often provided "gratis" for a feasible (optimal) solution. The lower bound information can supplement, or even replace the summary of the terminating solution that is provided by some computer codes (as described earlier); and the bounds offer an excellent basis from which to begin examining the more detailed picture of the model that a print-out of selected rows and columns can provide.

References

1. Bradley, S., Hax, A. and Magnanti, T., *Applied Mathematical Programming*, Addison-Wesley, Reading, Mass., 1977.
2. Charnes, A. and Cooper, W. W., *Manangement Models and Industrial Applications of Linear Programming*, Vol. I, Wiley, New York, 1961.

Notes* II

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MANAGING SICKLE CELL ANEMIA IN ZAIRE*†

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This paper analyzes the long term effects of various genetic policies that could be applied at a national level in Zaire to fight sickle cell anemia: the prohibition of marriages between individuals with the sickle cell trait, increased efficacy of the medical cure of sickle cell anemia, selective birth control, and eradication of malaria. We show that combined application of the last two policies would lead to progressive disappearance of the disease. The first two policies lead to disastrous effects in the long run, since the proportion of those who have the sickle cell trait would increase from the present 25%. Due to major differences between Zaire and the United States, the results differ markedly from those of Meredith [4] who presented the results of a similar study in the United States in a previous article in *Management Science*.
(POPULATION; HEALTH CARE–EPIDEMIOLOGY)

1. Introduction

Sickle cell anemia (SCA) is an abnormal and hereditary form of the blood hemoglobin. It almost exclusively affects blacks. In Zaire and some neighboring countries of Central Africa, SCA is a scourge, since it is responsible for an infant mortality of 1.6%. Twenty-five percent of the Zairians have the sickle cell trait (SCT), i.e., they can transmit the disease to their descendants.

This paper examines the long-term effects of various policies that could be applied at a national level: the prohibition of marriages between individuals with the SCT, increase of effectiveness of medical cure of SCA, selective birth control, and a strategy of eradication of malaria. We shall show that a combined application of the last two policies would have profitable short-term effects, and would lead to progressive

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disappearance of the disease in the long run. The first two policies would result in catastrophic long-term effects, since the rate of SCT would increase sharply.

In a previous paper in Management Science, Meredith [4] studied the effects of genetic counseling on the SCA rate among blacks in the United States. A different study is necessary in Zaire because of differences between the countries. The discrepancy between the two countries can be explained mainly by three factors:

(a) the absence of malaria in the United States,

(b) the fact that racial intermixture can be neglected in Zaire, and

(c) sanitary conditions in Zaire that prevent practically any individual affected by SCA from reaching puberty.

(a) and (b) are a disadvantage to Zaire. (c) is a favorable factor, but it does not fully counteract the others, so that the future rate of SCA will always be higher in Zaire than in the United States.

2. The Genetics of SCA

The chromosomes inside the nucleus of a cell govern the inheritable characteristics of the organism. The quantity controlling a character is called a gene. During sexual reproduction, or meiosis, each chromosome doubles and four new cells, called gametes, are formed, each of which has one chromosome. Two gametes then combine to form a fertilized cell or zygote.

The type of hemoglobin is determined by the genes transmitted from parents to children. Each gene can only belong to one and only one of the following two types: type A (normal form) and type S (abnormal form). During reproduction, three arrangements can form: 2 homozygotes AA and SS, and one heterozygote AS. In a simplified way, one can consider that each parent transmits one of their genes to each child, with equal probability. We can then compute the probabilities of each genotype, given the parents' characteristics. For example, the children of two AS-parents have one chance out of two to be AS, one chance out of four to be AA, and one chance out of four to be SS. Table 1 lists the possibilities.

TABLE 1

Probabilities of all genotypes given the parents' types

Father / Mother	AA	AS	SS
AA	all AA	1/2 AA 1/2 AS	all AS
AS	1/2 AA 1/2 AS	1/4 AA 1/2 AS 1/4 SS	1/2 AS 1/2 SS
SS	all AS	1/2 AS 1/2 SS	all SS

The AA-individuals are absolutely normal. As the S gene is largely recessive, the AS-individuals are also normal. In fact, the presence of the S gene—the SCT—affords better protection against malaria, which is endemic in Central Africa. S genes are only dangerous because they can pass an S gene to a descendant. The SS-individuals have SCA and usually die early, after long and painful attacks. They require extensive and expensive medical care, in a country badly under-equipped in hospital beds and medical staff. It is estimated that their mean age of death does not exceed three years.

The effects of SCA in Zaire are dramatic: it has been ascertained [2] that the rate of SCT is equal to 25%, and that this figure has remained constant over the past three generations. Since 1/16 of all marriages bring together 2 AS, 1/64 of all the children born in Zaire have SCA and are condemned to die early. Consequently SCA, on its own, accounts for an infant mortality rate of 1.6% comparable to the overall observed rates in the Western countries, from all disease causes.

Because the disease is inherited, and incurable, only genetic policies, applied at the national level, could control and eventually eliminate SCA. We shall study the long-term influence of various strategies, under the following assumptions:

1. generations occur at discrete points in time;
2. the population size remains fixed;
3. the generations do not overlap (these three hypothesis are common of all genetic studies. They eliminate the effects of changing life spans);
4. no SS reaches the age of reproduction (this assumption, largely verified in Zaire at present, will be dropped later on). The adult population thus consists today of 75% of AA and 25% of AS;
5. mating occurs at random. Since there are no physical differences between AA and AS, no "caste" is likely to form;
6. migrations are neglected. In fact, very few people leave or settle permanently in Zaire. Furthermore, SCA is also prevalent in the neighboring countries;
7. mutations are also neglected. Since the order of magnitude of the mutation rate of SCA is estimated at 10^{-8} [1], only one mutation of a gene from A to S is expected to appear in Zaire every century;
8. finally, we neglect the effects of racial intermixture. In the United States where the percentage of blacks is 11.25%, the rate of weddings between blacks and whites is only 0.28% [1]. In Zaire, whites form only 0.27% of the total population, and, for social and economic reasons, marriages between blacks and whites are the exception. This is unfortunate, because a high level of racial intermixture would appreciably reduce the SCA-rate, due to the flow of white A genes in the black population.

3. Effects of Various Policies

Policy 1: No Genetic Policy

Given assumptions 4 and 5, in the first generation,

9/16 AA-AA-marriages,

6/16 AA-AS-marriages, and

1/16 AS-AS-marriages

should occur. We can then easily compute the probability of the different genotypes in the offspring:

$$\begin{aligned} P(\mathrm{AA}) &= 9/16(1) + 6/16(1/2) + 1/16(1/4) = 49/64, \\ P(\mathrm{AS}) &= 6/16(1/2) + 1/16(1/2) = 14/64, \\ P(\mathrm{SS}) &= 1/16(1/4) = 1/64. \end{aligned}$$

After the death of the SS in the population, the first offspring having reached adult age, should consist of

$$49/63 = 77.78\% \text{ of AA}, \quad \text{and}$$
$$14/63 = 22.22\% \text{ of AS}.$$

Due to the elimination by death of some S genes, the proportion of AS should decrease. As this phenomenon should continue in the next generations, SCA should disappear by itself (as has happened in the United States where the rate of SCT is only 9% today [1] without any genetic policy at all). The predictions of the model contradict reality, since the percentage of AS has been constant at 25% for 3 generations. Our model is thus inadequate from the very first result on! It has to be modified because it does not take into account the higher resistance of the AS to malaria, resistance that makes up, generation after generation, the shortage of S genes formed by the death of the SS.

The model will be made more realistic by assigning to each genotype a selection index σ expressing that genotype's advantage or disadvantage over the other types [3, p. 379]. We shall see how to measure σ from the following argument. We assume that these relative advantages are independent of time and of the frequencies of the gametes. Let σ_{AA}, σ_{AS} and σ_{SS} be these indices, p_n the frequency of A genes in the nth generation, and $q_n = 1 - p_n$. Table 2 summarizes the situation in generation n.

TABLE 2

Frequencies and relative advantages

	AA	AS	SS
Frequency in generation n	p_n^2	$2p_nq_n$	q_n^2
Relative advantage	σ_{AA}	σ_{AS}	σ_{SS}

In the $(n+1)$th generation, the frequencies of the three genotypes AA, AS, SS are defined to be, respectively

$$\frac{\sigma_{AA}p_n^2}{w}, \quad \frac{2\sigma_{AS}p_nq_n}{w} \quad \text{and} \quad \frac{\sigma_{SS}q_n^2}{w},$$

where the normalizing factor $w = \sigma_{AA}p_n^2 + 2\sigma_{AS}p_nq_n + \sigma_{SS}q_n^2$. Then

$$p_{n+1} = \frac{\sigma_{AA}p_n^2 + \sigma_{AS}p_nq_n}{w}, \quad q_{n+1} = 1 - p_{n+1}, \quad \text{and}$$

$$\Delta p_n = p_{n+1} - p_n = p_nq_n\frac{(\sigma_{AA} - \sigma_{AS})p_n + (\sigma_{AS} - \sigma_{SS})q_n}{w}.$$

The population is said to be in equilibrium if there exists a p^* such that $p_n = p^*$ implies $p_{n+1} = p^*$. The equilibrium is stable if for p_n near p^*, p_{n+k} $(k \to \infty)$ converges to p^*. Karlin [3] has demonstrated that a stable equilibrium is attained at

$$p^* = \frac{\sigma_{AS} - \sigma_{SS}}{2\sigma_{AS} - \sigma_{AA} - \sigma_{SS}}$$

in the case of heterozygote advantage ($\sigma_{AS} > \sigma_{AA}$ and $\sigma_{AS} > \sigma_{SS}$). Then, for sufficiently large n,

$$\frac{p_n}{q_n} = \frac{\sigma_{AS} - \sigma_{SS}}{\sigma_{AS} - \sigma_{AA}}, \quad \text{since } \Delta p_n = 0.$$

In Zaire, $\sigma_{SS} = 0$ (assumption 4). As $p_n/q_n = 7$ is the observed equilibrium for the last three generations, we can deduce that σ_{AS} must be equal to $7/6$ (if $\sigma_{AA} = 1$).

We have thus constructed a model that takes into account the better protection against malaria provided by the SCT. With the selection indexes, the rate of SCT remains constant at 25% if no genetic policy is applied. We shall use this model to evalutate the other proposed policies.

Policy 2: Prohibition of Marriages Between AS

Intuitive justification: since no SS reaches reproductive age, only marriages between AS can produce SS children. If such marriages are prohibited, SCA is no longer a problem since no SS children can be conceived.

Under this policy, the proportion of each type of marriage has to be modified. There will be

50% of AA-AA-couples, and
50% of AA-AS couples

in generation 1. Then

$$P(\text{AA}) = 1/2(1) + 1/2(1/2) = 3/4,$$
$$P(\text{AS}) = 1/2(1/2) = 1/4,$$
$$P(\text{SS}) = 0.$$

Introducing the selection coefficients σ, the frequencies become

$$P(\text{AA}) = 0.7347,$$
$$P(\text{AS}) = 0.2653,$$
$$P(\text{SS}) = 0.$$

This means that the percentage of AS effectively will rise! The same computations have been performed for subsequent generations. Curve 2 in Figure 1 shows that the rate of SCT will continue to increase. This apparently attractive policy turns out to be a catastrophe. Since no S gene is eliminated by death, the percentage of AS gradually rises, attaining 50% in the 20th generation, and remains there; in fact the assumptions imply that from that moment on, all the marriages will be AA-AS. In reality, the policy will be practically impossible to implement long before that, since many persons would not find a partner to marry.

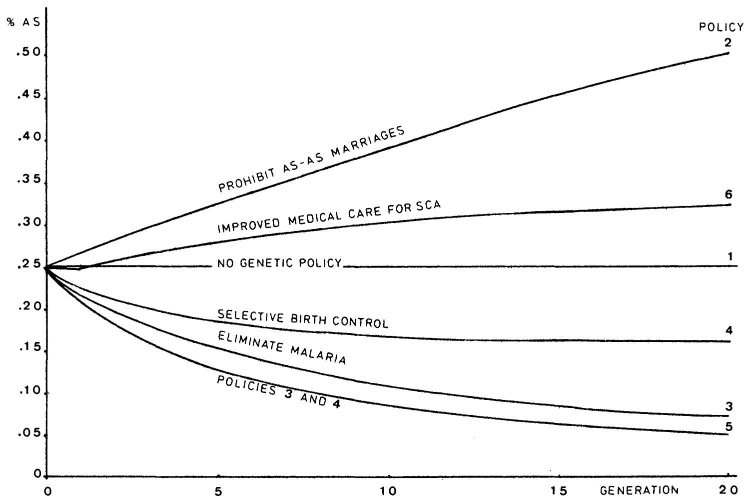

FIGURE 1

Policy 3: Fight Against Malaria

Intuitive justification: since the AS are protected against malaria, the eradication of this disease would suppress the relative advantage of the AS. The elimination of S genes by death would not be offset by the resistance of the AS any more, and the rate of SCT would decrease.

The computations are the same as in Policy 1 (but without the σ's). Extended to the future generation, they demonstrate the merits of the above reasoning. The rate of SCT indeed decreases, falls below 10% in 12 generations, and asymptotically tends to zero (Curve 3, Figure 1).

Policy 4: Selective Birth Control

Intuitive justification: as Policy 2 proves to be a disaster, one can think of authorizing marriages between AS, under the condition that the number of children would be limited (it would be socially impossible to enforce a complete prohibition of children among those couples). A number of S genes would then be suppressed by birth control.

Suppose that descendants of AS-AS couples are halved by birth control. The computations of the probabilities of the genotypes must be slightly altered. For example, in generation 1,

$$P(\mathrm{AA}) = 9/16(1) + 6/16(1/2) + 1/16(1/4)(1/2) = 97/128,$$
$$P(\mathrm{AS}) = 6/16(1/2) + 1/16(1/2)(1/2) = 26/128,$$
$$P(\mathrm{SS}) = 1/16(1/4)(1/2) = 1/128.$$

Taking the selection coefficients into account, Curve 4 Figure 1 effectively forecasts a tangible diminution of the percentage of AS. It drops below 20% fairly rapidly, but does not tend towards zero: a new equilibrium point is reached, at 16.27% if the birth rate is halved.

Policy 5: Fight Against Malaria and Selective Birth Control

As the two preceding policies prove to be efficient, one can combine them. Curve 5 (obtained as curve 4, but without inserting the selection indexes in the computations) effectively presents a sharper decline in the SCT-rate. The percentage of AS tends more quickly to zero, the level of 10% being crossed after only 8 generations.

Policy 6: Improvement of the Medical Cure for SCA

SCA, being an inherited abnormality, is technically incurable. However, its effects can be ameliorated by the use of certain chemicals, frequent blood transfusions, and urea perfusions. These techniques, widely used in the United States, have yet to be introduced in Zaire; they certainly would relieve the pain of the patients and increase their average life span. In the United States, the median age of death of SCA patients is now 20 [5] compared to 64 for the normal black population. If American medical techniques are introduced into Africa, a growing proportion of SCA patients will reach reproductive age, and the elimination by death of the S genes will be slowed down. Meredith [4] has established a "fitness" ratio of 0.376 (i.e., 37.6% of SCA patients reach reproductive age). This corresponds to a selection index σ_{SS} of 0.3838. The computations of the probabilities of the 3 genotypes, with the modified selection coefficients, confirms the progressive increase of the percentage of AS (curve 6), with a limit of 32.81%. This means a supplementary burden of more than 330,000 SS children for each generation for Zaire, if the population is not growing.

4. Conclusion

The conclusion may seem paradoxical: to fight SCA, one must first attempt to eradicate malaria. The preceding analysis demonstrates that only the suppression of the relative advantage of AS genotypes against malaria leads to an asymptotic disappearance of the disease. A selective birth control policy coupled with a fight against malaria would accelerate the eradication of sickle cell anemia.

References

1. Cavalli-Sforza, L. L. and Bodner, W. F., *The Genetics of Human Populations*, Freeman, San Francisco, Calif., 1971.
2. Fiasse, R., "Le Traitement de la Sicklanémie à l'Hôpital Universitaire de Kinshasa," *Comptes-Rendus du Premier Colloque sur la sicklanémie*, Presses Universitaires de l'Université Nationale du Zaire, Kinshasa, 1975.
3. Karlin, S., *A First Course in Stochastic Processes*, Academic Press, New York, 1968.
4. Meredith, J., "Managing the Incidence of Sickle Cell Anemia through Genetic Counseling," *Management Sci.*, Vol. 23 (1977), pp. 1261–1272.
5. Scott, R. B., "Health Care Priority and Sickle Cell Anemia," *J. Amer. Medical Assoc.*, Vol. 214 (1970), pp. 731–734.