were 676 DA cells and 793 IA cells. Therefore the proliferation rates were 12.4 DA cells and 13.4 IA cells per day in 6-OHDA–treated retinas and 7.5 DA cells and 8.8 IA cells per day in untreated retinas. At present, there is no evidence that such mitotic stimulation following cellular destruction with 6-OHDA is specific for monoaminergic cells or general for other retinal cells.

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Identification of the Constant Chromosome Regions Involved in Human Hematologic Malignant Disease

Abstract. *Specific consistent chromosome translocations are regularly observed in certain human leukemias and lymphomas. For the myeloid leukemias, the constant recombinants are: the long arm of 9 to chromosome 22 in chronic myeloid leukemia, the long arm of 21 to chromosome 8 in acute myeloblastic leukemia, and the long arm of 17 to chromosome 15 in acute promyelocytic leukemia. Three related translocations are seen in Burkitt lymphoma and B cell acute lymphocytic leukemia; in each one, chromosome 8 is involved with chromosome 2, 14, or 22. Analysis of a complex translocation affecting chromosomes 8 and 14 indicates that the translocation of chromosome 8 to chromosome 14 is the critical constant rearrangement. The analysis of the DNA at the translocation sites of these chromosomes, rather than the reciprocal of each translocation, appears to be the most productive focus for initial study. The various immunoglobulin loci are located on chromosomes 2, 14, and 22, the chromosomes regularly involved in translocations in Burkitt lymphoma and B cell acute lymphocytic leukemia.*

Several consistent translocations that are relatively specifically associated with particular types of human leukemia and lymphoma have been identified during the past 8 years (*1*). These include the translocations between chromosomes 9 and 22 in chronic myeloid leukemia (CML) (*2*), between chromosomes 8 and 21 in acute myeloblastic leukemia (AML-M2) (*3*), and between chromosomes 15 and 17 in acute promyelocytic leukemia (APL-M3) (*4*). Three variant translocations, each involving chromosome 8, have been observed in Burkitt lymphoma and acute lymphocytic leukemia (ALL) of B cell origin, which may be two clinical manifestations of the same malignant disease. The three translocations include the one originally identified by Zech *et al.* (*5*) involving chromosomes 8 and 14 (*5*, *6*) as well as two recently described variants, one between 8 and 2 (*7*) and the other between 8 and 22 (*8*). The break point in No. 8 appears to be in the same band in the long arm (8q24) (Fig. 1) in all three translocations. These various translocations appear to be reciprocal; DNA measurements show that there is no gross loss of chromosomal DNA in the 9;22 translocation in CML (*9*).

Interest in defining the DNA sequences at the sites of these translocations has been further stimulated by the recent finding that the three immunoglobulin (Ig) loci, for the heavy chains, the kappa light chain, and the lambda light chain, are each located on one of the three chromosomes involved with No. 8 in these translocations. Thus, the locus for heavy chains is on No. 14 (*10*), that for kappa is on No. 2 (*11*), and that for lambda is on No. 22 (*12*) (Fig. 1). Moreover, with the use of chromosome hybridization in situ, Malcolm *et al.* (*11*) mapped the kappa light chain genes to the short arm of No. 2 (band 2p12–13), the band that is involved in one of the translocations. Finally, Lenoir *et al.* (*13*) reported on the complete concordance of karyotype with the Ig secreted by cells with variant translocations; they have shown that all three tumors with a 2;8 translocation secrete kappa light chains and all seven tumors with an 8;22 translocation secrete lambda light chains.

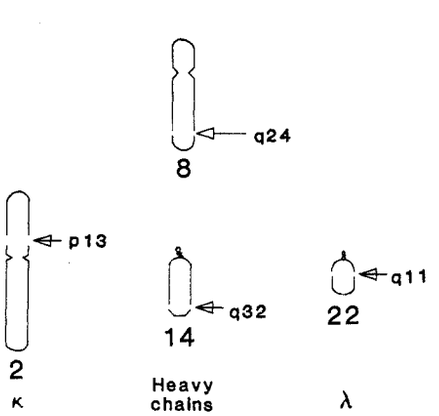

Fig. 1. Diagrammatic representation of the break points (arrows) in the translocations in Burkitt lymphoma and B cell ALL. The short arm of a chromosome is identified by *p* and the long arm by *q*. The kappa light chain (κ) is located on No. 2, the Ig heavy chains on No. 14, and the lambda light chain (λ) on No. 22.

Recently, the 9;22 translocation has been analyzed with the use of somatic cell hybridization (*14*) and with cloned probes from DNA of sorted human chromosome 22 (*15*). In the interest of increasing the efficiency of the latter experimental approach, it would be useful to distinguish which of the two rearranged chromosomes that result from a reciprocal translocation merits initial detailed analysis. In the myeloid leukemias, the two translocation chromosomes are each involved only with the other in most instances, and there appears to be no reason a priori to choose one recombinant chromosome rather than the other. Fortunately, each of the three common translocations, 9;22 (*1*), 8;21 (*16*), and 15;17 (*17*), also occurs in a variant form in a limited number of patients, and these can be used to determine whether one recombinant chromosome is constant in the variant forms (Fig. 2). For the translocations in AML and APL, one recombinant chromosome is constant and one is variable (the constant one is enclosed in a box in Fig. 2). For CML, the situation is more complex; this may merely reflect the fact that we have data on more than 1100 CML patients whose cells were studied with banding, compared to only about 100 AML patients with 8;21 translocations and 50 to 60 APL patients with a 15;17 translocation. The standard 9;22 translocation occurs in about 92 percent of

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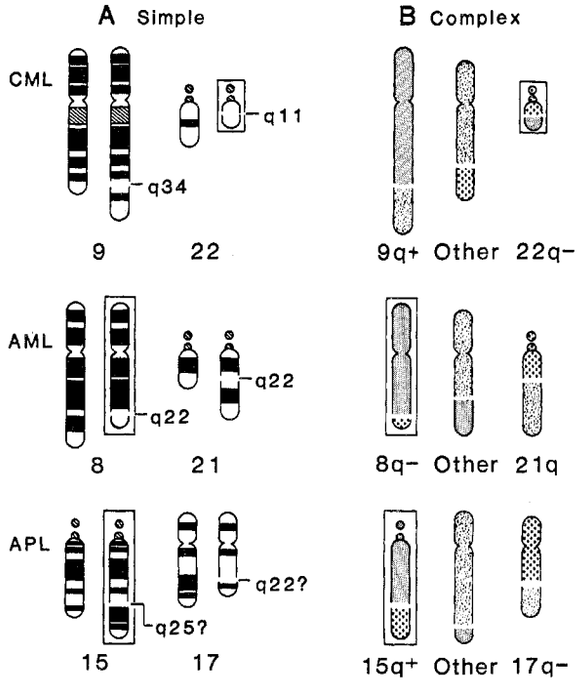

Fig. 2. (A) Diagrammatic representation of the break points and the chromosome exchange in the simple consistent translocations in CML, AML, and APL. (B) Schematic drawing of the break points and the typical pattern of chromosome exchange observed in the complex variants affecting each of these translocations. The other chromosome involved in these complex rearrangements varies. For each type of leukemia, the rearranged chromosome that is constant in both the simple and complex translocations is enclosed in a box.

those CML patients with a Philadelphia (Ph^1) chromosome whose cells were studied with banding (*18*). About 4 percent of these patients have a simple two-way translocation involving chromosome 22 and some other chromosome. The $Ph^1(22q-)$ chromosome generally resembles that in the 9;22 translocation, but the translocated portion of No. 22 moves to some chromosome other than No. 9, most commonly 12p, 17q, or 19q. In the other 4 percent of translocations, the rearrangement is more complex and involves three and occasionally four or five chromosomes. With rare exceptions, the translocations affect Nos. 9 and 22 as well as some other chromosome, with 1q, 3p, and 4q involved more often than others. The typical pattern of rearrangement is diagrammed in Fig. 2. Thus, in about 96 percent of patients with CML, the constant feature is the apposition of the end of 9q to the remainder of 22q.

On the basis of these data, therefore, the critical event leading to malignant transformation in these types of myeloid leukemia appears to be related to the translocation of 9q to 22q in CML, of 21q to 8q in AML, and of the end of 17q to 15q in APL. The 4 percent of translocations in CML that do not follow this rule may affect sites containing genes that are functionally related to the genes on 9q.

In Burkitt lymphoma and B cell ALL, one chromosome—No. 8—is common to all three translocations, and 2p, 14q, or 22q is the other chromosome (Fig. 1). There is no obvious reason to assume that the critical rearrangement is chromosome 8 with a portion of one of the other three chromosomes, rather than the translocation of a small portion of No. 8 to each of the other three chromosomes. I recently studied a patient with B cell ALL who had a complex translocation involving chromosomes 5, 8, and 14 (*19*). A portion of No. 5 had moved to No. 8, and the end of 8q was translocated to 14q; the latter rearrangement is identical to that seen in many Burkitt lymphomas and B cell ALL's and indicates that the critical event is the translocation of the end of 8q to 14q32. It seems reasonable to assume by analogy that, in the other two translocations observed in Burkitt lymphoma and B cell ALL, the translocation of 8q to 2p and of 8q to 22q are the significant rearrangements. Translocations involving No. 14 are frequently seen in other types of lymphoma and in B cell ALL. A 14;18 translocation is commonly detected in poorly differentiated lymphocytic lymphoma; however, the donor chromosome varies in other lymphomas (*20*). The chromosome rearrangements in the latter types of lymphoma, which involve 14q with a variable donor chromosome, may be analogous to the 4 percent of variant translocations in CML that affect No. 22 but not No. 9.

These consistent translocations may be examples of chromosome changes that are causally related to the malignant transformation of cells. The present understanding of the human genome and of the complex interactions in the control of gene function is too limited to allow more than general notions. However, the observations of Neel *et al.* (*21*) suggest an explanation for the function of consistent chromosome rearrangements. Their studies have shown that, in chickens, tumors induced by the avian leukosis virus have viral integration sites in common, and that certain cellular genes are expressed at high levels (*21*). They suggest that there has been proviral integration adjacent to a specific cellular gene, with the viral promoter enhancing the expression of this gene.

These concepts can be applied to the consistent translocations summarized in this report to yield the following model. For the translocations seen in lymphoid tumors, it is proposed that the genes adjacent to the Ig locus or the Ig locus itself is related to control of cell proliferation. The gene on 8q would act as a promoter; this gene might be one of the long terminal repeats or pseudogenes that are scattered throughout the genome. As a result of the translocation, this promoter would be moved next to the Ig genes, causing expression of the latter, with subsequent cell proliferation and transformation. It is equally possible that the activation occurs in the other direction; that is, that the promoter of the Ig locus, which is active in B cells, when placed next to certain sequences on chromosome 8, would activate a locus on No. 8 whose function might be to stimulate lymphoid cell division with subsequent transformation. Unfortunately, the gene loci in myeloid cells that are analogous to the Ig loci in lymphoid cells have not yet been distinguished. It is thus possible and, given the current pace of investigation, highly probable that the DNA sequences at the sites of specific translocations will be identified before their function is defined.

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Suppression of Reflex Postural Tonus: A Role of Peripheral Inhibition in Insects

Abstract. *Postural reflexes act through a single excitatory motoneuron of the several that innervate a flexor muscle of the cockroach leg. A peripheral inhibitory neuron whose axon accompanies this excitatory motoneuron is able to suppress muscle tensions developed from postural reflexes without affecting centrally generated muscle tensions. The inhibitory neuron could thus serve to rapidly suppress postural tensions at the initiation of escape.*

Posture and locomotion are viewed as being programmed by the central nervous system and modulated by sensory feedback (*1*). Elements of central pattern generators for walking have been identified in vertebrates and invertebrates (*2*), but little is known about how postural reflexes interact with them. In rapid running, for example, such reflexes may be incompatible with centrally programmed locomotor patterns (*3*). Are these reflexes then suppressed or overridden? We studied this problem in the American cockroach and found an effective mechanism for the rapid suppression of reflexly developed muscle tension through the action of inhibitory motoneurons at muscle cells.

The posterior flexor muscle of the trochanter (*4*) lifts the cockroach leg in upright walking (*5*) and provides postural support when the animal is climbing or standing inverted (*6*). The nerve to this muscle contains at least 12 axons, but no more than four (axons 3, 4, 5, and 6) are active in quiescent or walking cockroaches (*5*). Each of these four motoneurons can be accurately identified in extracellular recordings (*7*). Axons 4, 5, and 6 are slow excitatory motoneurons that generate graded tension by facilitating depolarizing postsynaptic potentials (*8*). Axon 3 is a branch of the common inhibitory neuron that produces hyperpolarizing potentials in muscle cells and decreases the tension developed by the excitatory motoneurons (*8*).

Centrally generated patterns of activity in these motoneurons have been investigated. The common inhibitor (axon 3) and two excitors (axons 5 and 6) discharge regularly with the locomotor-like bursting seen in deafferented preparations. Nonspiking interneurons that can generate these patterns and set a bursting rhythm have been identified; they affect only the same three flexor motoneurons (*9*). Axon 4 is only irregularly active in locomotor-like bursting, and its inputs have not been determined.

We studied reflex effects on flexor motoneurons of two groups of leg proprioceptive sense organs, the coxal chordotonal organ (*10*), which responds to extension of the coxotrochanteral joint, and the distal tibial campaniform sensilla (*11*), which monitor cuticular strain generated by muscle contractions. Adult cockroaches were briefly anesthetized with CO_2, pinned ventral surface up on a resin-coated block, and dissected to expose the trochanteral flexor nerve and another small motor nerve containing a branch of the common inhibitor (*8*). These nerves were lifted onto chloridized silver hook electrodes (diameter, 75 μm) for conventional recordings.

Stimulation of the coxal chordotonal organ by extending the coxotrochanteral joint with a wire mounted to a piezoelectric crystal elicited vigorous reflex activity in one flexor motoneuron, axon 4, and had no discernible effects on other flexor motoneurons (Fig. 1A). Stimulation of individual distal tibial campaniform sensilla with a fine etched tungsten wire driven by a piezoelectric crystal elicited bursting from the same flexor motoneuron (Fig. 1B). Thus, both of these proprioceptive sense organs reflexly excite a single flexor motoneuron not driven by central locomotor interneurons.

What is the function of this subdivision of flexor motoneurons? In their study of the distribution of flexor axons to muscle cells, Pearson and Bergman (*8*) observed that excitatory axon 4 and inhibitory axon 3 invariably accompany each other when they innervate flexor muscle cells. The other flexor excitatory axons innervate many muscle cells unaccompanied by the inhibitor.

To determine whether muscle tensions developed in postural reflexes can be inhibited at the muscle cell, we monitored tension developed in the posterior flexor trochanter muscle tendon in response to repetitive stimulation of the coxal chordotonal organ and also stimulated the common inhibitory axon. Stimulation of the common inhibitor at 50 Hz (less than half the rate seen in spontaneous bursting) completely inhibited re-

Table 1. Axon 4 spikes in the flexor nerve with and without stimulation of the common inhibitor. Values are means ± standard deviations.

Leg extension (degrees per second)	Axon 4 discharge (N = 4) (Hz)	Axon 4 discharge with common inhibitor stimulation (N = 4) (Hz)	
		At 10 Hz	At 60 Hz
25	8.2 ± 2.2	8.7 ± 2.8	8.0 ± 1.9
150	63.6 ± 13.1	68.0 ± 14.6	64.1 ± 15.3

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