What so often happens in the treatment of fossils is that the specimen is unique in shape and does not resemble any extant species. This problem was noted in one of the first reports on the application of discriminant functions to early hominid fossils (*10*).

The most important results of the discriminant analysis are represented in Fig. 1 (*11*). Discriminant function 1, which accounts for 69.0 percent of the total discrimination, acts to separate the humeri primarily on the basis of size (*12*), with male gorilla humeri at one extreme and human humeri at the other. All measurements are highly correlated with the discriminant scores of the first function. The fossil humerus projects between the male and female *Pongo* humeri.

The second function accounts for 14.1 percent of the discrimination. Since each function is uncorrelated (and hence orthogonal) with each other function, the effects of overall size are probably minimized here, having played the dominant role in function 1. This is not to say that the function is not influenced by the effects of size; there is no reason why size could not influence shape in more than one way. But the distribution of the species on this axis is not at all according to size. Again, the discriminant scores for the human humeri are maximized. All of the great ape scores are minimized except those for the gorilla. The traits which are most highly correlated with the function concern the shape of the olecranon fossa and the size of the proximal extension on the lateral trochlear ridge. The human humerus is unique in having a wide olecranon fossa compared with the width of the shaft as measured at the position just proximal to the fossa, and in having practically no lateral ridge extending proximally to form a sharp wall on the lateral surface of the olecranon fossa. In both of these traits the gorilla humerus is somewhat more similar to the human one than are those of the other great apes. The fossil discriminant score is almost equal to the mean score for the female gorilla.

On the third function the fossil projects most closely to the orangutan humeri. This function accounts for 11.3 percent of the total discrimination. It maximizes the chimpanzee discriminant scores and minimizes the orangutan ones. The traits most closely associated with the function are the depth of the olecranon fossa and the anterior-posterior diameter of the shaft just proximal to the olecranon fossa. Both of these dimensions are relatively large in *Pan*, especially compared with the total length, which is the third most highly correlated measurement with this function.

The last three functions account for little over 5 percent of the total discrimination. Function 4 maximizes the male orangutan scores and minimizes the female gorilla values. An important trait which affects this separation is the shape of the capitulum, which is much wider from its distal edge to its proximal edge in *Pongo* than in the other hominoids. Function 5 separates the pygmy chimpanzee humeri from the rest. The last function accounts for only 0.5 percent of the total discrimination. It separates the male and female humeri of both *Pongo* and *Gorilla*.

Figure 1 is a plot of the relative positions of the centroids for functions 1, 2, and 3. These three functions account for about 95 percent of the total discrimination. The significance of Fig. 1 is in the placement of the fossil: it does not approach any of the centroids very closely, but the nearest groups are female gorilla and man. If all six discriminant functions are considered, a similar result is obtained by determining the geometric distances between the centroids in the six-dimensional discriminant space. The fossil is placed well away from all the hominoid humeri, but approximates the female gorilla and, in this case, the male orangutan, most closely.

The morphological uniqueness of the East Rudolf humerus may imply a functional uniqueness as well. This would be compatible with the conclusions of Napier (*13*), Rightmire (*8*), and others on the hand: at least one kind of early hominid was equipped with forelimbs somewhat unlike those of extant hominoids. The question is still open whether or not this early hominid was a habitual biped equipped with forelimbs used solely for manipulation.

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Anticoagulant-Resistant Rats: Possible Control by the Use of the Chloro Analog of Vitamin K_1

Abstract. *Strains of wild rats that are resistant to the anticoagulant action of coumarins and derivatives of indandione have been discovered in a number of geographic areas. These rats have now been shown to be more susceptible than normal rats are to the anticoagulant action of the vitamin K antagonist, 2-chloro-3-phytyl-1,4-naphthoquinone. This compound, either alone or in combination with warfarin, would appear to be an effective rodenticide in areas where resistance to the indirect anticoagulants is a problem.*

Strains of wild rats that are resistant to the action of the widely used anticoagulants were first discovered in a number of areas in northern Europe where warfarin was being fed as a rodenticide (*1*, *2*). More recently a similar resistance to these anticoagulants, which act by suppressing the synthesis of the

Table 1. Effect of the chloro analog of vitamin K_1 on prothrombin synthesis.

Dose of chloro-K (mg/kg)	Normal rats		Warfarin-resistant rats	
	Male	Female	Male	Female
0.2		240 ± 8*		113 ± 19
.4		240 ± 5		80 ± 01
2.0	204 ± 12	189 ± 26	27 ± 6	72 ± 10
4.0		166 ± 9		68 ± 10

* Units of prothrombin per milliliter of plasma ± standard error. All rats were given chloro-K in the tail vein 21 hours before blood was drawn by cardiac puncture and analyzed for prothrombin by the two-stage method of Ware and Seegers as modified by Shapiro and Waugh (*17*). Normal plasma prothrombin levels are 220 to 250 unit/ml.

vitamin K–dependent clotting factors, has been reported in this country (*3*). The trait is apparently inherited by an autosomal dominant gene (*4, 5*), and the resistance is not related to alterations of warfarin metabolism (*5, 6*) in these rats. These rats not only are resistant to the anticoagulant action of warfarin but they also have a greatly increased requirement for vitamin K (*6*). Metabolism of the vitamin is however unaffected (*7*), which suggests that the mutation may have influenced a binding site on a protein that is a receptor for both vitamin K and the anticoagulant. The microsomal membranes from warfarin-resistant rats lack a warfarin-binding protein that is present in normal rats (*8*), and there have been reports of other biochemical alterations in the warfarin-resistant rats (*9*). Although various strains of these rats have been reported (*1, 10*) to be resistant to a number of different coumarins and derivatives of indandione, other types of anticoagulants have apparently not been tested.

Lowenthal has described the preparation of the 2-halo analogs of phylloquinone (*11*) and has shown (*12*) that in contrast to the coumarin anticoagulants, 2-chloro-3-phytyl-1,4-naphthoquinone (chloro-K), appears to function as a direct antagonist of vitamin K Although the high vitamin K requirement of these rats raised the possibility that a direct vitamin antagonist such as chloro-K might not be as effective an anticoagulant in these rats as in normal rats, its effectiveness was tested.

The data in Table 1 show that not only is chloro-K (*13*) an effective anticoagulant when injected intravenously (*14*) in warfarin-resistant rats (*15*) but that it is considerably more effective in this strain than in normal rats. Also, chloro-K is a more effective anticoagulant in male warfarin-resistant rats, which have a higher vitamin requirement than do females.

These findings suggested that chloro-K might have potential as a rodenticide in geographic areas where rat populations can no longer be controlled by the commonly used anticoagulants. Varying concentrations of chloro-K were therefore dissolved in corn oil and added to the standard rodenticide test diet of the Environmental Protection Agency (EPA) (*16*). The effectiveness of these diets as a rodenticide was then compared to 0.025 percent warfarin in the same diet. As shown in Fig. 1, normal rats fed a diet containing 0.025 percent warfarin died within 1 week, but the warfarin-resistant rats all survived over 20 days. As the concentration of chloro-K in the diet was increased from 0.005 to 0.02 percent its effectiveness as a rodenticide increased until most of the warfarin-resistant rats were killed within 1 week of exposure to the diet. As expected from the data obtained by direct injection, the compound was less effective against normal rats. The toxic effects seen in the rats consuming the chloro-K diet were indistinguishable from the effects seen after warfarin administration—internal hemorrhage which in many cases resulted in paralysis of the hindquarters. The acceptability of the diets contain-

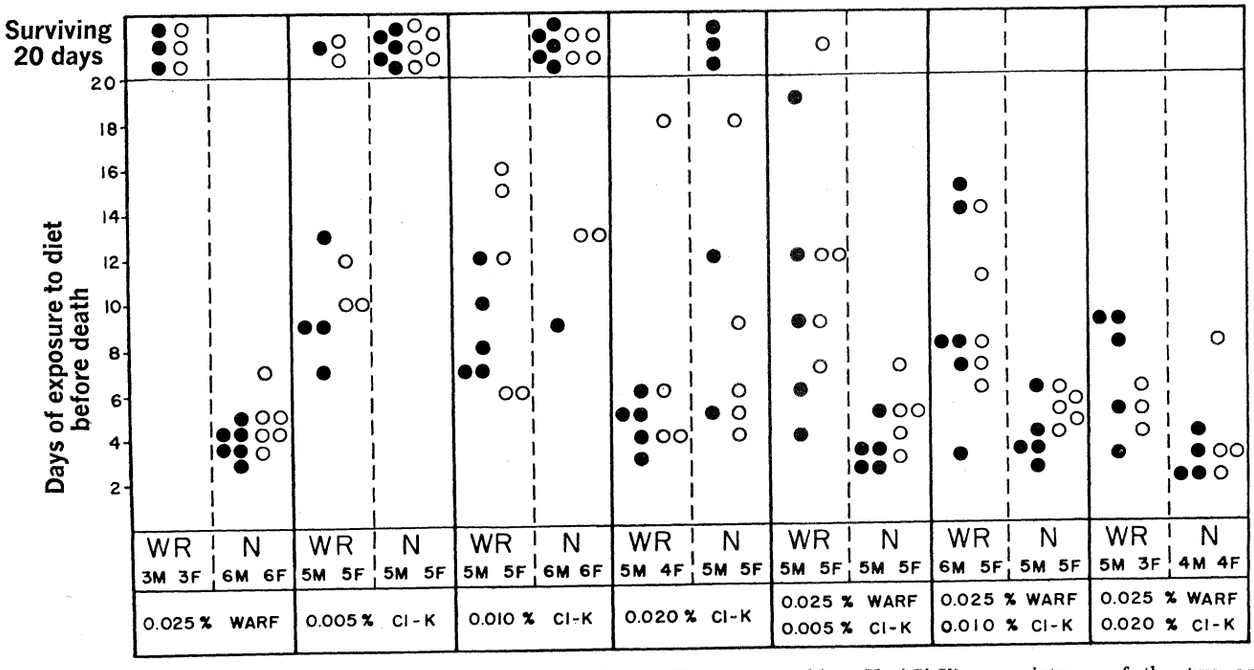

Fig. 1. Effect of diets containing varying amounts of warfarin (*WARF*) or chloro-K (*Cl-K*) or mixtures of the two anticoagulants on the survival of normal (*N*) and warfarin-resistant (*WR*) rats. The diets containing the anticoagulants were the only foods available to the rats during the 20-day period. The closed circles (for male rats) and open circles (for female rats) indicate the number of days after they were exposed to the diets that each rat was found dead.

ing chloro-K was excellent. When six male and six female normal rats (weight, 160 to 180 g) were placed in a cage containing both the EPA 0.005 percent chloro-K diet and the EPA diet with only 5 percent corn oil added, the ratio of the chloro-K diet to that of the control diet consumed over a 4-day period was 0.93. In a similar test with four normal males (180 to 190 g) that were given a choice of the 0.02 percent chloro-K diet or the control diet the ratio was 0.89.

To be effective as a general rodenticide, an anticoagulant would have to kill all the rats in the population, not just the warfarin-resistant strain. As a rather high dietary concentration of chloro-K might be required to control the normal rats, a mixture of chloro-K and warfarin would appear to be an effective treatment. The results of the exposure of warfarin-resistant and normal rats to such mixtures are also shown in Fig. 1. The mixture of 0.025 percent warfarin and 0.02 percent chloro-K was effective in killing both strains of rats in about 1 week. The amount of this diet consumed by these 150- to 180-g rats before they died was 39 ± 3 g (mean $\pm$ standard error) for the normal rats and 42 ± 4 g for the warfarin-resistant rats. In these rats, the total intake of the anticoagulant chloro-K was 45 to 50 mg per kilogram of body weight and that of warfarin was 55 to 60 mg/kg.

Chloro-K therefore appears to hold great promise as a rodenticide. Relatively low concentrations are lethal, and its mechanism of action is known. As is the case with the use of warfarin as a rodenticide, the available information (*12*) would suggest that accidental exposure of other animals to the compound could be counteracted by administration of vitamin K. These studies also indicate that the acceptability of the compound in the diet is good. If used alone, chloro-K could control local pockets of warfarin-resistant rats, and if used in combination with warfarin, it could prevent new areas of resistance from developing.

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14. The aqueous chloro-K preparation used for injection contained 2 mg of chloro-K, 14 mg of Tween-80, and 10 mg of ethanol per milliliter.
15. The warfarin-resistant rats used were descendants of a colony homozygous for this trait which has previously been described (*6*). These rats are fed Purina laboratory chow and, except when on experiments, are given water containing 0.5 mg of menadione sodium bisulfate (trihydrate) per liter. Without this supplement the male rats do not maintain normal prothrombin concentrations. Prothrombin concentrations in these rats are not affected by an intraperitoneal injection of warfarin (5 mg/kg) or by feeding them a diet containing 0.25 percent warfarin.
16. The diet contained: 65 percent coarse ground corn, 25 percent ground oats, 5 percent powdered sugar, and 5 percent corn oil. The chloro-K or chloro-K and warfarin mixtures were dissolved in an additional 5 percent of corn oil and added to the diet.
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Mucopolysaccharides: Comparison of Chondroitin Sulfate Conformations with Those of Related Polyanions

Abstract. *X-ray diffraction shows that chondroitin 6-sulfate, and some further sulfated derivatives, can occur in two ordered structures in stretched films. Both structures contain single helices with similar projected disaccharide lengths (9.6 and 9.8 angstroms) but with very different turn angles between successive disaccharides (120 and 45 degrees). In contrast, coaxial double helices of hyaluronates and ι-carrageenates have shorter projected disaccharide lengths (8.5 and 8.9 angstroms).*

We have obtained x-ray diffraction patterns from stretched films (*1*) of sodium salts of chondroitin 6-sulfate (*2*) and some closely related materials (*3*). The patterns (Fig. 1, A and B) indicate that, in these films, threefold or eightfold helical molecules (*4*) pack parallel to one another in regular arrays (*5*). Molecular conformations and interactions can therefore both be defined. Chondroitin sulfates occur in connective tissue as side chains on proteoglycans (*6*). We believe that our results may be useful in defining possible conformations and interactions of short lengths of these side chains.

Axial periodicities per disaccharide residue (h) are very similar (9.6 and 9.8 Å) for the two molecules and correspond to almost fully extended chain conformations. In contrast the turn angles per disaccharide (θ) are very different (120° for a threefold helix and 45° for an eightfold helix). We used computer methods (*7*), which combine stereochemical information (*8*) with the values of h and θ, to build preliminary molecular models (Fig. 2) (*9*). The resulting threefold helix (Fig. 2a) has no unacceptably short nonbonded distances, and the eightfold helix (Fig. 2b) has only one, which should be removed during detailed refinement (*10*). Packing considerations, supported by density measurements, indicate that the molecules are single helices (Fig. 2, a and b) packed so that their axes are 14.3 Å apart for threefold helices and 13.8 Å apart for eightfold helices. Intermolecular distances of about 14 Å are probably characteristic of sulfated mucopolysaccharides since they also occur for the seaweed polysaccharide ι-carrageenate, which has the same linkage pattern (*11*).

The two molecules have similar central cores of pyranose residues that are fringed with charged sulfate groups. Ionic bridges, involving counterions, are the only interactions possible between these molecules. The importance of counterions for the interaction of chondroitin sulfate chains is consistent with their envisaged biological functions in electrolyte physiology and in structural organization of the intercellular matrix (*12*). Although the threefold and eightfold helices have similar h values the azimuthal distribution of