produce and release prostacyclin but require some specific stimulating agent, such as thrombin. Similar observations have been made for vascular endothelial cells of human origin (*12*).

Cultures were exposed to aspirin at a concentration of 0.2 m*M* for 30 minutes. The aspirin was then removed, the cell monolayer washed, and the ability of these cells to synthesize prostacyclin from exogenously supplied [^{14}C]arachidonic acid was measured at intervals. After aspirin treatment the synthesis of 6-keto-$PGF_{1\alpha}$ from exogenous arachidonic acid was completely eliminated, but within 1 hour after removal of aspirin the levels of prostacyclin synthetic activity approached those found in untreated cells, and by 2 to 3 hours had increased to 2.5 times the concentrations in cells before aspirin treatment (Fig. 2). This recovery was completely blocked in cultures to which the protein synthesizing inhibitor cycloheximide (20 μM) was added.

The ability of aspirin-treated labeled cells to release prostacyclin in response to the initiator thrombin was measured in similar experiments (Fig. 2). In contrast to the rapid and full recovery of the cyclooxygenase as evidenced by prostacyclin synthesis from [^{14}C]arachidonic acid, the cells were completely unresponsive to thrombin even 5 hours after removal of aspirin in confluent nondividing cell cultures.

In longer-term experiments, thrombin responsiveness was still 75 percent impaired even 4 days after aspirin treatment. However, when parallel cultures were stimulated to divide by trypsinization and subculturing in fresh medium, substantial recovery occurred within 24 hours (Fig. 3).

Aspirin is known to irreversibly inhibit the cyclooxygenase by acetylating the enzyme (*9*). It must be presumed that the rapid recovery of prostacyclin synthesis from arachidonic acid in aspirin-treated cells represents synthesis of a new enzyme. This conclusion is confirmed by the observations that recovery of the cyclooxygenase is inhibited by cycloheximide. This rapid replacement of the cyclooxygenase indicates that synthesis and turnover of the enzyme are probably a continuous process even in nondividing cells. The failure of aspirin-treated cells to produce prostacyclin in response to thrombin, despite full recovery of the cyclooxygenase, indicates therefore that aspirin must also inactivate additional components of the prostacyclin-releasing system that are not continuously replaced in resting cells.

Thrombin normally functions as a pro-

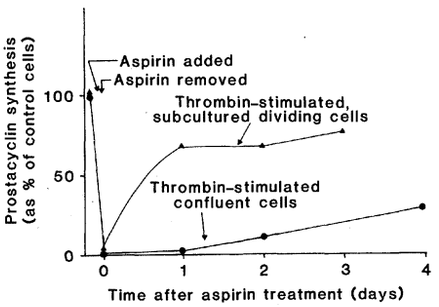

Fig. 3. Confluent cell cultures were labeled with [^{14}C]arachidonic acid and exposed to aspirin (0.2 m*M*) for 30 minutes as described in Fig. 1. The aspirin was removed and the cultures divided into two groups. One group was treated with fresh growth medium only. Cells in the second group were stimulated to divide by trypsinization and subculturing at a 1:2 ratio. Prostacyclin synthesis in response to added thrombin (0.5 unit) remained substantially impaired during the entire 4-day experimental period for confluent nondividing cells (bottom curve), whereas activity rapidly recovered in dividing cells (top curve).

aggregatory substance. It is believed that the ability of thrombin to induce synthesis of the anti-aggregatory substance prostacyclin may be an important control feature of thrombin-induced hemostasis.

The prolonged inactivation of this system in confluent cultures suggests that recovery of the vasculature after aspirin treatment may require more than mere replacement of the cyclooxygenase component of the prostacyclin synthetase system. Full recovery of the system in a functional sense may require replacement of cellular components that are regenerated only during cell division.

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Kin Selection: Its Components

Abstract. *Change in gene frequency under kin selection is the sum of two components, namely, $\overline{\Delta q_I}$, a change in gene frequency caused by individual selection, and Δq_G, a change caused by group selection. For the evolution of altruistic traits by kin selection, $\overline{\Delta q_I}$ is always negative—that is, individual selection operates against altruism—and Δq_G is always positive, so that selection between groups favors altruism. Hamilton's rule specifies the conditions under which $\Delta q_G > |\overline{\Delta q_I}|$—that is, the conditions necessary for intergroup selection to override individual selection.*

Kin selection (*1*, *2*) is the evolutionary process that occurs when individuals within a population interact with one another in a nonrandom way with respect to kinship, and these interactions affect fitness. This process is believed to have exerted a significant influence on the evolution of social behaviors—that is, on the ways in which individuals interact (*3*).

Maynard Smith (*1*) originally defined kin selection in contrast to, and as an alternative for, group selection. The key distinction between the two evolutionary processes was the presence or absence of discontinuities in the population breeding structure. Kin selection did "not require any discontinuities in population breeding structure" (*1*), whereas the existence of partially isolated breeding groups was "an essential condition for group selection" (*1*). Smith later proposed (*2*) that the term "group selection" be restricted to those cases in which the group was the unit of selection; that is, to those cases in which changes in gene frequency are brought about by the differential extinction and proliferation of groups (*4*). However, similarities between kin and group selection are pronounced. Kin selection depends upon the structuring of the population into kin groups, whether the groups exist as actual physical entities or exist as a result of the facultative expression of social behaviors (*5*). This feature of kin selection has led several authors (*3*, *6*) to consider that kin selection is a form of group se-

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Table 1. Family types, family frequencies, allele (a) frequency per family, offspring fitnesses, and mean family fitnesses, and allele frequency changes within families for the general single-locus model of kin selection.

Family type	Family frequency, F_i	Frequency of a in family, q_i	Offspring fitnesses within families*			Mean family fitness, W_i	$\Delta q_i'$ within families
			$W_i(AA)$	$W_i(Aa)$	$W_i(aa)$		
$AA \times AA$	p^4	0	1			1	0
$AA \times Aa$	$4p^3q$	1/4	$1 + D$	$1 + D + F$		$1 + D + F/2$	$F/8\overline{W}_2 < 0$
$AA \times aa$	$2p^2q^2$	1/2		$1 + 2D + F$		$1 + 2D + F$	0
$Aa \times Aa$	$4p^2q^2$	1/2	$1 + D + G$	$1 + D + F + G$	$1 + D + E + G$	$1 + D + G + (E + 2F)/4$	$E/8\overline{W}_4 < 0$
$Aa \times aa$	$4pq^3$	3/4		$1 + D + F + 2G$	$1 + D + E + 2G$	$1 + D + 2G + (E + F)/2$	$(E - F)/8\overline{W}_5 < 0$
$aa \times aa$	q^4	1			$1 + E + 4G$	$1 + E + 4G$	0

*The family types are indicated by $i = 1, 2, \ldots, 6$. $W_i(AA)$ represents the fitness of genotype AA in family i and $\overline{W}_i$ is the mean fitness in family i. $D = bN(1 - h)/2 > 0$, $E = (c - b) < 0$, $F = (c - b)(1 - h) < 0$, and $G = bN/4 > 0$.

lection intermediate between individual and populational selection, although this suggestion has been strongly opposed (*2*). Recently, Dawkins (*7*) called the idea that "kin selection is a form of group selection" one of the "common errors" in discussions of sociobiology.

The theoretical foundation of sociobiology is Hamilton's rule, $b_T r > |c|$ (*8*), which is widely recognized as specifying the conditions necessary for the evolution of altruistic social behaviors. An altruistic social behavior is favored by kin selection if the total benefit, b_T, dispensed by an individual performing the behavior, times the average degree of genetic relatedness, r, between performer and receiver exceeds the cost, c, of performing the behavior (*9*). Several genetic models of population have shown Hamilton's rule to be valid for a wide range of conditions (*10, 11*). When expressed as $b_T r > |c|$, Hamilton's rule seems to support the view that kin selection is an extended form of individual selection. However, deriving the equation for change in gene frequency under kin selection makes the importance of population structure explicit and clarifies the relationship to group selection.

The change in gene frequency under kin selection, Δq, has been independently derived by several workers (*10, 11*) interested in various problems in social evolution, from sibling altruism and parental manipulation to social selection against certain genetic diseases. The general features of all these family-structured models are summarized by Michod (*12*). For the fitness function used here, Δq has been shown (*11*) to be

$$\Delta q = Npq[(c - b)/N + b/2] \times [q + (1 - h)(p - q)]/\overline{W} \quad (1)$$

I will show that this expression is the sum of two components, $\overline{\Delta q_I}$ and Δq_G, that represent, respectively, the change in allele frequencies within groups and the response to selection between groups. The groups in this case will be families. The analysis will follow the tradition in population genetics of dissecting total selection into components within and between families (*13*). Although Δq in any model of selection could similarly be partitioned into components, kin selection is unique in that $\overline{\Delta q_I}$ is always negative for altruistic social behaviors and Δq_G is always positive. I will show that Hamilton's rule specifies the conditions for group selection to override the opposing force of individual selection, that is, for $\Delta q_G > |\overline{\Delta q_I}|$.

Let A, having frequency p, represent the "nonaltruistic" allele in a hypothetical diploid organism and a, having frequency $q = (1 - p)$, represent the "altruistic" allele. Define $(1 - h)$, where $0 \leq h \leq 1$, as the fraction of Aa heterozygotes exhibiting altruistic behavior. After mating at random, each female produces N offspring whose genotype frequencies conform exactly to the expected Mendelian ratios (*14*). The offspring remain together in what Wilson (*6*) calls a "trait group" and, during development, perform behaviors that affect the survival of themselves and their siblings. To focus solely on the evolution of social behaviors, I make the usual assumption that the initial fitness of each family member is 1. An aa or Aa individual performing the behavior incurs a cost c, but changes the fitness of every other family member by an amount b. The total fitness effect, b_T, of an altruist on the other $(N - 1)$ members of its sibship is $b(N - 1)$. For altruistic behaviors $c < 0 < b$.

If selection is weak and mating is random, the frequencies of the parental mating types, $F_i (i = 1, 2, \ldots, 6)$, are given by terms in the expansion of $(p^2 + 2pq + q^2)^2$ and are listed in Table 1 with the frequency q_i of allele a in family i, the offspring fitnesses within families, $W_i(AA)$, $W_i(Aa)$, and $W_i(aa)$, and the mean family fitnesses, $\overline{W}_i$. The change in gene frequency, $\Delta q_i'$, owing to selection among individuals in family i, is found from standard population genetics theory to be

$$\Delta q_i' = [W_i(aa)f_i(aa) + W_i(Aa)f_i(Aa)/2]/\overline{W}_i - q_i \quad (2)$$

where $f_i(Aa)$ and $f_i(aa)$ are the genotype frequencies expected in family i on the basis of Mendel's laws. The values of $\Delta q_i'$ are given in Table 1, column 8, and are less than or equal to zero for all i families.

Clearly, nonaltruists are increasing within families at the expense of altruists. The cause of the spread of the altruistic allele is the difference in fitness *between* families as is shown below. Each $\Delta q_i'$ is evaluated relative to the mean family fitness, $\overline{W}_i$. A different and uniform relative standard is needed to determine the mean change in q by selection within families. These changes in gene frequency within families must be evaluated relative to the mean population fitness, $\overline{W}$. Thus, $\Delta q_i = (\overline{W}_i/\overline{W})(\Delta q_i')$ and the mean change in q by individual selection within families, $\overline{\Delta q_I}$, is

$$\overline{\Delta q_I} = \sum_{i=1}^{6} \Delta q_i F_i \quad (3)$$

Substituting values from Table 1 yields

$$\overline{\Delta q_I} = pq(c - b)[q + (1 - h)(p - q)]/2\overline{W} < 0 \quad (4)$$

because $(c - b)$ is always negative and $\overline{W} = p^2\overline{W}(AA) + 2pq\overline{W}(Aa) + q^2\overline{W}(aa)$ (*15*). If families are treated as units, the change in gene frequency, Δq_G, owing to selection between family groups is obtained by substituting into Eq. 2 the family counterparts, $\overline{W}_i$, F_i, and q_i, for the genotypic fitnesses, frequencies, and allelic compositions, respectively

$$\Delta q_G = \sum_{i=1}^{6} q_i F_i \overline{W}_i/\overline{W} - q = pq(c + b_T)[q + (1 - h)(p - q)]/2\overline{W} \quad (5)$$

This expression is always greater than zero when $b_T > |c|$. It is positive because there is a positive covariance between q_i and $\overline{W}_i$. Kin selection for altruism is thus a special case of Price's model (*16*) of selection based on covariance mathematics. Here, the positive covariance between allele frequency and group fitness exceeds the negative covariance between the number of a alleles in a genotype and the genotype's fitness. However, for the altruistic gene to spread, not only must Δq_G be positive, but it must also exceed the absolute value of $\overline{\Delta q_I}$. That is, selection between family groups must override the opposing selection within family groups. Setting $\Delta q_G > |\overline{\Delta q_I}|$ and simplifying yields Hamilton's rule for family groups, $b_T/2 > |c|$ (*17*).

The total change in gene frequency under kin selection, Δq, is

$$\Delta q = \Delta q_G + \overline{\Delta q_I} = Npq[(c - b)/N + b/2][q + (1 - h)(p - q)]/\overline{W} \quad (6)$$

as was given in Eq. 1 and derived from other models (*11*).

This derivation illustrates that kin selection involves individual and group selection as opposing processes. Hamilton's rule specifies the conditions under which group selection in favor of sociality is sufficiently strong to overcome the opposing effects of individual selection against sociality. Whether a family is called a group or a set of kin, this derivation shows that kin selection involves two evolutionary processes (opposing one another in the case of altruism) which have been classically recognized (*13*) as different levels of selection.

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15. $\overline{W}(AA)$ is the fitness of a randomly chosen AA individual in the population and similarly for $\overline{W}(Aa)$ and $\overline{W}(aa)$. The value of $\overline{W}(AA)$ can be obtained from the sum
$$\sum_{i=1}^{6} W_i(AA)\Pr(i/AA)$$
where $\Pr(i/AA)$ is the conditional probability that one is in family type i given that one observes an AA individual among the offspring. It follows that
$$\sum_{i=1}^{6} \Pr(i/AA) = 1$$
and $\overline{W}(Aa)$ and $\overline{W}(aa)$ can be found in like manner. [See (*11*) for a more detailed discussion.]
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Adaptive Topography in Family-Structured Models of Kin Selection

Abstract. *Adaptive topographies provide a means of summarizing the qualitative dynamics of evolution. Inclusive fitness serves as an organizing concept in much of sociobiology. Through the use of Sewall Wright's "fitness function," the theoretical equivalence of these concepts for weak selection in family-structured populations is demonstrated.*

One of the most intriguing extensions of the Neo-Darwinian research program is the recent theory of kin selection (*1*). There are two key elements of this theory. First, Hamilton's rule (*1*), $c/b < r$, provides the conditions for increase of an allele that codes for an "altruistic" behavior between two individuals who are related by r. In this rule, c and b are additive increments to the fitnesses of, respectively, the donor and recipient of the altruistic act. Hamilton's rule has revolutionized research on the evolution of behavior, and there has been a considerable amount of theoretical work to determine the precise conditions under which the rule holds (*2–12*).

The second key element of kinship theory has received less theoretical attention, although it plays an important conceptual role in applications. Hamilton (*1*) claimed that gene frequency dynamics proceed along adaptive topographies (*13*) determined by the average inclusive fitness effect (*1*). The inclusive fitness effect of an individual's behavior is defined as the sum of the additive effects of the behavior on the individual fitnesses of the donor and the recipient, the effects on the latter being weighted by the degree of relatedness of recipient and donor. Hamilton's claim is fundamentally important for, if true, it relates kinship theory to Wright's (*13*) adaptive topography, which is one of the most useful theoretical and conceptual tools in evolutionary biology. However, Hamilton (*1*) was not able to demonstrate this claim rigorously. Consequently, inclusive fitness seems to have fallen into disuse in recent family-structured models of kin selection (*3–8, 10–12*). Yet, other studies (*14*) based on Hamilton's original model (*1*) have demonstrated this claim. However, genetic identity coefficients were used in these selection models (*14*). Since these coefficients have concrete meaning only for neutral genes, many workers have been unwilling to accept results of selection models based on them. For this reason, most recent theoretical studies of kin selection have focused on sibling interactions in family-structured models (*3–8, 10–12*). In these models, individual fitness is a function of the social interactions occurring in the

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