activities, we routinely assayed one set at an STI concentration of 200 μg/ml (6). This high concentration was utilized to ensure complete saturation of the fraction of kallikrein sensitive to the inhibitor.

Kallikrein activities in the plasma of children with cystic fibrosis (CF_1), control age-matched children, and control adults are shown in Table 1. Kallikrein activities in plasma of an additional group of patients with cystic fibrosis (CF_2), and their parents (obligate heterozygotes) are also shown in Table 1.

These data clearly demonstrate that there are significant differences between the levels of total kallikrein and STI-inhibited kallikrein activities in the plasma of control individuals and patients with cystic fibrosis ($P < .001$). The STI-inhibited component in heterozygotes was significantly different from that in their children (CF_2 being $P < .02$) and normal adults ($P < .05$).

Mixing plasma from controls and patients with cystic fibrosis either before or after activation yielded the expected intermediate levels of kallikrein activity; this result thus excluded the possibility that an inhibitor was present or that factors needed to activate prekallikrein in cystic fibrosis plasma were absent. Plasma, from controls and patients with cystic fibrosis, activated with chloroformellagic acid did not hydrolyze α-*N*-benzoyl-DL-arginine-*p*-nitroanilide, thus excluding the presence of trypsin. Initial experiments showed that levels of carboxypeptidase N and kallikrein inhibitor, two other components of the kinin system, are not significantly different in the plasma of controls compared to that in patients with cystic fibrosis. These findings indicate that the observed deficiency appears to be restricted to kallikreins in the kallikrein-kinin system. Since plasma contains a number of kallikreins (6), the reduction in total kallikrein and STI-inhibited kallikrein activities in plasma of patients with cystic fibrosis may be due to the reduction of a specific component.

Although our data show that the level of STI-inhibited component of kallikrein in the plasma of heterozygotes is significantly different from that in either controls or affected children, the individual heterozygote could not be identified in each case. In most families, parents had levels of STI-inhibited kallikrein activity intermediate between that of their children with cystic fibrosis and control adults. In two families, both the parents and the children with cystic fibrosis had levels of activity considerably higher that that of their respective groups. The reasons for the high enzyme activity in these families is not clear; however, they may represent examples of genetic heterogeneity.

The relation of the kallikrein system to the clinical manifestations of cystic fibrosis is not clear. With respect to the kallikreins, there is very little information on the effect of infection, respiratory acidosis, and other clinical manifestations of the disease. However, the reduced activity in heterozygotes suggests that the reduction in patients is probably not directly related to the clinical manifestations. It has been suggested that the adrenal glands may be overstimulated in patients with cystic fibrosis (8, 9) because of the finding of increased catecholamines in the adrenal medullas (8) and in urines of patients with cystic fibrosis (9). In experiments with healthy human volunteers, injection of high concentrations of epinephrine resulted in the reduction of kininogen and kinin (10). Such studies could possibly explain the reduction of kallikrein activity in cystic fibrosis.

Kallikreins are present in pancreas, salivary glands, plasma, sweat, and saliva (11)—organs, tissues, and secretions in which clinical and biochemical abnormalities are found in patients with cystic fibrosis (1). Therefore, the demonstration of a generalized deficiency of kallikreins may explain the clinical and biochemical manifestations of cystic fibrosis.

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Fission in the Evolution of a Lizard Karyotype

Abstract. *The lizard* Anolis monticola *has a diploid chromosome number of 48 (24 macrochromosomes and 24 microchromosomes). More primitive members of the genus, as determined by bone morphology, have 12 macrochromosomes and 24 microchromosomes. Since the higher chromosome number is the derived condition, this is a case of karyotypic change by centric fission.*

Chromosome fusion and fission (Robertsonian change) are two alternative explanations for the relation of karyotypes that differ in diploid number but agree in the number of chromosome arms [fundamental number (1)]. Controversy over the mechanism for fission and its frequency have caused many cytogeneticists to favor fusion, often to the complete neglect of fission. Recent studies have removed the grounds for disputing the simplest possible mechanism for fission, simple splitting of the centromere. Light and electron microscopy have shown that the centromere of a bi-armed chromosome contains twice the material in the centromere of a telocentric chromosome (2). Stable telocentric chromosomes, including some that are almost certainly fission products (3), have been demonstrated (2, 4). The frequency and importance of fission in karyotype evolution, however, remain undetermined (5). Cases are needed in which the direction of Robertsonian change can be demonstrated by unequivocal phylogenetic evidence. We present such a case here.

Phyletic relationships among West Indian species of *Anolis*, a large Neotropical genus of iguanid lizards, are now well worked out (6). There is karyotypic information for approxi-

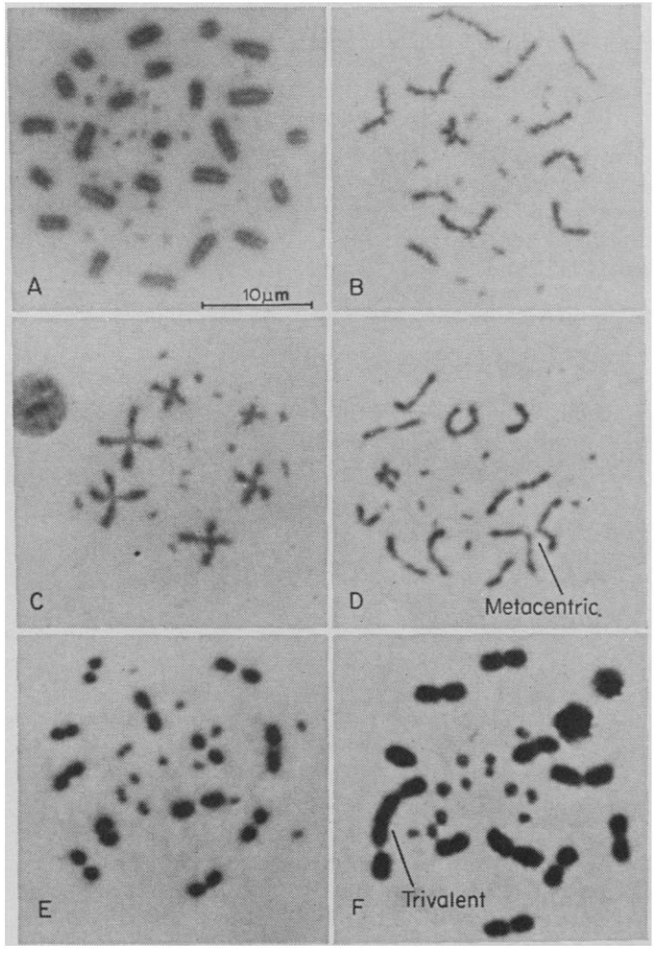
mately 85 percent of the more than 80 species in the West Indies (*7*). In this context it is possible to demonstrate unequivocally that the karyotype of *Anolis monticola*, a lizard restricted to the Massif de la Hotte in southwestern Haiti, originated through multiple centric fissions.

Using a slight modification of a standard method (*8*), we made chromosome preparations from testis tissue of 46 individuals from eight localities (*9*). Forty-one individuals had a diploid complement of 12 pairs of macrochromosomes and 12 pairs of microchromosomes (Fig. 1A). The morphology of the macrochromosomes was clearest in second-division meiotic metaphase (Fig. 1B). Four individuals had a diploid number of 46, with one pair of metacentric chromosomes (Fig. 1D), and one individual had a diploid number of 47. Chiasmata are almost invariably terminal in male *A. monticola* (Fig. 1E), so that the bivalents are linear or ring-shaped; in the $2n = 47$ individual the trivalent is linear (Fig. 1F). There is both inter- and intrapopulation variation in the morphology of the macrochromosomes (compare Fig. 1, B and D). In all individuals some but not all of the macrochromosomes are telocentric.

On the basis of the morphology of the caudal vertebrae the genus *Anolis* can be divided into an alpha and a beta section (*6*). Figure 2 presents the karyotypic and morphological information for the alpha section, to which *A. monticola* belongs. The shape of the interclavicle divides the alpha section into two groups, one with an arrow-shaped interclavicle comparable to that of other iguanids and the other with a derived T-shaped interclavicle. Primitive species groups within the group with an arrow-shaped interclavicle have a splenial (a bone in the lower jaw which is lost in advanced forms) and a high number of inscriptional ribs (reduced in derived forms) (*6*). In the Greater Antilles the osteologically most primitive species in this group (for example, the giant species *Anolis ricordii* of Hispaniola and *Anolis cuvieri* of Puerto Rico) have a karyotype of 12 metacentric macrochromosomes and 24 microchromosomes (Fig. 1C) (*7*, *10*). The most primitive species of the Lesser Antillean *Anolis roquet* group likewise have this karyotype (*11*).

Anolis monticola is one of the advanced alpha species with a T-shaped interclavicle. The only member of this group which retains the primitive splenial is *Anolis equestris* of Cuba, which again has the $2n = 36$ karyotype (*10*). The only member of the group which has a high number of inscriptional ribs is *Anolis occultus* of Puerto Rico, which also has $2n = 36$ (*7*). All members of the *monticola* species group are osteologically advanced in having the T-shaped interclavicle and a reduced number of inscriptional ribs and in lacking a splenial.

Most *Anolis* species are characterized by a well-developed dewlap, an



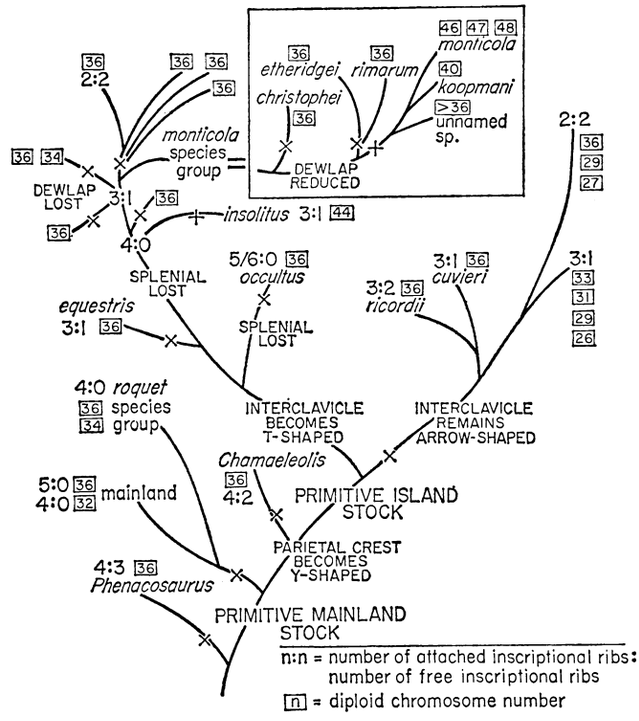


Fig. 1 (left). (A) *Anolis monticola*, mitotic metaphase, $2n = 48$; (B) *A. monticola*, second-division meiotic metaphase, $2n = 48$; (C) *A. christophei*, second-division meiotic metaphase, $2n = 36$; (D) *A. monticola*, second-division meiotic metaphase a showing large metacentric chromosome, $2n = 46$; (E) *A. monticola*, diakinesis, $2n = 48$; (F) *A. monticola*, diakinesis showing a chromosome trivalent, $2n = 47$. All chromosome spreads are from males and are reproduced to the same scale. Fig. 2 (right). Phyletic diagram of the West Indian alpha *Anolis* [modified from (*6*)]. The highly derived position of *A. monticola* is shown. An X marks each independent incident of homologous fusion that must have occurred if the karyotype of *A. monticola* is ancestral, that is, not the result of fission. A + marks each incident of fission according to the premises of this report. *Phenacosaurus* and *Chamaeleolis* are, respectively, primitive mainland and island anoline genera.

extensible throat fan supported by hyoid cartilages. The dewlap is secondarily reduced or lost in several unrelated species groups (*12*). Among the species of the *monticola* group *Anolis christophei* has a large dewlap and uniform squamation and lacks a bold body pattern, all characters suggesting that it is the most primitive species of the group (*13*); *A. christophei* again has the $2n = 36$ karyotype. *Anolis monticola* has a reduced dewlap, non-uniform squamation, and a bold ocellate body pattern. It is clearly a highly derived form.

The diploid number of 48 observed in *A. monticola* could be derived from the primitive $2n = 36$ karyotype by centric fission of the metacentric macrochromosomes. The telocentric morphology of many of the macrochromosomes in the *A. monticola* karyotype is compatible with a fission hypothesis. That the alternative explanation—the *monticola* karyotype is a retained primitive condition—is implausible can be seen in Fig. 2. If the high diploid number is ancestral, at each point marked by an × there must have been an independent evolution of a diploid number of 36. Even if this event occurred the requisite 12 times, it is extremely unlikely that the resulting karyotypes would be as uniform in chromosome morphology as they are known to be. If the diploid number of 36 is accepted as ancestral (*10*, *14*, *15*), then fission need be invoked at only two points in the phylogeny, marked by a +. Non-telocentric chromosomes in the karyotype of *A. monticola* are easily interpreted as fission products modified by pericentric inversion. The polymorphism for diploid number in *A. monticola* can be interpreted as secondary centric fusion or incomplete stabilization of a fully fissioned karyotype.

Single or multiple fissions have been advanced as the probable evolutionary pathway to a number of lizard karyotypes. Included are members of the families Teiidae (*15*), Anguidae (*16*), and Iguanidae: *Plica plica* (*10*), *Anolis oculatus* (*7*), and *Sceloporus grammicus* (*17*). The occurrence of multiple fissions in the evolution of the karyotype of *A. monticola* strengthens these interpretations.

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Dopamine: Mediator of Brain Polysome Disaggregation after L-Dopa

Abstract. *The disaggregation of brain polysomes which is produced by giving large doses of* L-*dopa to rats is not reproduced by administering its metabolite, 3-*O*-methyldopa, by giving* D-*dopa, which also depletes the brain of* S*-adenosylmethionine but is not converted to catecholamines, or by giving the* L-*dopa after a decarboxylase inhibitor. Polysome disaggregation is potentiated by the prior administration of a monoamine oxidase inhibitor, indicating that formation of a catecholamine is an obligatory requirement. These observations suggest that the mechanism by which* L-*dopa disaggregates brain polysomes involves its conversion to dopamine within the majority of brain cells.*

Administration of L-dopa (500 mg per kilogram of body weight, intraperitoneally) to rats is followed between 40 and 60 minutes by the disaggregation of polysomes obtained from whole brain. This disaggregation is unaccompanied by a decrease in the concentrations of any free amino acid; brain tryptophan levels actually increase significantly (*1*).

We have attempted to identify L-dopa or one of its metabolites as the agent causing disaggregation of brain polysomes. Administered L-dopa is transformed by the brain to the catecholamines dopamine and norepinephrine, and their metabolites, and to the amino acid 3-*O*-methyldopa (Fig. 1) (*2*). The *O*-methylation of exogenous dopa, catalyzed by catechol *O*-methyltransferase, depletes the brain of *S*-adenosylmethionine (*3*). To identify which of the compounds formed or utilized after administration of dopa is involved in polysome disaggregation, we examined the state of polysome aggregation in animals given (i) 3-*O*-methyldopa; (ii) D-dopa, which forms 3-*O*-methyldopa in the brain but does not undergo decarboxylation to dopamine; (iii) L-dopa along with an inhibitor (RO4-4602) of its decarboxylation to dopamine; (iv) L-dopa along with an inhibitor (pheniprazine) of monoamine oxidase; or (v) intracisternal dopamine or norepinephrine. Changes in whole brain polysome aggregation were correlated with alterations in the concentrations of dopa, 3-*O*-methyldopa, *S*-adenosylmethionine, dopamine, and norepinephrine in the brain.

Male Sprague-Dawley rats (Charles River Laboratories) weighing approximately 50 g were exposed to light from 9 a.m. to 9 p.m. daily. They were housed four per cage and given free access to Purina Chow and water. L-Dopa, 3-*O*-methyldopa, and D-dopa (Hoffmann-LaRoche, Inc.) were dissolved in 0.05*N* HCl and administered intraperitoneally; control animals received only the acidic diluent. The decarboxylase inhibitor RO4-4602 (Hoffmann-LaRoche, Inc.) and the monoamine oxidase inhibitor pheniprazine (JB 516; Lakeside Laboratories, Inc.) were dissolved in water and administered intraperitoneally. Dopamine hydrochloride