tin showed no toxic effects at 2.0 mg/kg. Mydriasis and tremors were seen at 5.0 mg/kg, and more pronounced toxic signs at 10 mg/kg; but death did not occur even at 20 mg/kg, which is 20,000 times higher than the dosage needed to suppress the development of heartworm in dogs. In horses, mydriasis was seen at 3.0 mg/kg and more pronounced toxic signs at 12 mg/kg, that is, 60 times the recommended dosage. Intramuscular injection of the drug in horses has, as with other such injections, been associated with clostridial myositis in a small percentage of cases. In some instances the clostrial infections were fatal, and strict aseptic precautions are necessary for intramuscular injection.

Treatment of pregnant laboratory rodents and rabbits with ivermectin resulted in abnormalities in fetal development only when the drug was given at or near maternotoxic dosages, and there was no evidence of teratogenicity in target animals treated repeatedly during pregnancy with dosages higher than those recommended (*29*). In cattle, for example, no fetal abnormalities were seen when the animals were treated subcutaneously at twice the recommended dosage on three occasions during pregnancy. Similarly, no teratogenic effects were seen when bitches were treated orally with ivermectin at 0.5 mg/kg on four occasions during pregnancy.

Metabolic Disposition

Studies on the metabolic disposition of ivermectin have been carried out in cattle, sheep, swine, and rats, with the drug labeled with tritium in the C-5 or C-22 and -23 positions. The animals were dosed once at levels of 0.3 to 0.4 mg per kilogram of body weight by the subcutaneous, oral, or intraruminal route. Regardless of the route only 0.5 to 2.0 percent of the administered radioactivity was excreted in the urine. The remainder appeared in the feces.

Animals were slaughtered over a period of 1 to 28 days after treatment, and about 25 tissues and body fluids were assayed for total radioactive residues. The liver and fat contained the highest radioactive residues in all species, with very little residue in the muscle and kidney. The radioactive residue in the edible tissues of cattle, sheep, and swine, as well as in plasma, was essentially all extractable in organic solvents such as toluene or methylene chloride. Thus, there were very little, if any, intractable, macromolecularly bound drug or metabolite residues. Solvent partition followed by reversed-phase high-performance liquid chromatography (HPLC) proved extremely effective in separating the components of the tissue residues. Analysis of these tissues showed that the major single component in the edible tissues of the cattle, sheep, and swine was the unaltered drug.

An unusual nonpolar fraction consisting of several HPLC peaks, and accounting for about 60 percent of the total residue in steer fat collected 28 days after treatment, was isolated by solvent fractionation and HPLC. Remarkably, when this isolate was hydrolyzed with either *p*-toluenesulfonic acid or by the enzyme cholesterol esterase, the major hydrolysis product was identified as the same 24-hydroxymethyl metabolite found in steer liver. These compounds were probably present in fat as the acyl esters of the metabolite. The metabolites found in the edible sheep tissues were very much like those found in the steer, and the metabolic disposition of the drug in the rat was very similar to that in the other species.

Discussion

Combination of activity against nematodes and activity against arthropods is of great practical importance because, in most species of domestic animal, separate treatments are routinely used for parasites of each group. Data obtained in many trials and many countries indicate that ivermectin possesses exceptional potency against an unprecedented array of nematode and arthropod parasites. It possesses a novel chemical structure and mode of action, which probably accounts for the fact that tests have failed to demonstrate any cross-resistance between ivermectin and several antiparasitic agents to which resistance has developed, namely organophosphates, chlorinated hydrocarbons, pyrethroids, amidines, benzimidazoles, and levamisole (*19–21*). Ivermectin is active when given orally or parenterally (although high efficacy against certain ectoparasites may require parenteral administration). It offers the practical advantages of being odorless and colorless, and it offers an unusually wide safety margin.

Ivermectin is not effective against all parasites. It has not been shown to be active against protozoa, flukes, or tapeworms, presumably because neurotransmission in these groups is not GABA-dependent. It is not active against all lifecycle stages of all nematode species; but the insusceptible stages are few in number and usually minor in importance. It has a wide range of activites against parasitic arthropods. In the case of ticks it does not cause prompt death or detachment of the parasites at dosages used for the control of parasites in general. It does, however, suppress engorgement, molting, and reproduction of ticks, and studies are being conducted to determine whether these effects can be exploited by special treatment stratagems.

On the basis of its spectrum of efficacy, safety, and novelty of biochemical action (lack of cross-resistance with other drugs), invermectin seems to have the potential to contribute in important measure to the control of parasites in animals. Sufficient data have not yet been collected to assess its potential contribution to the control of parasites in man.

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In other words, as can be judged from rather extensive, if scattered, evidence, parity-related limitation of childbearing was absent in most populations before there was a modern, sustained reduction in birth rates. Such a reduction began in more developed countries in the late 19th or early 20th century (with exceptional early starts in France and the United States) and has begun in many LDC's in the past two or three decades.

Earlier Sources of Fertility Limitation

Despite the absence of parity-related restriction of fertility, the rate of childbearing before these modern reductions was only moderately high compared to the rate that might be attained if marriage were early and universal and the fertility of married women were at the high rates reliably recorded in some populations. For example, women married before age 20 and experiencing the birth rates at each age of 17th-century French Canadians would have an average of more than ten children by age 50; yet the total fertility rate achieved with the birth rates at each age characteristic of preindustrial European populations was between four and six children; the estimated total fertility rate of the rural population of China around 1930 was only 5.5; and in India early in the 20th century it was 6.2 (*2*).

Two mechanisms kept the overall rate of childbearing moderately high instead of very high in the preindustrial populations in which parity-related fertility limitation was evidently absent. One mechanism was marriage customs (late marriage, high proportions permanently single, prohibition of remarriage of widows) that prevented a large fraction of potentially fertile women from living in fruitful sexual unions. The other was the prolongation of intervals between births by various practices or conditions that were not related to parity. The most prominent of these practices is prolonged and frequent breastfeeding; another is a tabu on the resumption of intercourse for a period (extensive in some societies) after the birth of a child; still another is seasonal migration or other factors that force frequent separation of married couples. West European populations maintained total fertility rates as low as four to six primarily by late marriage and by permanent celibacy for a substantial fraction of men and women; Asian and African populations, in which marriage was early and nearly universal, maintained relatively long interbirth intervals by one or more of the other practices or conditions mentioned above.

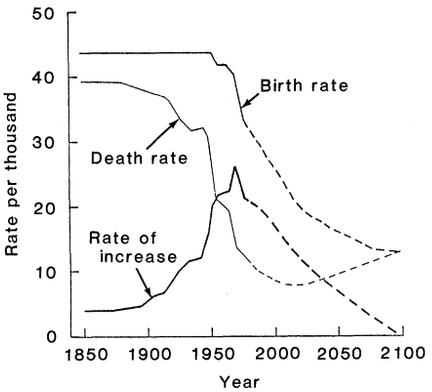

Fig. 1. Birth rate, death rate, and rate of population increase in less developed countries, 1850 to 2100.

If for several centuries the territory to which a society has access is limited and if the technology that it employs changes only gradually, there must be an approximate balance, on the average, between its birth and death rates. At a mean rate of increase of a mere half percent annually, a population is multiplied by more than 12 in five centuries. Since moderate average rates of increase over the long run are thus inevitable in traditional societies, the total fertility rates of ten or more that might in principle be achieved would be accompanied by such high mortality—average duration of life of perhaps 15 years, and only one woman in five surviving to the mean age of childbearing—as to be disadvantageous to the society's resistance to catastrophe or to its capacity to compete successfully with others.

The relatively high rates of childbearing sometimes recorded in populations of European origin—for example, total fertility rates of more than seven in the United States at the beginning of the 19th century and of nearly seven in Russia about 100 years later—may be the result of the weakening of former restraints when new economic resources became abundantly available. The West Europeans who came to America were able to marry earlier in the new world than they would have in the old, no longer having to postpone marriage because of poor inheritance prospects or because sufficient wages were attainable only after a long apprenticeship.

Features of the Modern Transition

The birth rate began a sustained decline as early as 1800 in France and the United States, in the later part of the 19th century in Western Europe other than France, and early in the 20th century in Southern and Eastern Europe. The source of the relatively early decline of the birth rate in the more developed countries was the initiation and progressive extension of parity-related limitation of fertility. In those countries today, couples employ contraceptives and abortion to determine the timing as well as the number of children born to them. A little noted feature of the "transition" to a declining birth rate is that the fertility of married women often rose before the major reduction began. Such a rise was common in the *départements* of France; Etienne van de Walle referred to the phenomenon as a "ski-jump" (*3*). It was also apparent in Denmark, England and Wales, Germany, and some regions of Italy.

Increases in marital fertility that precede any sustained decrease have also occurred in many LDC's. Such increases result from shortened or less intensive breastfeeding, from reduction in the frequency of separation of spouses because of a decline in seasonal migration, from abandonment or curtailment of postpartum abstinence, and from effective treatment of pathological sterility. Increases in marital fertility have occurred in Korea, in Taiwan, in the Central Asian populations of the Soviet Union, and in West Africa. Much of the increase in Korea coincided with a recorded decrease of some 40 percent in the proportion of women nursing their firstborn for more than 18 months (*4*).

The present-day populations of countries in which the total fertility rate is about eight children per woman (Jordan and Kenya are examples) are not believed by any who have published estimates of relevant populations to be an enormous multiple (such as 20 or 30) of the populations of the same territory a few centuries ago. It therefore appears that one must choose between the hypothesis that mortality was very high in the past (to account for moderate growth in conjunction with such high fertility) and the conjecture that fertility has recently risen from more moderate levels, as it has in countries listed in the preceding paragraph.

Projecting LDC Trends

The period of rapid growth (Fig. 1) from 1930 to 2030 (as projected) will surely prove to have been a relatively short one when viewed in a long historical perspective. If the peak rate of increase of 2.5 percent were to persist, the population of the LDC's would reach 33 billion (from the current 3.3 billion) by

2100 and 330 billion about a century later. If the projected decline of the rate of increase to zero by the end of the next century is realized, their total population will increase to about 10 billion.

The rate of increase in the LDC's has already turned down. In the 1960's the birth rate, which had begun to fall a little earlier, began to fall more rapidly than the death rate. According to the median projections of the United Nations made in 1980, the birth rate of the LDC's will decline to 18.7 per thousand in 2025; the projected decline is here extended beyond 2025 in such a way as to bring the rate of increase to zero in 2100. Note that the projected death rate rises during most of the next century. This increase occurs because the projected population contains a progressively larger proportion of old persons as low fertility progressively reduces the fraction of younger ones. Mortality rates at each age in the LDC's are in fact assumed to become as favorable as any in the world today.

In Table 1 the reduction in the total fertility rate for a list of LDC's in which there has been a large recent decrease is shown. Some of the populations at the top of the list have reduced fertility to levels typical of more developed countries. The first eight have had a reduction of at least 50 percent in a very short period; in all eight the total fertility rate is lower than in the United States only 20 years ago, and in six of the eight fertility is no higher than in Europe as a whole in the early 1960's.

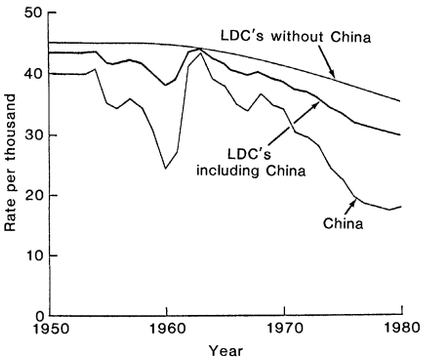

Fig. 2. Birth rates in less developed countries as a whole, in China, and in less developed countries not including China.

Note that the first five populations in Table 1 all have a culture of Chinese origin, and that six of the first ten, and ten of the list of 26, inhabit islands. The total population of the LDC's with a large recent decline is about 2.4 billion. There has been no significant decline, and in some instances a recent increase, in Africa, except for Egypt, Tunisia, and South Africa (total population about 400 million); in Haiti, Honduras, Nicaragua, and Bolivia (total population about 20 million); in Burma, Laos, and Vietnam (total population about 90 million); in Nepal, Bangladesh, Pakistan, Iran, and other populations in South Central Asia (total population 250 million); and in Arab countries (total population about 50 million). The grand total population of LDC's with no significant recent decline in fertility is about 800 million. In the remainder of the LDC's, with a total population of about 100 million, there has been at most a slight decrease in the rate of childbearing.

Of the total population of some 2.4 billion in LDC's with a substantial recent fall in fertility, about 42 percent is in China and 29 percent is in India. The importance of China in the recent decline of the birth rate is seen in Fig. 2. In the past 2 or 3 years in various Chinese publications data have appeared from which a series of annual birth rates can be derived (*5*). Two remarkable features of the birth rate in China since 1950 are the large dip in 1958 to 1961 during the Great Leap Forward and the ensuing economic crisis, and the very large decline from 1963 to 1980, after recovery from the low birth rates around 1960. The population of China is so large (nearly one-third of the total LDC population during the past three decades) and its birth rate has been so variable that much of the variation in the overall LDC birth rate since 1950 is contributed by China. In particular, the impressive overall decline from a birth rate of 44 per thousand in 1963 to about 30 per thousand in 1980 would have been much smaller without the remarkable fall of fertility in China.

Table 1. Recent reductions in fertility (total fertility rate) in selected less developed countries (*6*).

Country	Total fertility rate		Reduction (%)
	Earlier	Later	
Singapore	6.3 (1959)	1.9 (1977)	70
Taiwan	6.5 (1956)	2.5 (1980)	61
China	5.5 (1953)	2.4 (1978)	56
Hong Kong	5.1 (1960)	2.4 (1977)	53
South Korea	6.0 (1960)	2.9 (1976–80)	52
Cuba	4.7 (1960–64)	2.3 (1977)	52
Mauritius	6.4 (1952)	3.1 (1977)	52
Puerto Rico	5.0 (1950–54)	2.4 (1975–79)	51
Costa Rica	7.4 (1960)	3.8 (1976)	49
Thailand	6.6 (1965)	3.9 (1979)	41
Chile	5.3 (1955–59)	3.1 (1975–79)	41
Colombia	6.8 (1964)	4.2 (1978)	38
Malaysia	6.9 (1957)	4.3 (1976)	38
Sri Lanka	5.9 (1950–54)	3.7 (1970–74)	37
Mexico	7.2 (1965)	4.7 (1979)	35
Brazil	6.2 (1945–49)	4.3 (1975–79)	31
Venezuela	6.8 (1960–64)	4.8 (1975–79)	30
Turkey	6.8 (1945–49)	5.1 (1970–74)	25
Philippines	6.6 (1960)	5.1 (1976)	23
Dominican Republic	6.7 (1960–64)	5.3 (1975–79)	23
India	6.2 (1951–60)	4.9 (1979)	21
Tunisia	7.3 (1965–66)	5.9 (1974–75)	19
Panama	5.9 (1960–64)	4.8 (1975)	19
Egypt	6.7 (1959–60)	5.5 (1975–76)	18
Peru	6.6 (1964)	5.5 (1974)	17
Indonesia	5.5 (1968)	5.0 (1977)	10

Changes in Age at Marriage

In all the countries listed in Table 1 there has been a decline in the rate of childbearing of married women, a decline achieved by parity-related resort to contraception or abortion. A less noticed, but often important, factor in the change in fertility in LDC's is a tendency for age at marriage to increase in populations in which marriage has traditionally been very early (Fig. 3). For example, in Bangladesh the proportion ever-married in 1961 was 92 percent at ages 15 to 19 and 99 percent at 20 to 24; in 1974 it was 76 percent and 97 percent. In South and East Asia every population except Indonesia and Thailand showed a large change from the 1960's to the 1970's. Among the very early marriers (Bangladesh, India, Nepal, and Pakistan), the big change was at 15 to 19; the population ever-married at 20 to 24 remained high. Where few were married at 15 to 19 at the earlier date (Korea, Taiwan, and Hong Kong), there was a big decrease at ages 20 to 24. Taken together, this set of points suggests a general pattern of evolution in modernizing Asian populations

that were at one time characterized by very early marriage. The dotted line showing the change from 1930 to 1960 in South Korea indicates that an evolution following such a general pattern has indeed occurred within this population.

The changes in proportions ever-married at 15 to 19 and 20 to 24 in predominantly Muslim countries of West Asia and North Africa fit the same general pattern. In Latin America, on the other hand (where the ever-married include those in consensual unions), proportions ever-married at the younger ages were in no instance as high as found in Asia or Africa, and the changes were generally smaller and less consistent. For example, there are three Latin American countries with a recorded increase in proportions ever-married at both 15 to 19 and 20 to 24.

The large decreases in proportions married accompanying an increase in mean age at first marriage in several populations of Asia or North Africa would have caused a sizable drop in the total fertility rate even if married women had not started to use contraceptives and had retained fertility rates at each age unchanged. In Korea the total fertility rate that would have resulted from 1976 proportions married and 1930 marital fertility rates is lower than the total fertility rate that would result from 1976 marital fertility rates and 1930 proportions married. In Egypt between 1960 and 1976 the total fertility rate fell by 18 percent. Two-thirds of this decline would have occurred with no change in marital fertility, as a consequence of reduced proportions married, especially at ages 15 to 19 and 20 to 24.

Summary and Conclusions

There has been a historic, unmistakable reversal of the acceleration in the rate of increase of the population of LDC's, a reversal caused by a major fall in the birth rate, which since the mid-1960's has been more rapid than the continuing fall in the death rate. The reduction in fertility in some countries

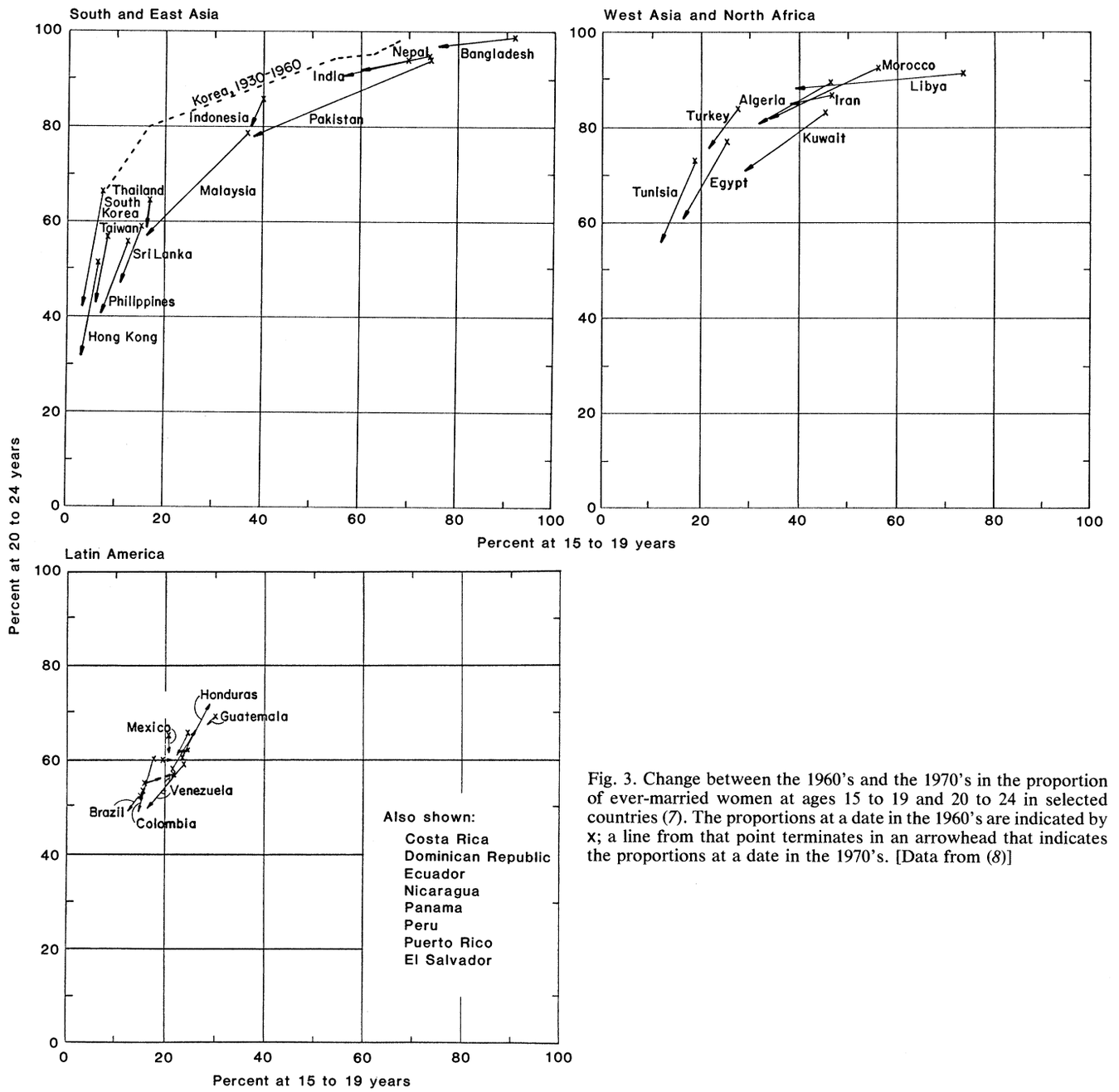

Fig. 3. Change between the 1960's and the 1970's in the proportion of ever-married women at ages 15 to 19 and 20 to 24 in selected countries (*7*). The proportions at a date in the 1960's are indicated by x; a line from that point terminates in an arrowhead that indicates the proportions at a date in the 1970's. [Data from (*8*)]

has been more than 50 percent, and it would not be surprising if in some or all of these the rate of childbearing would soon be at or below the 2.1 births per woman needed for long-term replacement of the population when mortality rates are low.

There is an important element of momentum in population growth that will cause a continued increase in numbers in LDC's long after couples merely reproduce themselves. The future number of parents will be much larger than the current number in these populations because of past growth; it is the large numbers now under age 20, born when fertility was still high and thus greatly outnumbering their parents, who will be replacing themselves early in the next century.

The large decline in the overall LDC birth rate is composed of a very large decline in a few populations, a modest decline in others, and no change, or even some increase, in the remainder. The very large declines are in East Asia and in several countries of small population elsewhere. There has been a major reduction in Brazil, Colombia, Venezuela, and Mexico as well as in Thailand, an important but lesser reduction in Turkey and the Philippines, and more modest declines in India, Tunisia, and Egypt. In Pakistan, Bangladesh, Nepal, Afghanistan, rural Iran, Iraq, Jordan, Libya, Algeria, and Morocco there has been little change; nevertheless, in several of these populations surveys show that as many as half the women of moderate fertility (three or four living children) say they want no more. In tropical Africa there has also been no decline in the birth rate, or possibly an increase. In Kenya and Senegal, it is only among women with nine living children or more that as many as 50 percent say they want no more. With current fertility and a further reduction in mortality (expectation of life at birth increasing moderately from about 50 to about 60 years), the population of tropical Africa would be multiplied by 2.3 in 25 years, to a total of 900 million.

The reversal of the acceleration in the growth of LDC populations is a welcome change in trend. Momentum in growth means that further large increases in numbers are inevitable, even in the populations where the decrease in fertility has been sharpest. The absence to date of a decline in the birth rate in most of the poorest countries in the world, with a total population of about 800 million, is reason for continued concern. In particular, the demographic implications of continued high fertility for another 25 years in Africa, a quite likely eventuality, pose a real challenge for development strategies.

References and Notes

1. This distinction (parity-specific versus non-parity-specific limitation of fertility) was first proposed by Louis Henry, who applied the terms controlled fertility and natural fertility, respectively [L. Henry, *Eugen. Q.* **8**, 81 (1961)].
2. The total fertility rate is a useful measure of the rate of childbearing at a given time in any population; unlike the ordinary birth rate, it is not affected by the age composition of the population, being dependent only on the rate of bearing children at each age of mother. It is defined as the average number of children that would be borne by women who pass from age 15 to age 50 subject at each age to the age-specific birth rates occurring in the population in question. Thus the total fertility rate of 1.9 in Singapore in 1977 means that at the fertility rates in Singapore in that year, women would finish childbearing having experienced an average of 1.90 births.
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6. The choice of the earlier date was determined by the availability of a valid estimate of the total fertility rate and by the likelihood that fertility at that date had not yet begun a sustained decline. Because of differences in the availability of data, and the date of the initiation of the reduction in fertility, the ordering of populations by the size of the proportionate decline in fertility is not an ordering by the rate of decline. Moreover, in some populations listed (Hong Kong, Cuba, Chile, and Indonesia), the total fertility rate in the not very distant past was higher than at the earlier date shown; also, there are in several instances indications of a further decline after the later date. The sources for Table 1 are as follows: United Nations, *Demographic Yearbook, Historical Supplement* (United Nations Publications, New York, 1979), Costa Rica, Hong Kong, Mauritius, Singapore; *World Population Prospects as Assessed in 1980* (United Nations Publications, New York, 1981), Chile, Puerto Rico; Republic of China, *Statistical Year Book, 1981*, Taiwan; National Research Council, Committee on Population and Demography, reports on Brazil, Colombia, Egypt, India, Indonesia, Korea, Thailand, and Turkey (National Academy Press, Washington, D.C., 1980, 1981, 1982, and forthcoming); J. Knodel *et al.*, *Int. Fam. Plann. Perspect.* **6**, No. 3 (1980), Thailand; A. Coale, *Popul. Dev. Rev.* **7**, 512 (1981), China; R. Rutherford *et al.*, "Estimates of current fertility derived from the 1980 census of Korea" (East-West Population Institute, Honolulu, unpublished); N. Goldman and J. Hobcraft, *Birth Histories, Comp. Stud. No. 17* (World Fertility Survey, London, 1982), Panama, Peru, Philippines, Sri Lanka; J. Hobcraft and G. Rodriguez, *The Analysis of Repeat Surveys, Scientific Studies No. 29* (World Fertility Survey, London, 1980), Dominican Republic; S. Diaz-Briquets and L. Perez, *Popul. Ref. Bur. Bull.* **36**, 1 (1981), Cuba; D. Tabutin, in *Nuptiality and Fertility*, L. Ruzicka, Ed. (Ordina, Liége, Belgium, 1981), Tunisia.
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9. This work was supported by NSF grant BNS 8206304 and by the Exxon Education Foundation.