The "Thrifty Genotype" in 1998[1]

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Introduction

In 1962, under the title "Diabetes mellitus: A 'thrifty' genotype rendered detrimental by 'progress'?," I published the suggestion that the basic defect in diabetes mellitus was a quick insulin trigger.[1] This was an asset to our tribal, hunter-gatherer ancestors with their intermittent, sometimes feast-or-famine alimentation, since it should have minimized renal loss of precious glucose. Currently, however, it was hypothesized that overalimentation in the technologically advanced nations resulted in insulin levels that elicited the insulin antagonists popularized by Vallance-Owen and colleagues, resulting in diabetes mellitus.[2-3] The changing dietary patterns of Western civilization had compromised a complex homeostatic mechanism. My paper was written before the clear distinction between type I and type II diabetes had been drawn, but in retrospect it was directed at type II or non-insulin-dependent diabetes mellitus (NIDDM). This quick insulin trigger was under a (still) poorly-defined genetic control. Since too quick an insulin trigger might be as disadvantageous as one that is too slow, it was suggested that this genetic control might take the form of a balanced polymorphism, by analogy with the polymorphisms for the sickle cell allele (ßS) then receiving so much attention. When other laboratories could not confirm Vallance-Owen's insulin antagonists (except in rare cases), the original physiological basis for the hypothesis collapsed.[4] Although alternative "balance" hypotheses came to mind, they were neither as simple nor as intellectually satisfactory.[5] However, the problem remained: why is the predisposition to NIDDM so frequent? Explanations based on the "thrifty genotype" hypothesis continue to be invoked.[6-17] Over the past 35 years, it has become increasingly clear that essential hypertension and obesity share many of the epidemiological features of NIDDM. Both are diseases of civilization, with a very gradual onset. Both are familial, with the disease the result of a complex interplay of genetic and environmental factors. This essay will compare and contrast current facts concerning the genetic bases for all three diseases and their pathophysiology, and review the arguments for regarding the genetic predisposition to all three of these conditions as formerly adaptive genotypes, the functioning of which is now compromised by the changing lifestyles of the technologically advanced nations. Finally, we will discuss the probable relative effectiveness in the future of a genetically based in contrast to an environmentally based program of prevention and therapy for these diseases.

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Some Recent Developments Concerning NIDDM

In recent years, the concept of NIDDM has been evolving rapidly. Although impairment in glucose metabolism in populations is a continuous distribution, the usual "cut-point" for the diagnosis of NIDDM is a one-hour post-glucose-challenge blood glucose concentration greater than 224 mg/dL or a casual level greater than 124 mg/dL. Four developments are of special relevance to this presentation.

NIDDM in Amerindians

Although NIDDM "obviously" blossomed with inactivity and overalimentation, the striking prevalence in various Amerindian groups created the suspicion that there might be a particular predisposition to the disease in some tribal groups, a predisposition that surfaced with reservation-style living, i.e., that the thrifty genotype hypothesis was of limited ethnic applicability.[18-26] With some difficulty, we were able to carry out glucose tolerance and related tests on representatives of two groups of remote and relatively unacculturated Amerindians, the Yanomama and Marubo of the Brazilian Amazon Basin.[27] Although there were statistically significant differences among the plasma glucose, insulin, pancreatic polypeptide, and growth hormone responses of the two Amerindian groups, neither of these groups exhibited the dramatic glucose intolerance of the highly acculturated (and quite obese) adult North American Pima. Although the study was limited, we saw no evidence for a strong ethnic predisposition to NIDDM in Amerindian groups pursuing a traditional lifestyle, al-

[1]This paper is an abridged version of an article recently published in *Perspectives in Biology and Medicine* 42:44–74 (1998).

though the data, of course, did not rule out the possibility that various ethnic groups might differ in the frequency of the alleles involved in the postulated balanced polymorphism.

A more telling observation concerning the role of lifestyle in the emergence of NIDDM in Amerindians involves the Pima Indians of southern Arizona and a closely related group, the Pima Indians of the Sierra Madre Mountains of northern Mexico, two groups estimated to have separated some 700-1000 years ago. The results of the studies done in those groups give no support to the notion that the high frequency of NIDDM in reservation Amerindians might be due simply to an ethnic predisposition—rather, it must predominantly reflect lifestyle changes.

The Heterogeneity of NIDDM

It has become clear that NIDDM is an etiologically (genetically) heterogeneous entity. The most important affirmation of this statement stems from the recognition of a distinctive maturity-onset-type diabetes of youth (MODY) in which the impairment of sugar metabolism has an early onset, progresses slowly, and appears to be inherited as a simple dominant trait.[28] In the 25 years since its recognition, MODY has by now been divided into some five subtypes, each associated with a specific aspect of glucose metabolism, and the locus for each subtype generally characterized by numerous different mutations at the molecular level.[29-32] There are also a number of other rare genetic syndromes that seem to carry an increased risk of NIDDM. A recent intriguing development involves the polycystic ovary syndrome, long known to be strongly associated with NIDDM. It now appears that this syndrome is closely linked to the occurrence of the III allele of the VNTR locus on chromosome 11p15.5 (see below), an allele already implicated in the etiology of NIDDM in some studies.[33] At this writing, it does not appear that these rare, monogenically inherited subtypes will collectively comprise more than about 10% of what is commonly diagnosed as NIDDM.

These developments require that the concept of the thrifty genotype has to be considered in light of the precise subtype of NIDDM under consideration. Specifically, I propose to restrict these considerations to NIDDM not yet demonstrated to be of simple genetic etiology — still the vast majority of NIDDM. With respect to the possible genetic basis of this remaining body of NIDDM, the long-standing evidence for an important genetic component in the etiology of NIDDM has been reinforced by a number of recent studies.[34] Several groups of investigators have presented evidence for the action of alleles at a single major locus in the etiology of NIDDM. Bogardus et al. report that in the Pima Indians, fasting insulin levels have a trimodal distribution, suggesting a major role for a biallelic system,[35] and segregation analysis of the familial distribution of NIDDM in the same group by Knowler et al. also yielded evidence for the action of a single major gene.[6] Mitchell et al. have recently reported evidence for a major (dominant) allele affecting postchallenge insulin levels in Mexican Americans, this allele accounting for 35% of the variance in the logarithm of the 2-hour insulin levels.[36] A more recent genome-wide search for susceptibility genes in Mexican Americans with NIDDM, employing the sib-pair approach, produced evidence for a major susceptibility locus on chromosome 2, the allele, as in the study of Mitchell et al., accounting for 30% of the familial clustering.[37] A possible link between these studies and the earlier studies on the Pima is suggested by the fact that approximately 31% of Mexican American genes are descended from Amerindians.[38] Interestingly, the same group reporting a major locus for NIDDM susceptibility on chromosome 2 in Mexican Americans found no evidence for such an allele in smaller samples of non-Hispanic whites and Japanese. On the other hand, Schermacher et al. have earlier reported, from segregation analysis on Caucasian families in which NIDDM occurs, evidence for a recessive allele determining fasting insulin levels with a frequency of 0.25.[39] This allele contributed 33.1% to the variance in fasting insulin levels.

A recent development involves the association with the occurrence of NIDDM of variation in the number of tandem repeats 5′ to the gene encoding insulin (INS). Some 596 base pairs (bp) from the INS translation initiation codon (ATG), on chromosome 11p15.5, there is a region characterized by a variable number of tandemly repeated (VNTR) 14-15 bp sequences. These repeated units vary in number from 26 to over 200, but the differences in length are not unimodally distributed. Rather, there are three modal values, of about 40, 80, and 160 repeats.[40] On the basis of these modes, the distribution has been divided into three classes (treated as alleles): Class I, with 26 to 63 repeat units; Class III, with 141-209 units; and a rare Class II, with 64 to 140 units. A number of studies suggest that with respect to this polymorphism, there is an association between Class III alleles and NIDDM,[41] but the results of the various studies are not consistent.

Considerations of MODY aside, the various single gene effects described in the papers just discussed—if confirmed—only account for a minor fraction of the genetic component in the etiology of NIDDM. Assuming the validity of these findings, that leaves the precise genetic contributions to the remaining genetic variance yet to be worked out. NIDDM at this point is still a multifactorial or oligogenic trait, but the enormous range of individual and group socioeconomic circumstances in the industrialized nations badly interferes with an estimate of the genetic susceptibilities. Furthermore, since there may well be epigenetic interactions between the components of the genetic contribution to NIDDM, and of these components

with the environment, the precise attribution of a "major" or "minor" role for any given allele must be approached with some circumspection.

Although it is customary to think of NIDDM as a disease with onset in middle age, in fact statistical studies some 30 years ago suggested that on average, already in the 10–29 age interval, there were small departures from normality in the glucose tolerance tests of the children of parents one or both of whom had NIDDM.[42] In recent years, this observation has been repeatedly confirmed, but, in addition, children in the 5–19 age interval and one or both of whose parents has NIDDM exhibit elevations of fasting and 2-hour blood insulin levels. They also tend to be obese, and follow-up studies reveal that all these findings are significant predictors of future NIDDM.[43] Thus, the physiological abnormalities that characterize NIDDM will typically have onset as early as the teens.

Syndrome X

Parallel to these developments regarding NIDDM has been the emergence of interest in the confluence of the three diseases under discussion, namely, NIDDM, hypertension, and a truncal/abdominal (android) obesity, a confluence variably termed Syndrome X, the insulin resistance syndrome, or the deadly quartet.[44-50] There is no doubt that individuals are encountered exhibiting this association. From the genetic standpoint, however, the term "syndrome" is in its strict (and most useful) sense applied to a non-random association of phenotypes tied together by some common genetic pathophysiology. Given the relatively high prevalence of obesity, essential hypertension, and NIDDM in most affluent societies, this triad can also be a chance association, without the implication of some common etiological basis.

The recognition of Syndrome X created an obvious problem for the thrifty genotype concept. Was this the "complete" manifestation of the thrifty genotype, and, if so, would this require an expansion in the definition of the thrifty genotype? Recently, we have completed an analysis of the prevalence of obesity, hypertension, NIDDM, and their various combinations in two adult populations, one in the United States and one in Japan, for which data were available on these three entities and their various associations.[51] There was indeed a substantial excess of females (but not males) exhibiting the triad of Syndrome X. However, a log-linear regression analysis revealed that the really significant association in these data was in the first-order interaction between obesity and hypertension, with a weaker interaction between obesity and NIDDM. When allowance was made for these two associations, no second-order interaction term to account for the excess of Syndrome X was necessary. Syndrome X is thus not a true syndrome whose elements share a common (genetic) pathophysiology but a combination attributable to first-order interactions. The observation that individuals with birth weights of 6.5 pounds or less were 10 times more likely than persons with birth weights greater than 9.5 pounds to exhibit the attributes of Syndrome X at maturity is an interesting pointer toward a primarily nongenetic factor in the etiology of this "syndrome."[52]

The Physiological Complexity of the Stone Age Industrial Age Transition

Finally, it is now clear that the original thrifty genotype hypothesis, with its emphasis on feast or famine, presented an overly simplistic view of the physiological adjustments involved in the transition from the lifestyle of our ancestors to life in the high-tech fast lane. Eaton has emphasized how different in composition the Stone Age body that received that intermittent alimentation was compared with our modern bodies.[53] Although trained athletes retain the relative muscle mass of early man—at least until the competitions are over—modern man is characterized by a striking sarcopenia, with the interstices between muscles well padded with fat. Because fat and skeletal muscle cells have strikingly different insulin sensitivities, the overall sensitivity to insulin of skeletal muscle is profoundly altered in the transition to a technological society. This differential is emphasized by the high conditioning of the muscle of our tribal, hunter-gatherer ancestors, with a corresponding greater efficiency of insulin utilization. Whereas the total daily energy expenditure in adult members of hunter-gatherer and traditional agricultural societies was in the neighborhood of 3000 kcal/day,[54-56] now in industrialized societies it is of the order of 2000 or less.[57-58]

Finally, the composition of the diet, and more specifically the use of highly refined carbohydrates, with the resulting almost instantaneous "sugar highs," has, of course, altered dramatically with civilization, as has the mix of dietary components. Exactly how this might influence the development of insulin resistance is a matter of active debate.[59]

Despite all these advances in our understanding of NIDDM, the nature of the environmentally precipitated genetic maladjustments that result in the disease remain obscure. Given the intensity of the current effort to localize and characterize the genes, the functioning of which seems to be compromised in NIDDM, speculation at this time concerning their nature seems of little value. However, the concept of a "thrifty genotype" remains as viable as when first advanced, and it now seems desirable, in view of the direction this essay is taking, to begin to put the concept of a "compromised" thrifty or adaptive genotype into a broader context that will include two other diseases presenting similar epidemiological characteristics.

Essential Hypertension and Obesity

The two additional diseases to be considered are essential hypertension and obesity, both of which share many of the epidemiological characteristics of NIDDM. We have documented these shared characteristics in detail elsewhere; space permits only a brief enumeration.[60]

Increase in Frequency

Like NIDDM, essential hypertension and obesity are "diseases of civilization," rarely encountered in tribal populations whose sustenance is gained from hunting, foraging, and limited agricultural practices. Now, however, in a country such as the U.S., hypertension (seated diastolic pressure 90 mm/Hg) will be encountered in some 40% of adults, as will obesity [BMI (weight in kg/height in meters^2)> 27]. The emergence of these two diseases is not limited to scattered populations but is widespread wherever technological transition is creating affluence while individual expenditure of physical activity to gain a livelihood is declining.

Genetic Complexity

Although in recent years some rare, monogenically inherited forms of hypertension and obesity have been recognized, the genetic component in the etiology of the vast majority of instances of these two diseases seems to be multifactorial or polygenic. This terminology is consistent with multiple genes with approximately equal effects, or several major genes with a larger number of modifiers. In any event, different genes may be involved in different pedigrees, i.e., there is genetic heterogeneity. Numerous efforts to map the positions of these genes are underway, but the results are often conflicting, and it will be some years before consensus is achieved.

Early Onset

Essential hypertension and obesity, like NIDDM, are often characterized by minor departures from normal early in life, although clear clinical disease may not be apparent until adulthood. Thus, the children of hypertensives, known to be highly predisposed to hypertension themselves, often exhibit a hyperkinetic borderline hypertension, as well as departures from normal in red blood cell lithium-sodium counterparts.[61-62] Likewise, chubby children tend to become obese adults, although, of course, not all obese adults were chubby as children, and not all chubby children are obese as adults.[8, 63-64] That there are subtle harbingers of obesity very early in life is suggested by the observation that babies of overweight mothers often exhibit an aggressive feeding style.[65-67]

Complex Relationships with Other Diseases

Finally, as mentioned earlier, there are poorly understood nonrandom associations between hypertension and obesity, and between NIDDM and obesity, which may be taken as indicating some overlap in genetic or environmental basis, but stopping short of the Syndrome X concept.

Implications of the Emerging Understanding of These Three Diseases for Their Future Therapies

An Improved Terminology

While the concept of NIDDM as a "thrifty genotype" now expressing itself under the conditions of civilization seemed appropriate 36 years ago, the various recent developments regarding this disease, and the developments regarding hypertension and obesity, suggest both a modification and a broadening of the original concept. It now seems preferable to conceptualize these diseases as resulting from previously adaptive multifactorial genotypes, the integrated functioning of whose many-faceted genetic components is seriously disturbed by the complexly altered environment in which they now find themselves. Some terminological problems must be dealt with. The term "thrifty genotype" has served its purpose, overtaken by the growing complexity of modern genetic medicine. If our thesis that the three disease entities briefly discussed in this review are, in fact, all in very large measure the reflection of genetically complex homeostatic systems now pushed to and beyond their limits, a collective term would be useful. With respect to these three entities, the genes involved are very predominantly fine old genes with, of course, some allelic variation, honed by millennia of selection for harmonious interactions and appropriate epigenetic relationships, the proper functioning of which is overwhelmed by extraneously imposed parameters of very recent origin. The ultimate genetic complexity of each of these diseases qualifies it for the term "syndrome." Perhaps collectively we can speak of the "syndromes of impaired genetic homeostasis" or, more colloquially, the "civilization syndromes," or the "altered lifestyle syndromes," to which other diseases may yet be added.

Future Prevalence

We have already commented on the increasing prevalence of obesity in the U.S. and, to a lesser extent, in other industrialized populations. This increase extends back into the pediatric ages.[68] Given the correlation of obesity with both NIDDM and essential hypertension, presumably these latter two diseases will also increase as obesity increases. The recent gross proliferation of computer game activities designed specifically to appeal to juveniles, not to mention the large blocks of time children are devoting to passive television viewing, will do nothing to halt this trend. The monogenic genetic disorders will maintain a relative constancy for the foreseeable future, but, barring the enforced return to a simpler lifestyle that the population/resources conflict might create, the prevalence of the

"syndromes of impaired genetic homeostasis" can only increase.[16]

Some Therapeutic Considerations

We now turn briefly to some therapeutic implications emerging from the foregoing considerations. They can be subsumed under three headings: the genetic, the euphenic, and the pharmacological. However, because of time limits, I will not consider the third approach.

The Role for Genetic and Gene Therapy

Already, as the search for genes associated with the complexly inherited types of NIDDM, hypertension, and obesity gathers momentum, there are allusions to how these future discoveries will lead to genetic and gene therapy. (Genetic therapy is the provision of a missing gene product; gene therapy the introduction of functional DNA into the tissues of an individual in whom that DNA is nonfunctional.) With respect to genetic therapy, the use of insulin in the management of diabetes mellitus constitutes one of the early examples of genetic therapy. A more recent significant development in this field is the possibility of the amelioration of some types of obesity by treatment with the newly discovered hormone leptin, produced in the adipocyte, on the assumption that the serum level of leptin normally plays a major role in some individuals in regulating food intake.[69]

Additional opportunities for genetic therapy may be defined for these "diseases of civilization" in the future. However, there is reason for humility of genetic thought with respect to the genetic therapy of these disorders. The monogenic disorders for which genetic therapy is feasible represent, for the most part, defects in a well-understood metabolic cascade. By contrast, the multifactorial "diseases of civilization" represent perturbations of complex systems in which the various genetic components are, for the most part, normal genes with unknown functional ramifications, and until these are well understood, clear thinking regarding genetic therapy is impossible.

With respect to actual gene therapy for these complex disorders, the prematurity and shallowness of much that is in the literature concerning this prospect have been adequately discussed by others and will not be treated here.[70-73] (This comment is not meant to detract in any way from the current amazing insights into the nature of our genetic material resulting from the molecular approaches but rather to emphasize that a new order of complexity must enter into our thinking concerning genetics and gene therapy for the three conditions we address.)

The Euphenic Approach: The "Paleolithic Prescription"

Some years ago, as the term "genetic engineering" began to gain currency, I argued for the need for a counterbalancing concept and term, namely, "culture engineering." Even as genetic engineering implied a conscious effort to improve the genome, culture engineering implied a conscious effort to develop in all dimensions the environment (in the broad sense) in which the human genome finds its optimal expression.[74-75] Shortly thereafter, Lederberg suggested the more felicitous term euphenics for essentially the same concept, and this is the term we shall employ in this section — while limiting our considerations solely to the three disease entities under discussion.[76]

For these diseases, the euphenic approach is defined broadly by what Eaton et al. have termed the Paleolithic Prescription.[77-78] Basically, this constitutes, in the interest of health, a twentieth-century "return," where feasible, to aspects of a Paleolithic lifestyle, with reference to diet and physical activity. With respect to diet, based on a careful analysis of data on hunter-gatherer or forager societies, Eaton and colleagues suggest dramatic dietary modifications: much higher dietary fiber content, the corollary being a decrease in refined carbohydrate foodstuffs; less saturated fat in the diet; a decreased sodium intake; greater intake of micronutrients, either through an increased intake of fruits and vegetables or dietary supplementation. With respect to sodium, the evidence from clinical trials suggests that an intake of less than 70 mmol/day would be appropriate.[79] Simultaneously, a return to a much higher level of physical activity must be stimulated.

All of these suggestions have been repeatedly advanced by a variety of scientific interests in recent years. The specific value of the Paleolithic Prescription is that it seeks to document with precision the exact changes in diet and caloric needs that accompanied the transitions of civilization, thus providing a more objective background against which to consider modifications in current lifestyles. Obviously, a literal implementation of the Paleolithic Prescription is inconsistent with both the structure and economics of modern society, but discussion of the question of what aspects of the concept are feasible and how these can best be implemented is just as timely as the multitudinous discussions of the practice and ethics of gene therapy.

Should society and its various instrumentalities undertake increased preventative measures with respect to these diseases, a number of decisions must be made. The basic pathophysiology of these disorders is still so poorly understood that any present approach would be largely empirical. There is a strong argument for an increase in the level of research activities, leading to rational therapeutic approaches based on more detailed genetic knowledge. This program consists of far more than gene identification — the mechanism whereby these genes interact to create the predisposition must be elucidated. In any endorsement on our part of the Paleolithic Prescription, the as-

sumption is explicit that the knowledge base of the key critical physiological factors in the transition to civilization is still weak and needs to be greatly strengthened.

But even the present level of knowledge is certainly consistent with some empirical action. The primary euphenic approach to these diseases would appear to be dietary modification coupled with a program of regular moderate exercise. But any significant implementation of this generality requires a number of decisions. The initial decision to be made is what population(s) to target in the interests of efficiency and cost-effectiveness. There are three obvious and nonexclusive possibilities. The first is an all-inclusive, general population approach, through which a general educational campaign should be launched similar to that currently put in place by the U.S. government to curtail smoking. The second is to target the predisposed, especially the children of persons found through the practice of medicine to exhibit the diseases under discussion. Here the incentive to follow a prescribed regime should be substantially higher than in the "general population" approach. Finally, preventative approaches could focus on a particular phenotype. For these diseases, the obvious phenotype is obesity, not only because of the ease of diagnosis but because of its association with both NIDDM and essential hypertension.

The second decision to be reached in formulating a comprehensive program is what constitutes an acceptable and feasible Paleolithic Prescription in contemporary society, and how it might be implemented/phased in. An overly ambitious program might be considered by its target population to demand unacceptable lifestyle modifications — and also an unacceptable impact on the food industries. One example of a dietary intervention modest enough to be acceptable in the long term yet robust enough to produce a clinically relevant impact on hypertension is described in the recently completed Dietary Approaches to Stop Hypertension (DASH) trial. DASH trial participants were randomized to one of three diets: 1) a control diet low in fruits, vegetables, and dairy products with a fat content typical for the United States; 2) a diet rich in fruits and vegetables; or 3) a "combination" diet rich in fruits, vegetables, and low-fat dairy products with reduced saturated and total fat. The combination diet, targeted to maintain body weight and sodium intake at levels comparable with the other diets, resulted in an average blood pressure lowering of 11.4 mm Hg systolic and 5.5 mm Hg diastolic in hypertensives and more modest (but highly statistically significant) blood pressure reductions in normotensives (3.5 and 2.1 mm Hg, systolic and diastolic, respectively). The investigators suggested that broad application of the combination diet could both treat hypertension and perhaps prevent its development.[80] I would like to urge that replications and variations of this approach, not only to hypertension but also to NIDDM and obesity, in a variety of ethnic groups, difficult though such studies may be, should have a high priority. Such studies lack the glamour of the molecular approach, but, in my opinion, they offer better prospects for yielding data that will be helpful in the amelioration of the impact of the diseases of civilization.

A third decision would be the age at which to institute the Paleolithic Prescription. There is, of course, an enormous literature on the benefits of caloric restriction and weight loss in the management of NIDDM and obesity, and one could not argue against intervention at any age at which the disease is present. Unfortunately, past experience has demonstrated a discouraging frequency of recidivism in individuals attempting to control obesity. Put very simply, it is as if early in life an insistent and demanding biological drive to consume more calories than is appropriate to maintain normal body weight was established, and although this drive can be temporarily abrogated, it almost irresistibly reasserts itself. Understanding how this "calorie-stat" gets set is probably the number one priority in the study of obesity. But it now appears that no matter what the detailed mechanism, intervention should be as early as is practical, and consist not just in cutting back on calories while maintaining the standard diet of the high-technology society but incorporating as many elements of the Paleolithic Prescription as possible.

In closing, I state the obvious: the implementation of the euphenic approach to the "syndromes of failed genetic homeostasis" will require personal discipline in societies that are increasingly hedonistic. The various technological cultures of the world are much more accustomed to thinking in terms of "medical miracles" and "quick fixes" that require no effort on the part of the recipient. The need for such self-discipline in many other aspects of human activities is increasingly evident as we enter the third millennium. Perhaps how we undertake to manage these syndromes will be a barometer for how we will cope with the larger issues of population and resources. If we cannot summon the self-discipline to improve our personal health, then is it likely society can summon the discipline to meet the many problems created by expanding populations and diminishing resources?

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