterogeneous in terms of its lethal *t* genes, whereas *M. musculus* is homogeneous.

RANDOM DNA SEQUENCES

In addition to repetitive sequences (high, intermediate, and low) and coding sequences (genes), the mouse genome also contains nonrepetitive, noncoding sequences. These are apparently distributed randomly over the genome, but their function is not known. They may represent extinguished genes in various degrees of randomization.

We have studied two such sequences, D17Tul and D17Tu2, in detail (Kasahara *et al.*, 1987; Figueroa *et al.*, 1987). The D17Tul sequence maps near the centromere on chromosome 17. It shows polymorphism among wild mice and laboratory strains (Fig. 6); in wild mice, however, this polymorphism is restricted to the *M. domesticus* species, whereas *M. musculus* is monomorphic. Altogether, seven variants of D17Tul have been found in the former species and only one in the latter, in samples of mice from widely separated localities (from Brno, Czechoslovakia to Novosibirsk in the Soviet Union). Here again, *M. domesticus* is polymorphic, and *M. musculus* monomorphic.

ORIGIN OF MUROIDS

Before we attempt to explain these observations and speculate on the origin of the house mouse, we shall very briefly summarize what is known about the origin of muroids. Although the oldest (>55 MYR old) true rodent fossils have been found in North America (the species *Paramys atavus*; reviewed by Vianey-Liaud, 1985), these are probably derived from a stock that moved into this subcontinent from Asia, where it must have lived some 65 MYR ago. The oldest muroid remains are also found in North America (the genera *Simimys* and *Nonomys*, the former dating back to about 41 MYR B.P.); the animals from which they are derived were again apparently immigrants from Asia. Furthermore, the genera were

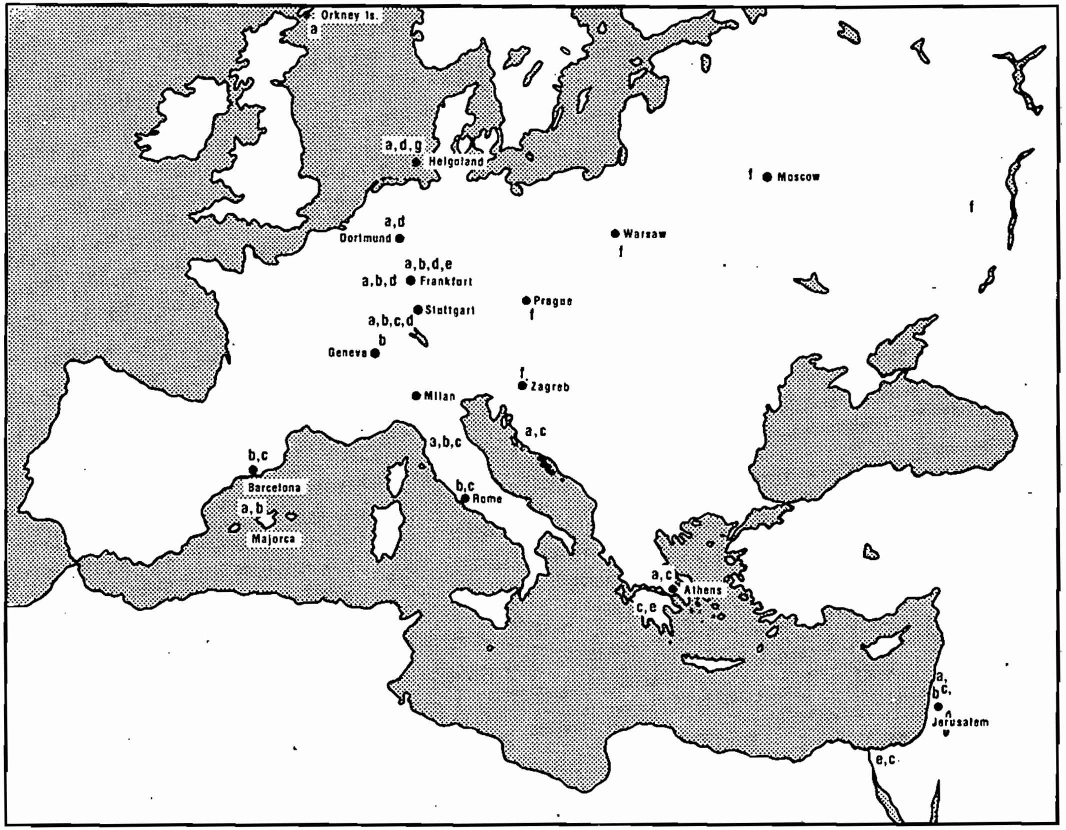


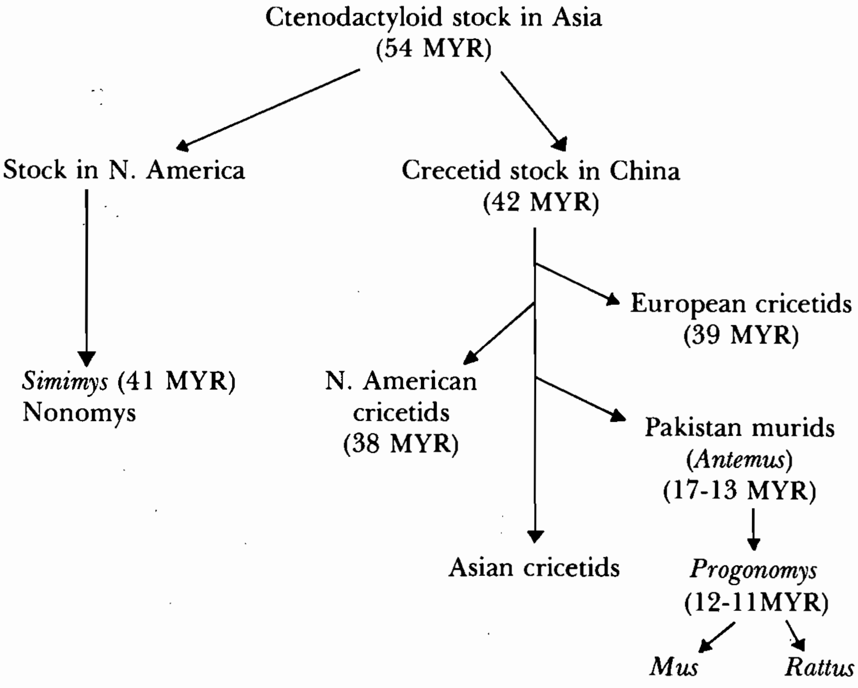
Fig. 6. Distribution in Europe of the various D17Tu1 patterns (*a* through *g*).

part of a blind evolutionary line from which no extant representatives remain. The modern muroids are derived from a cricetid line that may have lived in the area of present-day China some 42 MYR ago or more. The European cricetids diverged from this line some 40 MYR ago; the North American cricetids some 38 MYR ago; and the Asian cricetids, as well as the murids, some 17 MYR ago (Table 4). The oldest murid (genus *Antemus*) is known to have existed in Pakistan from about that time. The second oldest murid (genus *Progonomys*) has been dated to about 12 to 11 MYR B.P. According to the paleontologists, the *Rattus* and the *Mus* separated from each other some 10 MYR ago (Misonne, 1976; Jacobs and Pilbeam, 1980) and according to the molecular biologists, this occurred some 20 MYR ago (Sarich, 1985).

The paleontological data indicate that the representatives of the genus *Mus* probably originated in the area of present-day Pakistan. From there

TABLE 4

POSSIBLE EVOLUTION RECONSTRUCTED FROM FOSSIL FINDINGS



they spread to India and Southeast Asia in one direction, and via the Arabian peninsula to North Africa in the other. During one of the periods in which the Sahara was hospitable, they moved further south, reaching sub-Saharan regions perhaps less than 5 MYR ago. It was in these two centers, Southeast Asia and North Africa, that the genus underwent explosive differentiation, giving rise to most of the present-day species.

THE ORIGIN OF THE MUSCULUS-DOMESTICUS COMPLEX

It is generally assumed, and scanty archeological finds support this assumption, that the house mouse invaded Europe from the Middle East in relatively recent times. Its dispersion is believed to have occurred concurrently with the spreading of farming from the "fertile crescent", the region extending from Egypt to Syria, over Israel, Lebanon, and Jordan. The diffusion of agriculture began some 7,000 years B.P. (Ammerman and Cavalli-Sforza, 1984) and appears to have taken place in two main directions: along the Mediterranean coast, into Western Europe; and across Turkey, Bulgaria, and Rumania into Eastern Europe. (Uerpmann, 1983; Fig. 7). One can argue, therefore, that the mice which spread with farming along the Mediterranean coast evolved into *M. domesticus* and those which spread into Eastern Europe differentiated into *M. musculus*.

One can argue further that the mouse that spread, probably again with farming, from the fertile crescent toward India and into Southeast Asia, differentiated into *M. castaneus*. Japan is believed to have been invaded by mice in two waves, roughly corresponding to the two waves of human colonization. The country was populated by man during the later part of the Pleistocene epoch some 12,000 years B.P., at a time when its islands were still attached to the mainland (Rouse, 1986). (The land-bridge between Japan and the mainland was not severed until the final retreat of the Pleistocene glaciers had taken place). The second wave of human immigration occurred ca. 5,000 B.P. from Korea to the Kyushu Island and established the original Japanoids. Yonekawa and his colleagues (1986) postulated that the *M. molossinus* mice that inhabit the Japanese islands also arose by the intermixing of immigrants from southern China or Southeast Asia (*M. castaneus*) and from Korea (*M. musculus*).

The Americas were first colonized by *M. domesticus* in the post-Columbian time, at the earliest some 450 years ago. Australia received its first *M. domesticus* immigrants along with the Dutch settlers some 300 years ago (Hand, 1984).

The colonization of sub-Saharan Africa by *M. domesticus* has been

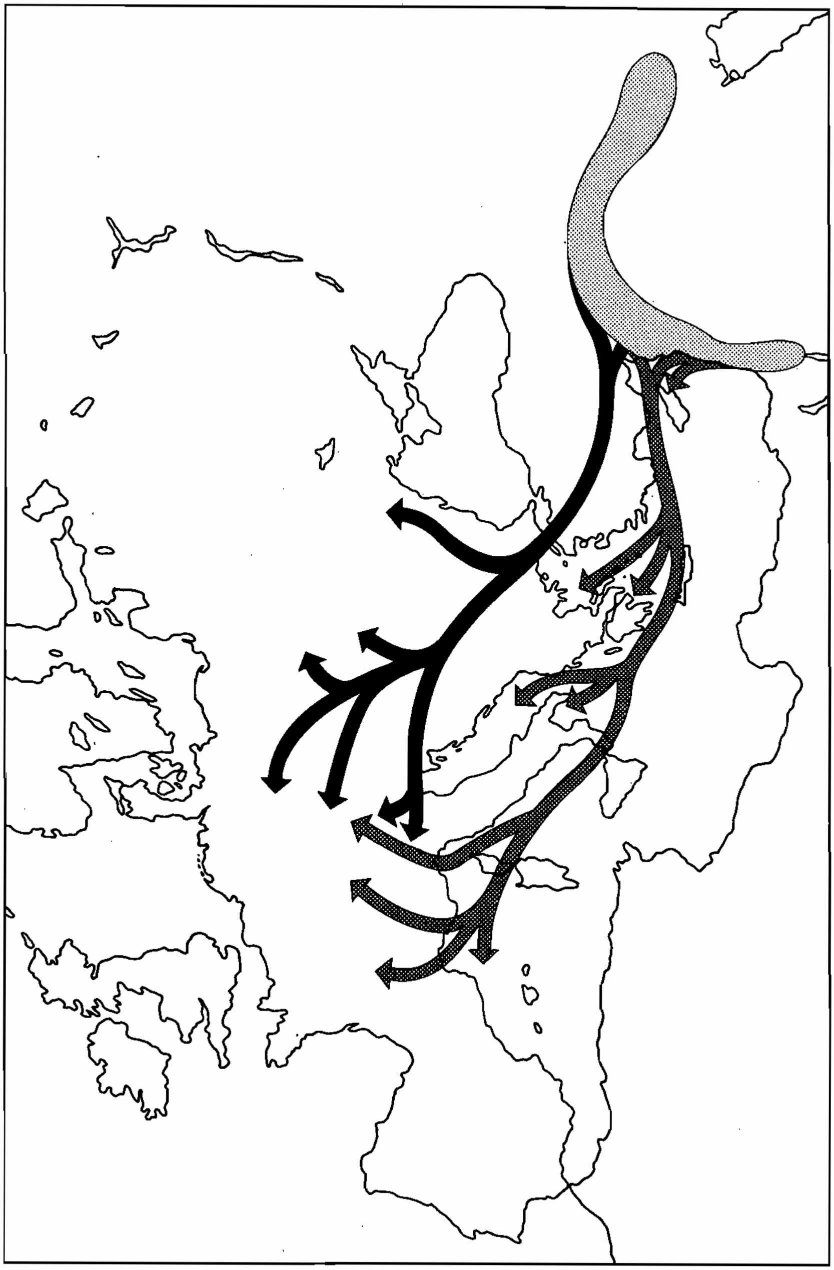


Fig. 7. Spreading of agriculture from the "fertile crescent" into Europe. (Based on Uerpman 1983).

taking place only in the last half of this century and it is still far from complete (Rosevear, 1969; Kingdon, 1974). There are still several large areas which the house mouse has not yet reached. This process, however, is rapidly continuing. In Kampala, for example, the first house mice were recorded in the mid-sixties, but now they are already common.

According to this interpretation, the different species of the *musculus-domesticus* complex, but in particular the *M. domesticus* and *M. musculus* species themselves, have not been separated from one another for more than 10,000 years. This estimate, however, contradicts molecular data, in particular those obtained from the study of mitochondrial DNA (Yonekawa *et al.*, 1981; Ferris *et al.*, 1983), which suggest that the separation of *M. musculus* from *M. domesticus* occurred 1 to 1.5. MYR ago! If the two species had their last common ancestor more than 1 MYR ago, the spread of agriculture obviously could not have been responsible for their differentiation. How can these different data be reconciled? One possibility is simply that the molecular data give a gross overestimate. The debate about the reliability of the molecular clock on which such estimates are based has never been resolved satisfactorily; however, it has been suggested that the clock can run faster at some times than at others (Kimura, 1983; Britten, 1986). Furthermore, the estimates based on the molecular clock become less accurate when one deals with short time intervals on the geological scale such as 1 MYR. Finally, the mitochondrial DNA data have led to a number of unexpected conclusions (Ferris *et al.*, 1982; Cann *et al.*, 1987) that contradict conclusions obtained by other methods; one must therefore ask oneself whether there is not some inherent "oddness" in such data.

On the other hand, if the spreading of agriculture was responsible for the differentiation of a common mouse stock into *M. domesticus* and *M. musculus*, this differentiation could not have started earlier than some 6,000 years ago, when farming began to reach Europe. This seems rather too short a time to achieve this degree of speciation. Furthermore, although there were apparently two main directions in which farming spread, there was no clear demarcation line between them (Uerpmann, 1983) that would have led to the separation of two mouse populations and would have favored speciation. (It seems inconceivable that mice lived in the fertile crescent area but were separated into the two different species, and that on took off with one group of farmers, and the other with another group; Fig. 7). Also, the borderline between *M. domesticus* and *M. musculus* in central Europe is not in any way related to an "encounter" of two farming cultures, so why did the two species establish their borders in this region? Moreover, how does the heterogeneity of *M. domesticus* and the relative homogeneity of *M. musculus* relate to the spread of farming? The homogeneity of *M. musculus* seems to be restricted to certain characters only, so its origin via a recent "bottleneck" is unlikely. But if not bottleneck effect, what then? Obviously the young-age hypothesis has quite a few problems associated with it.

To reconcile the conflicting data, we would like to propose that *M. domesticus* and *M. musculus* did indeed exist as two separate populations before the neolithic revolution some 8,000 years ago and that after the revolution, they spread to Europe in principally different ways. Perhaps the separation did not occur as long as 1 MYR ago, but it was long enough to ensure that farming could not have been the reason for the separation. The true reason must have been some geographical feature that kept the two populations apart so that a partial reproductive barrier could develop between them. The ancestral stock of the *musculus-domesticus* complex might have lived in the area of present-day Pakistan, where the murids seem to have originated. At one time, when the climatic conditions made the Iranian plateau traversable for mice, a group of these animals reached the steppes of Central Asia, only to become separated from the original stock when the plateau became impassable again. Alternatively, the stock might have spread into India and reached China via Southeast Asia by migrating along the coast. Whatever the route, two separate populations were established before the introduction of agriculture. This contention seems to be supported by the discovery of *Mus* remains in Choukoutien deposits in China, in strata that are at least 750,000 years old (Flynn *et al.*, 1985).

When the neolithic revolution occurred, mice began to associate with man in the two major agricultural centers: in the near East (either the mice spread from Pakistan to the fertile crescent before the onset of farming or after farming reached Pakistan and India) and in China. In the former it was *M. domesticus* that became associated with man, in the latter, *M. musculus*. Following the initial association, mice began to spread to Europe by two different routes and in two different ways. *M. domesticus* became primarily a seafarer, which colonized first the coast of the Mediterranean Sea and from there began to expand inland into Western Europe. *M. musculus* dispersed primarily on land from China across the Asiatic part of the Soviet Union into Eastern Europe. These two modes of dispersion had different consequences for the populations.

The *M. domesticus* colonization was rather erratic and occurred randomly, with small colonies being established at different sites along the coast. The colonies lost all contact with the parental population, and many became almost extinct, only to be replenished by new immigrants arriving

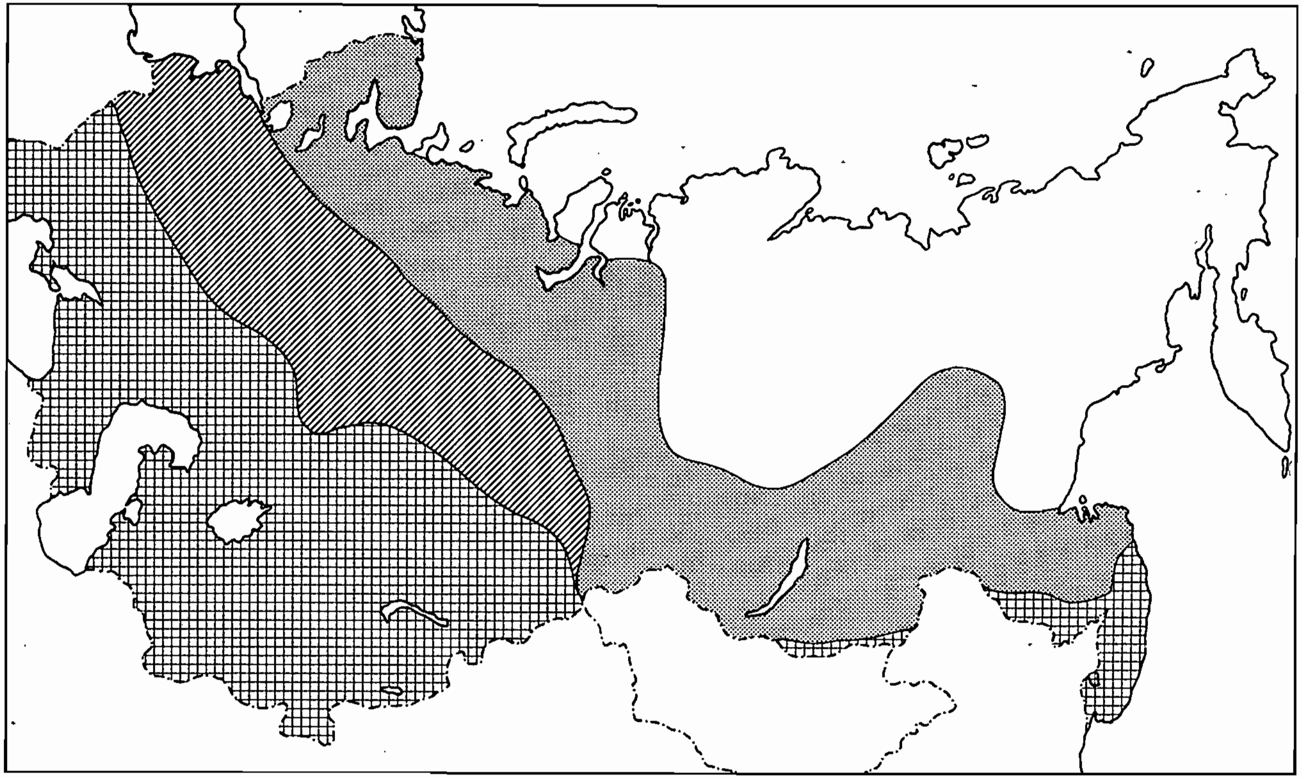


Fig. 8. Predominant living style of *Mus musculus* in the Soviet Union. ░, Mice living indoor all year round; ▨, mice living outdoor in summer and indoor in winter; ▦, mice living outdoor all year round. (Modified from Tupikova 1947).

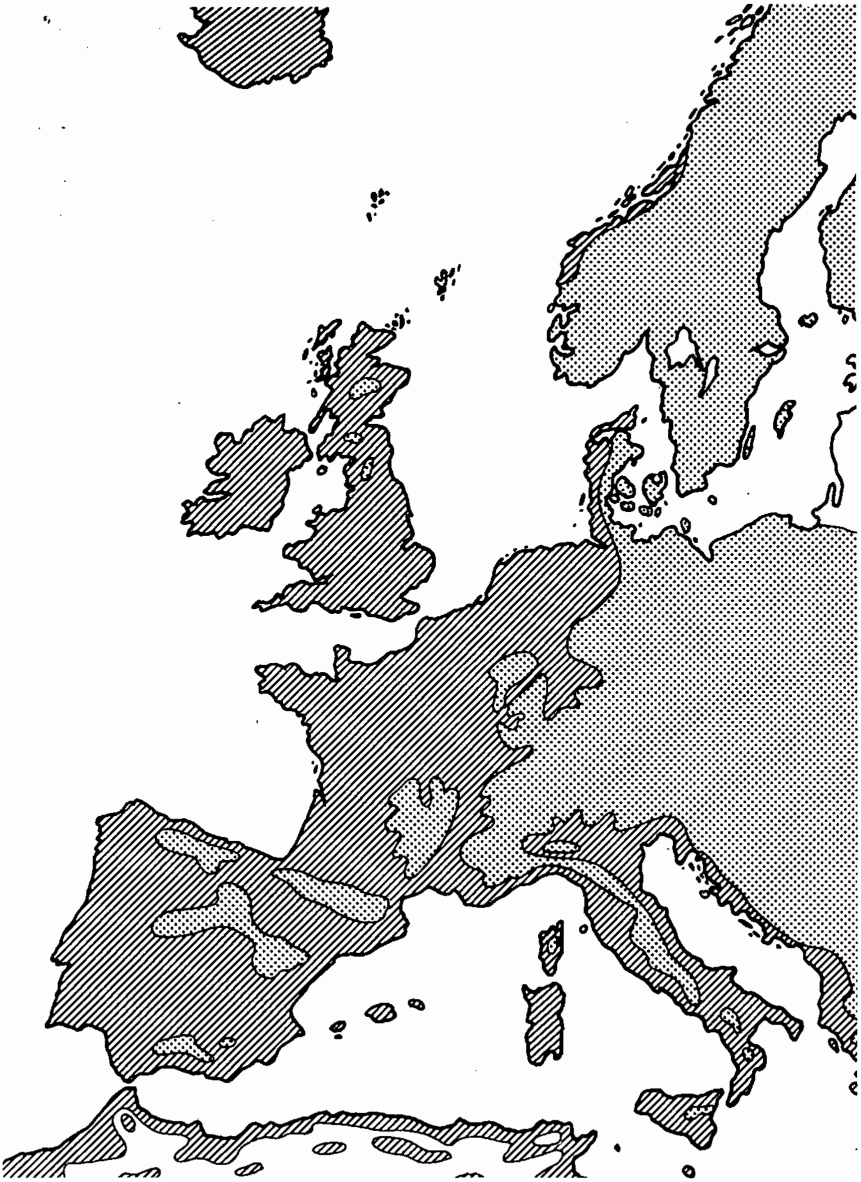


Fig. 9. The distribution of oceanic (▨) and continental (▒) climate in Europe.

with new ship cargos. When they move inland, the mice traveled primarily along the main north-south trading routes. Here again, they established small, isolated, and transient colonies that frequently went through bottlenecks and that intermixed with new immigrants. It was this dispersal pattern that became responsible for the great heterogeneity of *M. domesticus* in Western Europe and the intermixing of populations that continues to this day, as well as for the coast-inland clines of genetic variation observable for some of the traits.

The dispersal of *M. musculus*, on the other hand, assumed a different character. It was less erratic and more contiguous. It was perhaps a simple wave that moved westward without losing continuity with the parental population and probably exchanged genes with this population for a long time. There was less intermixing of subpopulations, and hence more of a tendency to remain homogeneous. Also, in contrast to *M. domesticus*, which became almost completely dependent on man for survival, *M. musculus* retained its ability to survive in the wild independent of man. Tupikova (1947) has documented extensively that throughout most of the moderate zones in the Soviet Union, mice move indoors only in the winter and spend the rest of the year for the most part living free (Fig. 8). In warmer climates, they live outdoors all year round, largely independently of man.

Why did the advance of *M. musculus* stop at the present border with *M. domesticus*? It could have been because the area further west was already occupied by *M. domesticus*, but is was more likely because of the climate. The border coincides almost exactly with the area of transition from the oceanic to the continental climate (Fig. 9). Mice are not the only species that are separated by this border. Several other animal and plant species display a similar separation. The best known examples of these are the two species of crows, the eastern form, *Corvus cornix*, and the western form, *C. corone*. They have divided Europe between them in pretty much the same way as mice have, with a hybrid zone in the area where they meet. Because *M. musculus* still has the ability to live outdoors, it may, in the northern areas, be more dependent on the climate than *M. domesticus*. *M musculus* may be more *adapted* to the climate so that it has not crossed over into the area of the continental climate.

CONCLUSIONS

The hypothesis proposed above may be entirely wrong, but it is the only hypothesis that explains all the data — paleontological, archaeological, zoogeographical, and molecular. The least we shoul be able to achieve by proposing it is to stimulate others to come up with better explanations. In formulating it, we moved freely from one area of human knowledge to another; that is one more pleasure that the mouse allows us to enjoy.

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