by comparing infarct size alone ($P < .01$) or by expressing infarct size as a percentage of the area at risk of developing necrosis ($P < .01$).

The mechanism by which fluorocarbons limit infarct size is not clear. Fluorocarbons may increase oxygen delivery because their oxygen-carrying capacity at high PO_2 is actually better than that of blood (*8*) or by increasing collateral blood flow to the ischemic myocardium, perhaps because the viscosity of fluorocarbons is less than that of blood (*14*). In addition, the small size (less than 0.1 μm) of fluorocarbon particles (*10*), in comparison with the much larger red blood cells, would improve the distribution of oxygen to the myocardium at risk. That increased oxygen delivery may be the mechanism of action was suggested by a recent study by Rude *et al.* (*15*), who showed that the decrease in intramyocardial PO_2 as measured by mass spectrometry during 5-minute coronary occlusions was considerably blunted by the administration of fluorocarbons with oxygen, but not by oxygen alone. Bleeding to a low hematocrit and the resultant anemia cannot explain the protection of ischemic myocardium in this investigation, since bleeding followed by volume replacement with Ringer solution appeared to have no significant effect on the size of the infarct in comparison with untreated controls.

The autoradiographic method used to determine the portion of myocardium at risk of developing infarction can predict the extent of myocardial damage (*9, 16*). The advantage of the technique is that, before an intervention, a well-defined region at risk of developing necrosis is identified. The percent of the myocardium at risk that became infarcted in the control group was similar to that which we had previously found in control animals that were not bled (*9, 17*).

A significant amount of ischemic myocardium can be salvaged by use of fluorocarbons. These agents, which have already been safely administered to humans, deserve further study for their potential benefits in patients with acute myocardial infarction.

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F-Cell Production in Sickle Cell Anemia:

Regulation by Genes Linked to β-Hemoglobin Locus

Abstract. *Strong correlation of F-reticulocyte levels within sib pairs with sickle cell (SS) anemia suggests that the wide-ranging levels found in the SS population are governed by genes linked to the β^S-site. Correlations between F-cell levels in parents and F-reticulocyte levels in their children indicates that these same genes regulate F-cell production in nonanemic persons. Comparison of outcrossed and inbred SS populations suggests that relative well-being arises from homozygosity for alleles dictating high F-reticulocyte response to anemia.*

Fetal hemoglobin (HbF)–bearing red blood cells (F cells) are resistant to sickling in most patients with sickle cell (SS) anemia (*1*). In turn, severity of SS disease is governed in part by numbers of F cells produced, that is, by the level of F reticulocytes (*2*). Those uncommon persons who synthesize HbF in every cell (*3*) or in a large fraction of cells (*4*) are comparatively free of disease. We supposed that the signs and symptoms of SS anemia might be attenuated in others were it possible to increase the relative abundance of their F reticulocytes. With this goal in mind, one of the first questions we attempted to answer was whether the capacity to produce F reticulocytes in SS anemia is inherited and, if so, where the gene or genes are located.

Genes for the production of F reticulocytes exist in other species. DeSimone (*5*) found that the capacity to produce HbF and F cells in baboons with phenylhydrazine-induced hemolytic anemia is inherited. Phenotypically, anemic animals fall into three clusters with respect to the maximum HbF level attained: low (1 to 8 percent), intermediate (12 to 24 percent), and high (31 to 59 percent). Progeny of any given sire exhibit either low to intermediate responses or intermediate to high ones. No sires produce other combinations of progeny. In addition, correlation between nonanemic parents and anemic offspring, as well as correlation between levels of HbF attained before and after induction of hemolysis, suggest that the genes governing HbF production in anemia also regulate the lower, but individually distinctive, amounts of HbF produced in nonanemic animals.

Past attempts (*6*) to apply equivalent genetic analysis to SS anemia have been confounded by the fact that HbF and F cells may be augmented by preferential survival of F cells in SS disease. Since preferential F-cell survival varies widely between SS individuals (*1*), estimates of HbF and F cells are relatively poor indices of F-cell production. In the study reported here we avoided this problem by measuring F reticulocytes directly (*2*) and adducing three lines of evidence to support the idea that F-reticulocyte responsiveness in SS anemia is inherited.

First, the percentages of F reticulo-

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Table 1. Relation between F-cell levels in well American black AS parents and F-reticulocyte levels in their SS children.

Kindred	F cells (%)*		Midparental value	F reticulocytes in SS child† (%)
	Father	Mother		
R	5.0	5.0	5.0	47.6
H	5.2	3.8	4.5	37.7
E‡	0.9	7.4	4.2	32.6
M‡	1.3	3.5	2.4	25.8
W‡	0.6	3.3	2.0	26.0
P	0.6	3.5	2.0	14.5
J‡	2.8	1.3	2.0	14.4

*F-cell and F-reticulocyte levels were measured as noted elsewhere (*1*, *2*). Parental levels, when reexamined at later times, were unchanged. †In two kindreds (H and M), F-reticulocyte levels represent an average of three SS siblings; values were not significantly different between siblings. ‡Some of the data from these kindreds have been described (*1*).

cytes, while widely divergent among the population of SS patients, are almost as alike within 14 sibling pairs [correlation coefficient (r) = .94] as the within-person percentages for successive samples (r = .95) from 14 subjects (Fig. 1). Analysis of variance shows that differences in F-reticulocyte levels within sib pairs contribute only 3.7 percent of total variance: a result remarkably like the 3.0 percent contribution of within-person differences to total variance. A notable feature of these comparisons is that the correlation (.94) for sib-sib correspondence is significantly greater (P = .001) than the sib-sib correlation of .5 ordinarily anticipated for codominantly inherited metric traits. This is to be expected if the degree of anemia-induced F-reticulocyte response in β^s homozygotes is truly inherited and the genetic locus (*7*) which governs the response is closely linked to the β locus. Under these circumstances, the degree of sib-sib correlation should be a function of the proximity of the two loci. If the loci are closely juxtaposed, recombination between them will be uncommon and therefore siblings who each inherit two β^s-bearing chromosomes should tend to inherit a like set of alleles for F-reticulocyte response. If the two loci are further apart, sib-sib correlation for F-reticulocyte response should decline toward .5 as the interlocus distance increases and recombinants begin to appear. While the data are too few and the method too inefficient (*8*) to assign any specific genetic distance, the high degree of correlation shown in Fig. 1 strongly suggests not only that F-reticulocyte response is inherited but also that the responsible locus lies somewhere within the linkage group containing the β-globin locus.

Second, comparisons between parents and their children substantiate the notion that F-reticulocyte response in SS anemia is inherited. In seven black American families (Table 1), the midparental F-cell levels in healthy heterozygous (AS) parents, although well within the normal adult range of 0.2 to 10 percent (*9*), are well correlated (r = .92) with the percentage of F reticulocytes produced by their SS offspring. Since F-cell level in normal adults is itself inherited (*10*), our result suggests that men and baboons (*5*) are alike in that the expanded level of F reticulocytes in anemia seems to be regulated by the same genes governing lower levels in health. If so, and if elevated F-

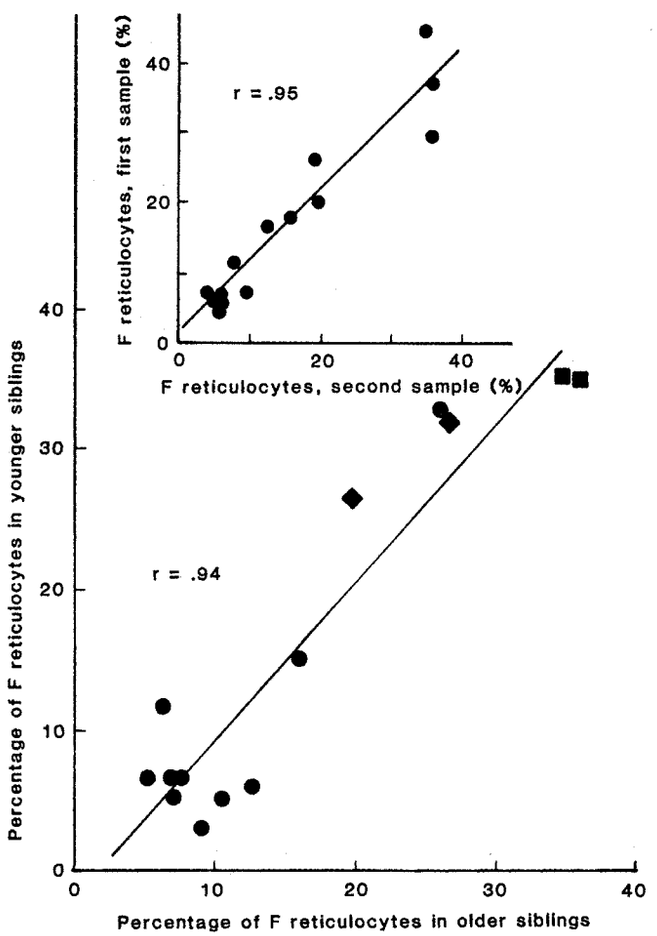

Fig. 1. Correlation between F-reticulocyte percentages assayed (*1*, *2*) in 14 American black SS sib pairs. At the time of sampling, none of the subjects shown here, in Fig. 2 or in Table 1, had been recently transfused; all were free of intercurrent disease and SS crisis. In most instances, subjects were repeatedly sampled; however, only the latest value for each subject was entered here. This rule facilitates comparison with the control analysis shown in the inset, wherein levels obtained in the two most recent samplings for each of 14 SS individuals are entered. Where the between-sample values entered in the inset were not drawn at random from one member of each sib pair, they were obtained from individuals whose F-reticulocyte level matched that of the sib pair in question. Subject ages ranged from 7 to 58 years (mean, 21 years); mean difference in age within sib pairs was 4 years. There was no correlation (r = −.08) between age and percentage of reticulocytes. In two families, indicated by ■ and ◆, three sib pairs were assayed in each. Consequently, three sib-sib entries could have been made for each symbol. However, to do so would overemphasize situations wherein two sibs were identical but one was discordant. Thus only the two most alike sib pairs are entered for these two families; substitution of values for the omitted pairs does not alter correlation. In contrast to the depicted relationship, sib-sib correlation for overall F-cell (F reticulocytes plus F erythrocytes) levels was not nearly as good (r = .51) even though correlation between repeated samples was good (r = .96).

cell levels of 10 to 50 percent sometimes found in nonanemic men (*9*) are governed by alleles at the same locus, it follows by extrapolation that this locus should be linked to the β-globin locus. Such is already known to be the case (*11*). Among variant heterozygotes with 10 to 30 percent F cells, an aggregate of three recombinants appeared in their 30 offspring (*11*). This finding, along with our extrapolation, suggests that the locus regulating F-reticulocyte production in anemia may be physically separate from the γδβ gene complex that governs hemoglobin structure.

A third line of evidence comes from between-population comparisons. In Fig. 2, the calculated 25 percent coefficient of variation for F-reticulocyte levels among ten SS subjects from genetic isolates in eastern Saudi Arabia is compressed relative to the 66 percent found for a genetically outcrossed American black SS population. Indeed, the coefficient of variation for F reticulocytes in these inbred Saudis is little more than the average coefficient (23 percent) found within 14 sib pairs in America (Fig. 1) and the average (23 percent) found in five sib pairs in the Saudi isolates. Thus, in this respect, individuals in the Saudi population are as alike as siblings. This uniformity among Saudi subjects with SS suggests that, in them, isolation and random genetic drift have caused the frequency of alleles for high levels of F reticulocytes to approach unity. Such homozygosity doubtless contributes to the comparative clinical well-being of SS individuals in this population (*4*). We suppose that the five American SS patients (Fig. 2) whose F-reticulocyte levels resemble those in Saudis are also homozygotes for alleles leading to increased percentages of F reticulocytes. If so, the frequency of such alleles in the 42 Americans represented in Fig. 2 is estimated from the Hardy-Weinberg principle to be $(5/42)^{1/2} = 0.35$. By subtraction, the estimated frequency of alleles for low levels of F reticulocytes becomes 0.65 (*12*). These putative differences in gene frequencies between Saudi and American individuals seem to extend to nonanemic individuals as well. Among AS subjects average (± standard deviation) F-cell levels in Saudi men (6.5 ± 2.8 percent) (*13*) were higher than found in Americans (4.9 ± 3.9 percent) (*14*). However, this was not true for healthy AA individuals in whom F-cell levels were not only lower but much the same in both Saudi males (3.0 ± 3.1 percent) (*13*) and black Americans (2.8 ± 1.6 percent) (*14*). The possibility thus arises that alleles governing F-cell production are in linkage disequilibrium with the β^s gene.

Since the seeming genetic polymorphism governing F-cell production in both anemic and nonanemic states is present in both baboons and men, it may have a common ancient origin: a possibility supported by findings (*15*) of various F-cell levels in diverse nonanemic apes and monkeys. Although the functions of the polymorphism are obscure, resistance to malaria may be implicated. Pasvol *et al.* (*16*) found that HbF forestalls the maturation of the malarial parasite *Plasmodium falciparum* within red cells. These workers also established that *P. falciparum*, like other plasmodia, preferentially invades young cells such as reticulocytes (*17*). Consequently, those individuals who can mount especially high F-reticulocyte responses following malaria-induced hemolysis might escape reinfection with malaria. The way in which alleles for such responses interact with HbS, which also promotes resistance to *falciparum* malaria (*18*), is conjectural. For example, the two loci could be additive, thereby favoring the combination of AS and high-level F-reticulocyte response. Conversely, resistance to *falciparum* malaria conferred by β^s heterozygosity may outstrip that attributable to HbF. The antisickling property of HbF might thereby offset its more direct role against *falciparum* malaria. Since sickling is the factor that interrupts the life cycle of the parasite (*19*), the combination of sickle trait and high levels of F reticulocytes may thus be disfavored.

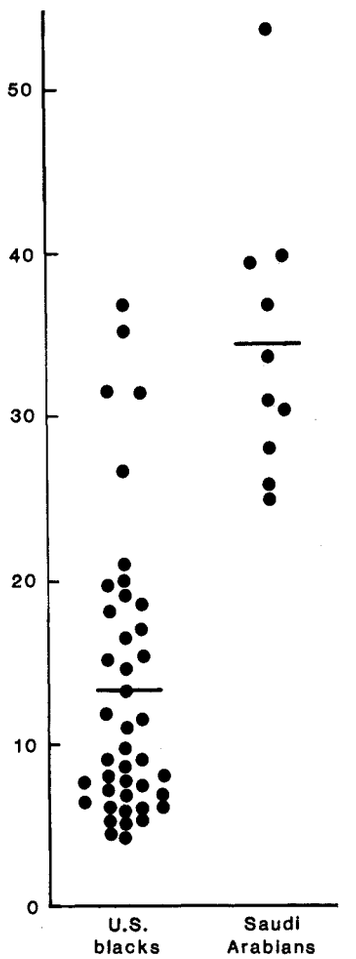

Fig. 2. Levels of F reticulocytes in 42 unrelated American black SS subjects and in ten SS subjects from genetic isolates in Saudi Arabia. Horizontal bars denote average levels. So as to approximate a cross section of the population, Americans (all more than 3 years of age) were examined without our having prior knowledge of their HbF levels. To exclude the contribution of genes producing elevated F-cell levels in the nonanemic state, we obtained parental F-cell or HbF levels for all but two of the eight American SS subjects with > 20 percent F reticulocytes; all those samples (for example, see Table 1) were within the normal adult range. The average F-reticulocyte level in five SS siblings of Saudi subjects (range: 27 to 47 percent) was identical to the average shown in this figure.

Whatever we hypothesize, it is likely that the β-globin locus and the locus that governs F-cell production interact with one another in a variety of ways. Because they appear to be linked and because both seem to be sites of genetic polymorphism, they must have mutually influenced the evolution of the gene region where they are located.

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Potent Contact Allergen in the Rubber Plant Guayule (*Parthenium argentatum*)

Abstract. *Chemical and dermatotoxicological investigations of the natural and processed resin of the Mexican rubber plant, guayule* (Parthenium argentatum), *has established the presence of a sesquiterpene cinnamic acid ester (guayulin A) that is a potent elicitor of allergic contact dermatitis in experimental animals. The guayule contact allergen is comparable to the poison ivy skin allergens as an elicitor of dermatitis in sensitized guinea pigs.*

Guayule (*Parthenium argentatum*, Asteraceae) is potentially an economically feasible source of natural rubber. This common shrub, native to the Chihuahuan desert of northern Mexico and southwestern United States, contains *cis*-isoprene rubber (up to 20 percent, dry weight) that is virtually identical to that from the Brazilian rubber tree *Hevea* (Euphorbiaceae) (*1*). In the United States, during World War II, there was an intensive effort to develop commercial rubber production from guayule when *Hevea* rubber imports from Asia stopped, but this program was halted with the discovery that synthetic rubber could be produced inexpensively from petroleum. Today the escalating price of foreign petroleum has made natural rubbers economical, and the development of a guayule rubber and resin industry is under way in Mexico and the United States. We therefore initiated phytochemical and dermatotoxicological studies to determine the potential dermatological hazard of guayule to agricultural and processing-plant employees.

One report of allergic contact dermatitis caused by guayule (*2*) and dermatotoxicological investigations of the genus *Parthenium* (*3*) suggested that a contact allergen was present. We isolated the principal contact allergen from an acetone extract of dried guayule leaves and stems (*4*). The concentrated extract was separated by liquid chromatography over silica gel, and each fraction was assayed for potential to elicit contact dermatitis on guinea pigs sensitized to the crude resin. The sensitization procedure used was the guinea pig maximization test (*5*) for predictive testing in humans. Guinea pigs were given intradermal injections of the crude guayule resin with adjuvant into the shoulder region, followed by topical application of the resin under an occlusive bandage. After 2 weeks, tests for skin hypersensitivity were conducted by applying the separated resin fractions to the shaved skin of the back. For each test, 5 μl of an acetone solution of the test substance was applied to an area of skin 8 mm in diameter. The test sites were not covered and were inspected for eczematous reactions after 24 hours.

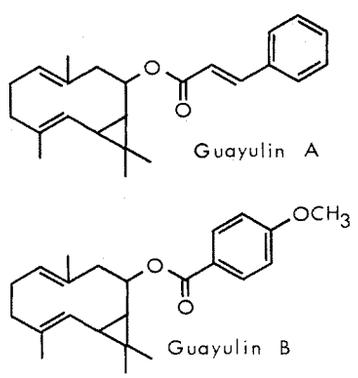

Fig. 1. Structures of guayulin A and guayulin B from *Parthenium argentatum* (guayule).

A single potent elicitor of contact dermatitis was isolated in this manner and purified by recrystallization from hexane. The compound was identified from the ^1H nuclear magnetic resonance (NMR) and infrared spectra (*6*) as the sesquiterpene cinnamic acid ester guayulin A (Fig. 1), which had been previously identified in guayule (*7*). The known sesquiterpene ester of *p*-methoxybenzoic acid, guayulin B (Fig. 1), was also isolated, but it did not exhibit significant allergenic activity. The sensitizing capacity of guayulin A was confirmed by the Freund's complete adjuvant test (*8*); guinea pigs were sensitized to the pure guayulin A and were challenged with serial dilutions of guayulin A in the manner described above. Within 24 hours after application, strong erythemas had appeared on all test sites in response to concentrations as low as 0.010 percent guayulin A (1.4 nmole), with one animal reacting to 0.003 percent (0.5 nmole). The erythemas persisted for 2 weeks. No irritant reactions were observed on a control group of animals sensitized to the adjuvant only.

These experiments show that guayulin A is an extremely potent contact allergen, comparable in potency to the catechol allergens of poison ivy (*Toxicodendron* sp.) (*9*) and to parthenin, a sesquiterpene lactone causing an epidemic skin dermatitis in India (*10*).

Guayulin A is present in both stems and leaves at 0.05 to 0.3 percent, dry weight (*11*), and is one of the major components of the processed resin byproduct obtained from the Saltillo guayule pilot plant in Saltillo, Mexico. Animals sensitized to guayulin A were not sensitive to cinnamic acid (a known contact allergen), to *n*-pentadecyl cinnamic acid ester, or to the sesquiterpene alcohol obtained from base hydrolysis of guayulin A. Nor were the animals sensitive to costunolide, a potent allergenic sesquiterpene lactone similar in structure to the guayulin sesquiterpene moiety. There was only weak cross-reactivity evident with guayulin B (0.42 μmole). These results suggest that delayed hypersensitivity reactions of guayulin A are specific to the intact molecule and are not the result of cleavage of the ester in vivo. The actual mode of action and antigen formation is not

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