In the Footprints of Future Man

by JAMES BONNER

We have in our hands the first rudimentary tools for escaping extinction and lifting ourselves to a new and better species. When will we start?

THE NORMAL expectation for an animal species such as our own is to arise through mutation, evolution, and selection and then to become extinct and to be replaced by a species more fitted to the existing environment. During the history of life on earth, mutation, evolution, and selection have invented literally millions upon millions of species of plants and animals, and almost all of them are extinct today. As a matter of fact, up to about 50,000 years ago there were two species of *Homo* living on earth — *Homo sapiens* (us) and *Homo neanderthalensis*. These two species lived together in the plains and mountains of central Asia, and they fought it out to see who would survive, and you know who won. It wasn't them.

They were replaced by a species that was more suited to the particular ecological niche, and so the normal expectation for us is that we will be superseded by a new species of mankind better suited for our ecological niche. (I like to think that it might derive from the Sherpas of Nepal, a super people.) Maybe the new species has already been invented, and we just don't know about it. Anyway, the only reason to think that we will come to a different end from that of past species is that we're the first species that really knows a lot about mutation, genetics, selection, and evolution. And therefore we should, in principle, be able to control our evolutionary destiny.

We have another thing going for us too — as Margaret Mead has pointed out — that human beings as a species have the ability to change their way of life. They're very adaptable; they learn how to cope with changed circumstances. So if new mutations come to us that enable us to do something new, our culture will probably be able to absorb vast changes. For example, I know a man who is the child of a headhunter of Borneo. He lived in Borneo until he was 5 years old, and then was taken to be educated first in Java and then at Harvard. Now he's a professor of mathematics at a great university. From headhunter to professor of mathematics in one generation is pretty good adaptation.

I don't want to get off onto the subject of genetic engineering, though I know it's a very fashionable subject and one that has both good and evil aspects. But one thing that we can be sure of is that genetic change will be a part of man's future, just as it's been a part of man's past. Just imagine the amount of genetic change and manipulation that has gone on, unknown to us, during the last 2,000,000 years when we changed from *Homo habilis* — the first primate *Homo* — to *Homo sapiens*. Even during the last 200,000 years there has probably been a great amount of mutation, selection, and evolution on the part of human beings — done not in any consciously directed way, but by the natural forces of selection and evolution. Genetic change is inexorable and inevitable.

A scenario for the future of human beings appears in an interesting book written by Olaf Stapledon, an English author. Called *Last and First Men,* the book was published in 1935, and republished by Dover Press in 1968. Olaf Stapledon starts out by writing about the history of the human species viewed one billion years from now (from 1935, actually). He notes that at one time it was necessary for children to enter into productive economic life at the age of 8, because they were going to die before they were 30, and for society to get some good out of them they had to start to work early and die early. They had a ratio of productive life to the educational part of life of about two to one.

In our society people have to be educated up to the age of about 25 before they can become societally useful, and they poop out at 65 or thereabouts. Again,

the ratio of productive life to educational life is about two to one.

So, in the book, in about 20,000 years from now, the people realize that this is a very uneconomic state of affairs, and they want to deliberately alter the ratio of productive life span to educational life span to 250 to one. They want to really get their money's worth out of a person after they've paid to have him educated. Now by that time it takes 200 years for a person to become educated enough to be societally useful. So he has to live to be 50,000 years old in order to get all his work in.

Note that, to accomplish this end, the society uses selective breeding and deliberate alteration of genetic material, and note that Olaf Stapledon realizes the necessity of death at the end of 50,000 years. People have to die in an evolving society, so that the old models of people can be replaced by the new ones that have been invented in the meantime. That's true wherever there's evolution.

Incidentally, Stapledon also foresaw that our species would have to abandon the planet Earth because it got so polluted. Mankind goes from one planet to another, until the only remaining planet is one that has a very high gravitational field. People are unable to walk upright any more, so they have to learn to walk on all fours again. This is also accomplished by deliberate genetic manipulation. Stapledon says of mankind: "First up, last down."

But all this is science fiction, and I cite it merely to show that science fiction writers in general are far ahead of the rest of us in looking into the serious technological and philosophical problems of the future.

It is, of course, widely held that we can outwit our normal evolutionary expectation of extinction. I, for one, am convinced that what we know about human genetics can be used right now to better the human condition, and that it could better it even more in the foreseeable future.

First, however, let's be sure we're all broadcasting on the same biological wavelength. Everybody knows, because we learn it in high school, that the genetic material is composed of DNA, and that the genetic information is encoded in the sequence of building blocks that succeed one another down the long linear DNA molecule composed of four building blocks which we call A, T, G, and C. And almost everybody knows that the DNA molecule is a two-stranded molecule; that wherever there's an A in strand Number 1, there must be a T in strand Number 2. Where there's a G in strand Number 1, there must be a C in strand Number 2, and vice versa. This is the basis of replication of DNA, and that's why DNA is the only molecule in a living creature that can replicate itself.

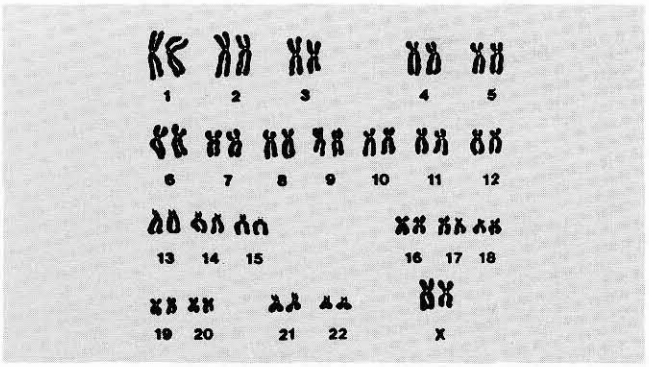
There are about three meters of DNA in each of our cells, and since cells are just a few microns in diameter, the DNA has to be packed up pretty tightly. In higher creatures the three meters are split up into individual chromosomes. We each have 46 chromosomes, and furthermore the DNA is complexed with proteins of a special class — the histones, for example — that make the DNA's shorter than they would otherwise be. These proteins compact the DNA to make chromatin. When it comes time for cell division, the DNA replicates itself, and condenses into what is called metaphase chromosome.

The metaphase chromosomes arrange themselves on the so-called metaphase plate in the middle of the cell. That's the stage at which people look at human chromosomes to see whether you have a normal human chromosome complement. They look at the metaphase plate in the dividing cell. Then the chromosomes separate from one another, and form two new nuclei. The cell splits in two; the chromosomes decondense into interphase chromatin; and we have two new cells each with a complete copy of the genetic information.

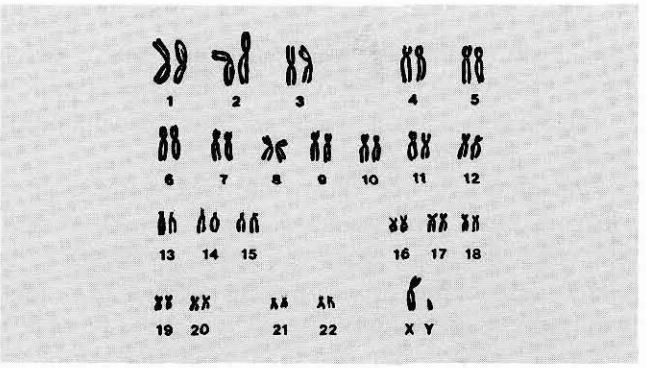
The DNA is not only split up into chromosomes, but each chromosome is split up into what we might call chapters of the DNA called genes. A gene is that length of DNA that contains the information about how to make some specific kind of enzyme molecule, and we have about 500,000 different genes in us. The three meters of DNA in the human chromosome set contain, I once calculated, about as much information as is contained in the *Encyclopedia Britannica,* which is quite a bit.

One further biological fact: Each of us has two sets of chromosomes, one set from our mother and one set from our father. So we have two chromosomes Number 1, and two chromosomes Number 2, and so forth. Obviously, when eggs and sperm combine to make the germ cells, the chromosome number must have been earlier cut in half so that the normal chromosome number for that species (46 in us) is restored by combination of sperm with egg. And this happens during the maturation of the germ cells by the process called meiosis. Before the first meiotic cell division, the chromosome Number 1, let's say from the mother, pairs with the chromosome Number 1 from the father, and at the division those two separate from one another. That's followed by a second division, but the end product is that we get germ cells that have half of the chromosome number characteristic of the normal body cells of that species. So that would be 23 chromosomes in each human sperm or human egg cell. Note also that

Female



Male



Karyotyping is an electronic method for drawing pictures of the metaphase chromosomes of human body cells and arranging them in linear order. The 22 pairs of non-sex chromosomes and two X chromosomes of the karyotype at the left indicate that it is that of a female. At the right is the karotype of a male, which also has 22 pairs of non-sex chromosomes, one X, and one Y chromosome.

the chromosomes from the mother and those from the father are absolutely and completely randomly reassorted in the making of sperms and eggs, so the sperm can contain some of the chromosomes from the father and some of the chromosomes from the mother and so forth. And this is one way of getting genetic diversity and one reason why our children don't all look exactly alike. They don't all get exactly the same arrangement of chromosomes.

Now the stage is set for us to look at the human chromosome complement. When we look at a metaphase plate of a dividing human cell, we see a vast mass of chromosomes, and it's pretty difficult for a person to know what he's looking at — unless the chromosomes are arranged by a process called karyotyping.

The human female has 22 pairs of non-sex chromosomes, called autosomes, and two X chromosomes. The human male also has 22 pairs of autosomes, a big X chromosome, and a very small Y chromosome. The process of looking at a metaphase plate of the chromosomes of a particular human male or female, drawing pictures of them, and arranging them in linear array is called karyotyping.

It takes about one day for a skilled human observer with a light microscope to make a karyotype of a single human being. Luckily, in Houston, Texas, there is a magic machine that can take a picture of the confused metaphase chromosome plate in the human cell, scan the chromosomes, and put all the information into a computer that knows how to recognize the individual chromosomes. This computer can look at the picture of the chromosomes of the metaphase plate and make a printout with all the chromosomes' numbers assigned, and do it within a minute or so. That machine needs to learn to replicate itself because we are going to rely more and more on rapid karyotyping to help us recognize chromosomal abnormalities.

For over 100 years it's been known that of all live births about 1 in 600 suffers from a characteristic set of abnormalities that includes a peculiarity in the folds of the eyelids, multiple developmental defects — particularly in the circulatory system — and very often mental retardation. This condition was described by a physician named Down in the 1860's, and is known as Down's syndrome. Its victims include both sexes, and it is not inherited. Nothing was known of the cause of Down's syndrome until 1959 when a French cytologist, Dr. Jerome Lejeune, karyotyped nine individuals of the Down's syndrome phenotype, and he found that they all possessed three rather than the normal two copies of chromosome 21.

It is now known that Down's disease is always characterized by this chromosomal condition. It is brought about by a mistake in meiosis in which both the chromosomes 21 go to one daughter cell during egg production while no chromosomes go into the other. The fertilization of such an egg by a sperm containing one chromosome 21 would result in three chromosomes 21 in the otherwise normal karyotype. This is called chromosome 21 trisomy, and it causes Down's syndrome.

Trisomys for chromosomes 18 and 13 are also known, but they are not as common as that of Down's syndrome. They are all attended by mental retardation, and generally individuals with these trisomys live for less than a year.

These are not the only chromosomal aberrations that beset human development. The best known are those that have to do with the sex chromosomes X and Y. One is the well-known Klinefelter's syndrome. Although the appearance of the Klinefelter's-syndrome-person is male, the testes are small and the breasts are in general enlarged. Karyotype analysis shows that these individuals possess two X's plus a Y, making them

XXY. They have the standard complement of 22 pairs of normal non-sex chromosomes (autosomes). I should also mention that if Klinefelter's syndrome is recognized very early in life, a male can have essentially normal development by being given supplemental male hormone therapy.

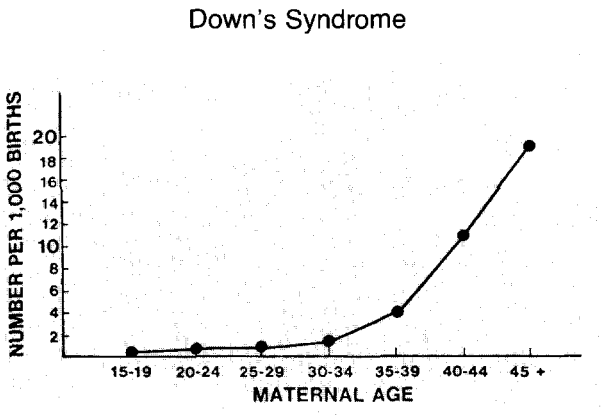
There are other abnormalities of the male chromosomal complement. A person can be afflicted not with just two X's plus one Y, but with three X's plus one Y, or even four or five of them and one Y. Or there can be an X and two Y's.

There are equally well-known aberrations of the female karyotype. There is Turner's syndrome, in which there is one X chromosome and no Y chromosome, and the afflicted person is female in phenotype and in appearance. Normal females have two X chromosomes. There are triple-X chromosome women, who are fertile and develop normally. And there are four-X women, about whom very little is known.

Abnormal chromosome complements, then, are very real risks that occur during the development of eggs and sperm and in their fertilization. Altogether, about one in 200 live births is attended by a major chromosome abnormality that leads to major developmental abnormality. The question is what to do about this situation.

Consider what nature is doing about it. Of all recognized pregnancies, about 20 percent or a little more end in spontaneous abortions. Of these spontaneously aborted fetuses, 25 percent or more have gross chromosomal abnormalities. For example, most of the XO fetuses are spontaneously aborted. A very considerable proportion of spontaneously aborted fetuses are triploids (with three complete sets of chromosomes), and almost half of the total are trisomic for the large chromosomes — that is, they have three chromosomes Number 1, or three chromosomes Number 2. Another common chromosome abnormality is to be a tetraploid — that is, to get four complete sets of chromosomes. All of these are incompatible with normal development. Other classes of chromosomal abnormalities are incompatible with development even to a recognized pregnancy. Such is the case with an embryo that is monosomic for an autosome. It has, for example, only one chromosome 1, or even only one chromosome 21. All the embryos of that class die before they are implanted in the uterus, and therefore they are never recognized as pregnancies.

Although 90 percent or more of chromosomally abnormal fetuses are spontaneously aborted, the remaining 10 percent form a large societal burden. Hugh Fudenberg, a physician who aspires to be an economist, has calculated that by abolishing the incidence of



Down's syndrome is a tragic burden to individuals and to society, and the frequency of its appearance increases catastrophically with increasing maternal age.

Down's syndrome alone we would save 45 million dollars a year. It would also save a great deal of societal suffering.

Fortunately, there is something to do about gross chromosomal abnormalities. It is now possible to accurately locate the position of the fetus in the uterus by sonography and then to put a hypodermic needle into the uterine cavity in a place where the fetus isn't and remove some amniotic fluid. This fluid contains cells that have been sloughed off from the lining of the bladder of the fetus. They can be tissue-cultured and karyotyped. Such amniocentesis is optimally carried out in the 16th week of pregnancy, but it can be done at a variety of times. If the karyotype proves to be abnormal, the fetus can be aborted, if the parents wish.

Amniocentesis is now done in more than 50 centers in the United States. Five years ago it was done in just 3 centers. I am sure that it will become general practice soon in all of the developed nations of the world.

In the meantime, one group of mothers are specially at risk with regard to the possible conception of fetuses of abnormal karyotypes. These are the older mothers. Up to about age 30 the incidence of Down's syndrome is very low, but with increasing maternal age the fraction of babies born with Down's syndrome increases catastrophically. Because this is so, older mothers deserve particular consideration, and I am told that the Colorado state legislature some years ago provided that any woman who becomes pregnant and is age 35 or older can have a karyotype on the house — and an abortion on the house too if an abortion is indicated. I think this will certainly become standard for older mothers.

Chromosomal abnormalities are not the only bad things that can happen to us by the random workings of our genetic lottery. Our species is heir to lots of genetic

defects and mutations, which cause the gene in question to produce either altered or inactive enzymes, and this causes some bad things to happen. These problems are all inherited, of course. Most of them, luckily, are recessive so that you have to have a double dose, from mother and from father, in order to show the symptom of the mutation. They range from hemophilia, for example, to sickle cell anemia, and a wide variety of enzymatic defects which cause mental retardation. We now know of more than 2000 human hereditary mutations.

My first genetics teacher, Thomas Hunt Morgan, former chairman of the biology division at Caltech and its founding father, always told me that human beings are no good for genetics research because you are never sure who the father was. That may be so, but it also turns out that human beings are good for genetic studies because the mutants always go to the doctor to find out what's wrong with them. The mutants come to you instead of your having to go and look for them, as you have to do with Drosophila and creatures like that.

For an increasing proportion of these hereditary genetic defects, the particular enzyme that is affected has become recognized. For many of these defects, especially mutations that cause mental retardation, the presence or absence of the relevant enzyme can be detected in the cells that are tissue-cultured by amniocentesis.

We can't diagnose all genetic defects yet in the amniotic cells. For example, we can't diagnose sickle cell anemia because the gene for making adult hemoglobin is not turned on in the amniotic cells. Since they do not produce the adult hemoglobin, you can't find out whether the adult hemoglobin will be normal or not. But as we find out how to turn on genes that are turned off, we'll be able to determine, I think, the entire genetic constitution of the fetus, and discover whether it has a good genetic constitution or not. This will make amniocentesis a really powerful tool for the prenatal diagnosis of genetic constitution.

I am sure these things will all be implemented because, once we recognize the physical and moral necessity to have only two children per couple — so that we won't have unlimited population growth — it is but a short step to a new morality that says: "Since we can have only two children, let them be free from genetic defects."

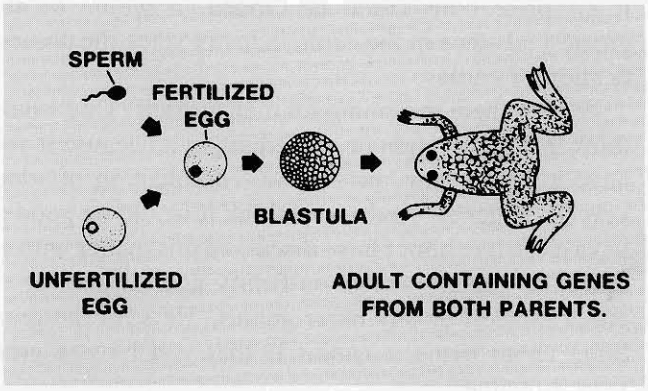
The next step might be a little harder to take. That's a newer new morality that will say: "Since we can have only two children, let us have them not only with no genetic defects, but let us endow them with the very best genes available in the world."

How could this goal be achieved in principle? One way is by the process known as cloning, which is not something inherently bad in spite of the adverse advertising it has had.

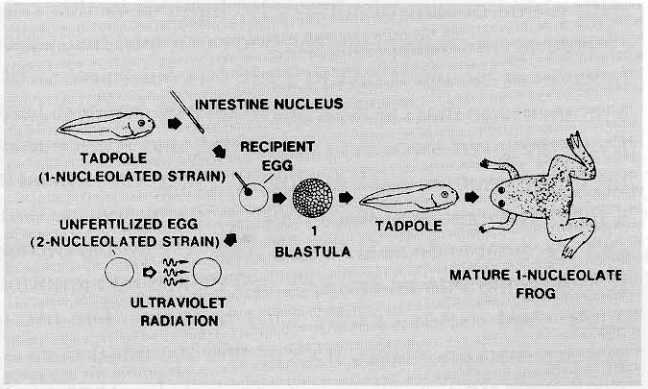
A clone is a group of genetically identical individuals derived, without the intervention of sex, from a single parent. A pair of identical human twins is a clone of two derived from a single fertilized egg. Essentially all of our fruit trees are cloned. Valencia oranges are one clone of orange trees, and navel orange trees are another. All of our ornamental shrubs are clones, and all patented roses are clones, propagated vegetatively from a single sexually produced parent. Dates have been multiplied vegetatively for over 5,000 years, and the same clones are still growing in the Middle East.

Cloning of animals hasn't been so successful. It has been carried through only with the African toad *Xenopus laevus* (by former Caltechian John Gurdon).

Sexual Reproduction



Clonal Reproduction



Vegetative cloning is almost as old as agriculture itself, but in the animal world so far only the toad has been successfully cloned. Normal sexual reproduction (left) is, of course, relatively simple, but the outcome is genetically random. To produce any desired number of genetically identical toads or frogs takes the more complex and rather recently developed process of clonal reproduction (right).

"I'm afraid, Son, this will never be yours. I'm having myself cloned."

Drawing by Lorenz; © 1973 The New Yorker Magazine, Inc.

When a toad wants to produce a toad normally, it produces some sperm that fertilizes a toad egg, which then divides and grows into the blastula, which then develops into a tadpole, and then into an adult toad containing genes from both parents.

The Gurdon method is to take a body cell from a toad (cells from the intestinal mucosa are convenient) and scoop the nucleus from that somatic cell. This body cell is a dead-end cell. It just produces digestive enzymes, and it's never going to divide again. It is going to be sloughed off into the intestine and digested. But Gurdon gets to it first, and gets the nucleus out of it. Then he takes an egg from a lady toad and destroys its nucleus with a microbeam of ultraviolet light. Into this enucleated egg he transplants the body cell nucleus, which behaves as though it says to itself: "I could have sworn a moment ago that I was an intestinal cell, but here I am. Everything out there says egg to me, and I've counted my chromosomes and I'm diploid. Therefore, I must be a fertilized egg. So I must look up in my genetic book and see what to do next." And what it is told to do next is to develop into an embryo, and thence into a normal adult. And that is exactly what happens. The use of genetic markers makes it clear that the adult does indeed have the genetic composition of the donor of the nucleus.

This is a very successful process for making completely normal, fertile toads. Furthermore, it is possible to produce clones of any desired number in this way, either by using large numbers of individual cell nuclei from the intestinal mucosa of a single donor, or by separating the cells of the developing embryo of the original transplant and using them as donors of nuclei to further enucleated eggs.

Such cloning has not yet been achieved with any mammal, because it is much more difficult to get the nucleus out of the mammalian cell, but I am sure that any day now somebody will announce successful nuclear transplantation and cloning of the mouse. Next will be the cow. The owner of the King Ranch says that if his prize bulls could be cloned, it would be the greatest advance in the cattle industry since the domestication of cattle.

What is there in cloning for man himself? One would think that there might be something in it because if you have a genius, say, he's a rare combination of some very good genes. And you'd think it would be good to have more like him. I have discussed this matter with an authentic genius, and he is firmly against cloning of either himself or any other genius. He says the great thing about being a genius is that you have a great scarcity value.

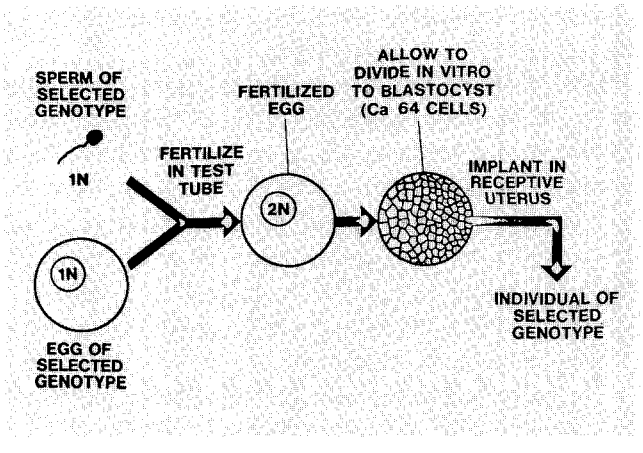
So let's try some other method for improving people. The human gene pool is enormously diverse. It's so

diverse that as between any two of us at least 15 percent of our genes are different. The human species includes people of all sorts of different resistances to diseases, different skills and abilities, so that amongst the population as a whole we should be able to survive almost any kind of catastrophe. Nonetheless, we might wish to increase in our population the frequency of particular genes that we all agree are good to have — like genes for longevity, for example. So how would we implement this newer new morality — making sure that if we have only two children they are not only free from genetic defects but have the best genes available to them in the world?

Well, here's how you would go about it. You take some sperm from an individual of selected genotype, and you take an egg from another person of selected genotype. You fertilize the egg with the sperm, and you let it grow into the 64-cell stage called the blastocyst. That's the size at which the fertilized egg implants itself into the uterine wall. You now implant the blastocyst into the uterine wall of a receptive uterus, and it grows in this host uterus into a normal baby and thence into a supernormal adult.

This is already done with cattle, of course, and with mice and rabbits. It has not been done with people so far as we know, and it would demand a certain humility on the part of humans. Each individual would have to say: "I'm not going to spray my genes around just because they're *my* genes. I want my children to have the best possible genes, even if they're not from me."

The next question is: On what basis do we choose the selected genotype? The points most of us could agree on, I think, are longevity (which is very hereditary), freedom from genetic defects, high energy (which has been shown to be controllable to a considerable degree and is also heritable), and broad spectrum high intelligence. On other points the selection would be more difficult, and there might be a wide diversity of opinion about them.



Idealized selective breeding is one way to improve the human species. The process begins with fertilization in a test tube of a chosen egg by chosen sperm, and continues through implantation in a receptive uterus to the birth of a genetically desirable baby.

A few years ago I participated in a round-table discussion on CBS News on this subject. The panel moderator, Eric Sevareid, asked: "Who will be the selectors?" And I said: "Well, it will be a committee of biologists, of course." My co-panel member, Cardinal Wright, disagreed. His view was that scientists would select only people suitable for being scientists, and not for special spiritual attributes. He wanted to be on the committee too. So you see the kind of trouble we would have right from the start.

The most extreme suggestion on how to go about selectively breeding human beings was made by the late geneticist and Nobel Prize winner H. J. Muller. He proposed that each child at birth have a sample of his or her germ cells removed and put in the deep freeze. The child would then be sterilized. The individual would live out his or her normal life span, and at a decent interval after he has died — so that all the heat of passion has gone away from the matter — the committee would meet and review the person's life. They would ask the question: "Would we like to have more people like that?" If the answer is no, the germ cells are thrown away. If the answer is yes, a selected egg is fertilized with a similarly selected sperm and goes through the ritual that I've already outlined.

That's a very logical suggestion, though it still leaves the thorny problem of how you select the reviewing committee. I think, however, that some anonymous and far-sighted way of conducting selective breeding of humans is not beyond the bounds of possibility.

Muller pointed out that if this sort of selective breeding of people were started in any country the average intelligence, average energy, and other aspects of human well-being could be increased very rapidly. So all the other nations of the world would have to conduct similar programs or face the fate of *Homo neanderthalensis* — elimination by the super people arising from selective breeding.

And so I conclude that man today stands in exactly the position in which *Homo habilis* found himself 2,000,000 years ago. Just as *Homo habilis* had in his hand the first rudimentary tool and just as the use of this tool led to his rapid evolution into us, so we stand today. We have in our hands the first rudimentary tools for escaping extinction and lifting our species to a new and better one. The only remaining question, to me at least, is not moral or judgmental, but temporal. *When* will we start on this new path? □