23 August 1974, Volume 185, Number 4152 SCIENCE

Brave New World?

Current approaches to prevention, treatment, and research of genetic diseases raise ethical issues.

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The public media in the last few years have been full of articles about research in molecular biology and genetics. These fields have come to interest the educated layman; DNA has become a household word. While the stories presented often are quite accurate, they must be digested by readers whose background in biology is usually sketchy. Even those previously exposed to biology usually learned the subject in a conventional way that usually had little relevance to their gaining an understanding of human biology.

The media outdo each other in presenting lurid stories likely to titillate the jaded appetites of their clientele. The results often are a preoccupation with artificial fertilization, cloning, man-primate chimeras, creation of man to genetic specifications, and other far-fetched consequences of the new biology. It is sometimes implied that further advances in biology *must* lead to the universal application of these methods accompanied by an abandonment of conventional reproductive methods and a lowering of the value of human life in general. In his *Brave New World*, Huxley (*1*) described a future society which practiced cloning and artificial fertilization of individuals preassigned to castes stratified by intellectual ability. Orwell portrayed a totalitarian state in his *1984* (*2*). Thoughtful human beings rightfully become frightened when these developments are painted as the ways of the future.

Comparisons have been made between the current state of biology and the state of nuclear physics before the atomic bomb. It is hoped that by intensive discussions of the possible consequences of the new biology, mankind will be better prepared for the coming of the "biological age" than it was for the "nuclear age." Professionals outside of biology and medicine have become interested in these issues. Lawyers, sociologists, philosophers, and theologians have joined biologists, physicians, and geneticists to discuss the current scene and how to approach the future (*3*). A new field—bioethics—is being born (*4*). While there is no dearth of literature in this new field, much of it is somewhat unrealistic.

Research and methods of management of birth defects are intimately tied up with modern biological techniques which, according to the "gloom and doom" prognosticators (*5*) will lead to the Brave New World. Most researchers in the biomedical sciences and practitioners of medicine have been less pessimistic than many of our confreres in the humanities, social sciences, and theology. In general, those trained in biology and medicine have taken a more pragmatic, but possibly a more short-sighted, view of these new developments. Problems of genetic counseling, intrauterine diagnosis, and screening are with us now and raise a variety of ethical issues quite different from the sensational ones drummed up by some of the mass media.

Biologic Origins of Ethics

Evidence for man having evolved from lower forms of life comes from many areas of biology, including protein chemistry—a field in which extensive studies have revealed similarities in the amino acid sequences of proteins from related species (*6*). While many details remain unknown, the grand design of biologic structure and function in plants and animals, including man, admits to no other explanation than that of evolution. Man therefore is another link in a chain which unites all life on this planet. Studies of proteins have indicated that man and his closest nonhuman relative—the chimpanzee—differ from each other by no more than do subspecies of mice or sibling species of fruit flies (*7*). Yet, man differs from all other animals, including the most intelligent chimpanzee, by his ability to use complicated oral and written languages and to conceptualize abstract thoughts. With these unique endowments, our species can create cultures and technologies. We can know our past and worry about our future. We no longer need be subject to blind external forces but can manipulate the environment and eventually may be able to manipulate our genes. Thus, unlike any other species, we may be able to interfere with our biologic evolution. It is most remarkable that the human brain had already reached this supreme position at the dawn of prehistory. The biological substrate that later created the philosophies of Plato and Spinoza, the religions of Jesus and Buddha, the poetry of Shakespeare, Molière, and Goethe, as well as modern science, may have been in existence about 50,000 years ago. There is little evidence that our brains have changed much during this period. Our ancestors

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some 2000 years ago were certainly similar to us (*8*).

The building of ethical systems by man may be considered a unique property of the human brain. No other species is known by us to have ethical systems. Just as the human brain gives man his unique language capacity, enabling him to learn to speak Chinese or English, so does the brain give man his "ethical capacity," allowing him to express his values in a variety of ethical systems. A biological substrate for cooperativity and altruism may have developed by natural selection (*9*). Lone hunters were less likely to survive than those who cooperated with each other. Thus, human "goodness" and behavior considered ethical by many societies probably are evolutionary acquisitions of man and require fostering. Alleviation of suffering, freedom from want, neighborly love, and peace are attributes practically all modern societies would aspire to. Unfortunately, man's altruistic instincts are often overpowered by his aggression. To curb this tendency without dogma and rigid rules is a difficult task facing present-day societies. The human brain is unlikely to change biologically in the foreseeable future. It is also unlikely that man will become extinct. Mass starvation and nuclear war may decimate human populations, but some men are likely to prevail and as long as records of cultural achievements remained in some libraries, high technological achievements would be possible in a few generations.

An ethical system that bases its premises on absolute pronouncements will not usually be acceptable to those who view human nature by evolutionary criteria. New knowledge and new ways of coping with nature offer new and different challenges which the past cannot necessarily help us with. Many persons feel that the consequences, immediate and remote, of a given act should be the sole criterion for judging whether the act is good or bad. Such an ethical system knows no absolutes, no black and white, no a priori do's and don't's, but must laboriously draw up a balance sheet of all the consequences of man's acts (*10*). Most of us are philosophic utilitarians; that is, we want to do the most good for the largest number. We want this goal achieved by consensus rather than by edict, and we value freedom of action. How free we really are, however, is not entirely clear. Data from such different fields as behavioral genetics and Skinnerian psychology (*11*) raise questions about our cherished beliefs of freedom of action, and until considerably more work has been done in human neurobiology, neurogenetics, and behavioral psychology, we will be unable to settle how open our choices really are.

Fried, a legal scholar with philosophical inclinations, has pointed out that we need a "philosophical anthropology"—a new system that would attempt to harmonize the scientific view of man with existing or new codes of ethics (*12*). He states that existing ethical systems are inadequate and that a consequentialist, situational ethics would also be unsatisfactory. Yet, where is this "philosophical anthropology" to come from? Biology itself cannot provide it, and all philosophical systems are relative and not absolute. In a search for a unifying philosophy of man's existence, Monod (*13*) suggested an "ethic of knowledge" to replace existing beliefs; objective search after the truth and after the truth alone would be the cornerstone of this ethical system. This code would omit all emotional, poetic, and aesthetic human aspirations. It is unlikely that such an austere system would appeal to most people.

Where do we go from here? I fully agree with Sinsheimer (*14*), a molecular biologist, who said that the enormity of our ethical problems should not paralyze us into inaction. Our recent triumphs in using the brain to help us in our understanding of ourselves and of the universe should not be the terminus but the beginning of a new era of man's life on this planet and even elsewhere. Nevertheless, I urge caution in our applications of current technology. Modern science has been around for only 200 years in man's evolutionary history; biology has been revolutionized only during the last 20 years. We know relatively little about most of human biology, particularly human genetics. Thus the genetic regulation of human behavior and the genetic determinants of normal traits as well as of common diseases and birth defects are largely unknown (*15*). Intensive research on these topics must be conducted and the underlying basic phenomena must be discovered before we attempt to apply genetic knowledge on a grand scale. Yet paradoxical forces exist that tend to spur us to action. People clamor for the fruits of research to be brought from the laboratory into the public domain. Public funds are spent and, for financial support to continue, practical applications are expected in the near future. As a result, premature applications are likely to be attempted. The public wants cures and prevention of disease; yet, for some of the most serious problems the basic knowledge that would enable us to "deliver the goods" is lacking.

The task of human biologists and physicians is to understand the biology of man and to apply research in a humane and cautious way, with respect for the individual human being. It is likely that in so doing, boundaries will be crossed that were previously considered absolute. The nature of man is to explore and to experiment; to stop exploration and experimentation at this juncture would be to act against those attributes which make us most human.

Surgically Treatable Birth Defects

Many common birth defects, such as a cleft palate, pyloric stenosis, several types of congenital heart disease, and retinoblastoma, can be treated by conventional surgical techniques. Most patients with these disorders are usually cured and made able to lead a normal life; untreated patients with these diseases, except for cleft palate, often die. Developed societies have a sufficient number of surgeons to take care of these defects, and societies now undergoing development include the provision of such surgical treatments in their long-term plans.

All these conditions (with the exception of most unilateral retinoblastomas) have a genetic etiology. The frequencies of congenital heart disease and of pyloric stenosis are 3 percent and 5 percent, respectively, among children of patients, a relative increase of 5 times and 20 times over the frequencies in the general population (*16*). In the past, patients with cleft palate often remained unmarried for cosmetic reasons. Surgically treated patients now have children and approximately 4 percent of these children are affected. Congenital heart disease, pyloric stenosis, and cleft palate are polygenic conditions that can be expected to double their frequencies in about 20 generations, or 500 years (*16*). Bilateral retinoblastoma is a dominant trait and will double in frequency from 1 in 70,000 to 1 in 35,000 in a single generation. From that time on, its frequency will slightly increase because new cases will be added by mutation.

Despite these findings, the dysgenic effects of modern medicine have been exaggerated because natural selection before birth, in the form of spontaneous abortions and genetic sterility, still

occurs and has not been changed significantly by modern medical practices. What should be done? To discontinue life-saving treatments because of future increases of patients appears unthinkable. Genetic counseling to advise treated patients to have fewer children is highly debatable, and is unlikely to have much success if a person feels that his own single surgical operation was no great problem. Why should his children not undergo such operations? To force parents to be sterilized is repugnant and makes little sense.

Various positive and negative financial incentives in the form of bonuses or taxation have been suggested to discourage high-risk patients from having children, and it is conceivable that future societies might initiate such practices. However, a doubling in the frequency of these conditions is unlikely to place a strain on healthy societies. Industrialized societies require fewer persons engaged in production and must provide more jobs in service industries. A larger number of surgeons and other health care personnel required to take care of more sick people fits modern economic trends. Far from being a serious societal problem, the increase in treatable genetic disease could easily be managed. Furthermore, in the time that it would take for the frequencies of these conditions to double, we might be able to develop methods for diagnosing them in utero or for preventing them. Any public action at this time therefore seems inappropriate.

Medically Treatable Birth Defects

The problems associated with medically treatable genetic diseases are similar to those associated with diseases that can be treated surgically. Restoration of full health and vigor leads to fertility and transmission of previously harmful genes. The problem is illustrated by hemophilia, a condition that can now be controlled successfully by frequent injections of antihemophilic globulin in the form of a special cryoprecipitate. This form of treatment, however, is not as simple a matter as, for example, a single operation at birth for pyloric stenosis. Because the cryoprecipitate is expensive, it costs many thousands of dollars per year to keep a patient well. With normal mortality and fertility, the frequency of the disease will double in four generations and triple in ten generations (*16*)—an increase from the current frequency of 1 in 14,000 to 1 in 7,000 in 100 years. Although we will need additional funds to treat these patients, considering the many other problems of cost in our society, this type of expenditure should not alarm us. Not only is the cost of cryoprecipitate likely to be reduced, but new ways to prevent transmission of the disease might be found. In any case, with education and counseling, many hemophiliacs might opt for a reproductive alternative that would avoid gene transmission (*17*).

Medically Preventable Birth Defects

Rational plans for the prevention of most birth defects will remain unavailable as long as we do not understand the etiology of these diseases. Preventive measures based on rational understanding of a disease constitute what Lewis Thomas (*18*) has called "high technology" of disease control. Immunization against rubella to prevent fetal birth defects, and the administration of Rhesus (Rh) antibodies to prevent Rh hemolytic disease would be examples of such "high technology." The only ethical problems associated with these two diseases concern the accessibility of treatments for all women at risk. Rh hemolytic disease might be entirely eradicated if all Rh-negative women were to receive Rh antibodies following pregnancies or abortion. It is conceivable that a significant proportion of birth defects may not be explainable by either genetic or environmental factors, or by genetic-environmental interaction. The complex dynamics of early embryonic organ formation may allow errors on a strictly random basis even after all the genetic and environmental factors affecting development have been fully elucidated. Thus, identical twins share identical heredity and a very similar intrauterine environment. Yet the frequent expression of a birth defect in only one of a pair of identical twins, when other data clearly point to a genetic etiology of that defect, suggests that random factors may play a part in its expression. The cause of the defect therefore could be chance errors that will defy logical explanation. Primary prevention of birth defects based on etiologic understanding is therefore likely to be difficult. For the prevention of most defects we can only recommend that pregnancy be avoided too early or too late in life and that exposure to drugs, chemicals, x-rays, cigarettes, and infection be avoided.

Special Problems of Transplantation

The use of organ transplants for the treatment of birth defects is becoming frequent. Kidneys, for example, are transplanted because of renal failure or as a source of a missing enzyme in conditions such as Fabry's disease (*19*). Bone marrow transplantation has been used in some cases of immune deficiency disease and may have a future in the treatment of hereditary hemoglobinopathies. The distinguished biologist Burnet (*20*) has criticized the use of complex operations, including transplants, in the treatment of disease. He said in 1971: "The application of science to treat any child with a genetic, metabolic, or immunologic anomaly which is potentially lethal, at the best level possible in the light of current knowledge will always be extravagantly expensive. It will require a small full-time team of biochemists and technicians and will subject the child to constant examinations, blood tests, and injections. In most cases such detailed control must be continued throughout life. It is a brutal fact that except in a research center in an affluent country and only when an individual scientist has a professional reputation to make or to maintain in the relevant field, such children can rarely receive empirical care and will die at the first crisis in their condition."

Considerable research effort is spent on transplantation. It is possible that better methods of dealing with the problems of graft rejection will be found so that transplantation might become a simple procedure. In the meantime the ethical problem raised by Burnet must be faced. However, current treatments of the type Burnet refers to must clearly be labeled as research and not as generally applicable therapy. Simpler approaches, however, may result from such investigations which may do away with the complex machinery now required.

Many of the problems that arise with organ transplantation are related to the fact that sibs are usually the best matches for transplants. For example, there are some physical risks in being a kidney donor, since one reserve kidney is removed for the rest of one's life. So should parents be able to volunteer one of their children as a kidney donor for their other sick child? At what age should a child have the right to refuse to become a donor? For what reasons should he be allowed to exercise this right? What are the psychological consequences of refusal and of

knowledge that the affected sib will certainly die without the donation? While a pragmatic view would suggest that parents should be able to volunteer their children as donors to siblings, it is evident that new legal safeguards need to be drawn up. We may hope that the use of organs from cadavers, matched to the donor by computer systems covering wide geographic areas, will ultimately obviate the need for sib donors.

Partially Curable Birth Defects

The treatment of spina bifida—failure of the spinal canal to close normally—illustrates how modern surgical techniques may cause serious ethical problems (*21*). Many children born with spina bifida and related disorders die unless they are given early neurosurgical treatment. However, a large proportion of children receiving such treatment remain paralyzed, or mentally retarded, or both, and require continual complex medical care. When they reach adulthood, many of them do not procreate; thus, they have little effect on the long-term genetic composition of the population. The magnitude of the problem is illustrated by the situation in South Wales, United Kingdom, where over the past few years the number of families having to deal with such patients has quadrupled from an initial frequency of 1 in 1500.

The principal ethical problem associated with partially curable defects concerns the rescuing of individuals from certain death whose quality of life will be seriously compromised. The general consensus in recent years has been to institute "triage" systems so that surgical treatment is withheld from those who, by empirical criteria, will later on be seriously retarded or paralyzed. Heroic treatments to save their lives are not instituted. The decisions about who should be operated on are generally made by teams of neurosurgeons and pediatricians, usually in consultation with the families of patients. The decision to withhold surgery is made without consultation of the public at large. While involvement by the public in establishing guidelines in such decisions is desirable, direct involvement has not worked too well, for example, in establishing priorities for renal dialysis in adults with kidney failure. Triage systems for these types of birth defects could be abused by governments bringing various pressures to bear on the professionals to extend their criteria for withholding of treatment. Free and open discussions of all such issues may be one of the best safeguards against perversion of biological and medical practices.

Tests to diagnose spina bifida and related disorders in utero have become available, and even blood tests for these conditions are on the horizon (*22*). Abortion of affected fetuses following intrauterine diagnosis is already possible if the mother is known to be at high risk because of a previously affected child. Complete prevention of this disorder would require amniocentesis of all pregnancies—a yet impractical suggestion—but such total prevention would be possible if a blood test were available.

Screening for Phenylketonuria and Related Conditions

Screening at birth for certain diseases that can be treated early in life has become accepted medical practice in many countries. Phenylketonuria (PKU) is one such disease that can be detected at birth by simple blood tests. The frequency of this condition, which leads to marked mental retardation in untreated patients, is around 1 in 10,000 births. Treatment consists of restricting the dietary intake of phenylalanine, and current results suggest that treated children with classic PKU develop normally or almost normally. However, a positive screening test does not necessarily mean that the baby has PKU, because variants exist which may not cause mental retardation. A team of experienced biochemists and pediatricians is therefore required to follow up children showing positive tests to ensure that treatment is administered properly.

Although it appears that in children with PKU the diet can be stopped at around 6 years of age, when high concentrations of phenylalanine no longer injure the brain (*23*), girls with PKU need to be informed about the risk of their children being mentally retarded. The high concentration of phenylalanine in the maternal blood crosses over to the fetus and causes severe mental retardation in all children of such women. Presumably, reinstitution of the phenylalanine-free diet during pregnancy would prevent this problem.

An affluent society can afford to screen 10,000 normal children to find the single child with PKU who can be protected against mental retardation by appropriate diet. Sponsors of screening plans have pointed out that in addition to the prevention of tragedy in a family, the cost of the screening program is significantly less than the cost of caring for a single patient with PKU over his lifetime. However, since there is no reason to believe that a decline in numbers of patients with PKU (1 percent of patients institutionalized with mental retardation) would have much effect on the total budgets of hospitals for the mentally retarded, it would be better to use cost-effectiveness analysis only for those disease categories that would reduce total patient load by a much higher proportion.

There are other inborn errors of metabolism, such as maple syrup urine disease, homocystinuria, and galactosemia, that can also be screened for at birth, but each of these conditions is extremely rare. Homocystinuria is probably the most common, with an incidence of 1 in 160,000 births (*24*). Screening for such rare diseases which often cannot even be effectively treated is difficult to justify. However, once testing has been established for PKU it may be relatively inexpensive to add tests for other more rare diseases to the screening system. Obviously, large-scale pilot investigations with careful long-term follow-up studies will have to be conducted, and all the psychological effects and the economic costs of following up false positives will have to be taken into consideration, before a final assessment can be made.

Screening for genetic diseases often causes racial problems. For example, PKU is so rare in the black population that the screening of black children for this condition can be seriously questioned. Yet some observers would object to a scheme whereby blacks were omitted from screening, on grounds of its being discriminatory. Should we test for Tay-Sachs carriers in non-Jews? For sickle cell trait carriers in whites? My recommendation would be to limit testing to relatively small populations in which the particular disease occurs at a high frequency, even if the disease occurs very occasionally in the more populous racial groups.

Screening for PKU is a problem of resource allocation, particularly in the developing countries. Many countries lack the required logistic system to reach and follow up each child. To screen for rare genetic diseases at a time when malnutrition and infectious diseases are the principal problems would be a waste of resources. The continuing and ever-growing contrast be-

tween health care in the Western world, the Soviet Union, Japan, and China on the one hand, and most other areas of our planet on the other, is an ugly monument to the failure of the human species to cooperate. The ethical problems related to birth defects are small when compared with the colossal health problems of the developing countries. How to bridge this gap is a moral problem which too many of us shrug off in helplessness. The population issue must be faced in this context. Reduction of nutritional and infectious disease in the absence of birth control raises worse problems.

Genetic Counseling

Genetic counselors usually are physicians with training in medical genetics who first make an accurate diagnosis of the disease in question, and then provide their patients with information about the natural history of genetic diseases, about the risks of these diseases occurring in offspring, and about the available alternatives to bearing affected children. The aim of such counseling is to enable a couple or a person to make rational decisions about whether or not to reproduce. Although at least one follow-up study has suggested that those who have been counseled get a good grasp of the meaning of risk and avoid reproducing if the risks of their having affected children are high (*25*), some data (*26*) have indicated that the meaning of genetic risk may not always be well understood.

Most counselors consider their work to be little different from any other medical practice; they put the interests of the patient and his family before the interests of society and the state, and pursue medical, not eugenic, objectives. Untoward effects on society may be pointed out, but most counselors do not attempt to give advice based on considerations of the gene pool.

Genetic counseling has thus, traditionally, been nondirective. It is usually maintained that every family situation is different and that the meaning of a given risk varies from family to family, so that in some cases even high recurrence risks may justify a future pregnancy. Some critics (*27*) have suggested that families expect more definite advice than is often provided, saying that because a genetic counselor understands the total impact of the disease and the real meaning of risks better than does the family, he should advise what he or she thinks would be the best course of action. Until better studies have been made of these matters, it will be impossible to make any firm conclusions. In the meantime, depending on the assessment of the counseling problem, many experienced counselors are usually nondirective, but may occasionally alter their approach.

There are also some broad ethical issues associated with genetic counseling. The motivation of a couple who by their own initiative seek counseling is usually different from that of a couple referred to counseling by a physician or some other interested party. Those who seek genetic counseling may be better educated than those who do not and they may, consequently, obtain a better understanding of the risks for their future offspring. With an increasing availability of genetic services, more people who may be unaware that a genetic problem exists or who may not be motivated to seek advice, may nevertheless receive genetic counseling. Under such circumstances, the counseling may be "forced" upon persons. Provided that the information given them is nondirective, they will probably not object, but if a counselor advises reproductive restraint, for example, when such advice has not been asked for, the problem will be more difficult. In countries where private health insurance programs are the rule, it might be possible for the insurance companies involved to withhold benefits from a sick child born to parents who were advised not to reproduce. In countries where health insurance is nationalized, regulations for withholding benefits from certain patients with genetic disease would probably be difficult to administer, and might not be passed for this reason.

Although laws authorizing the sterilization of certain patients have existed in the United States for many years, most of them are no longer applied. The excesses of Nazi Germany in this regard are not many years behind us. Recent newspaper reports of the sterilization of retarded black girls in the southern United States created much furor. Although a logical case can be made for the voluntary sterilization of persons who carry certain harmful genes, who should make the decision for those persons lacking the intellect to decide for themselves? Legal safeguards to prevent possible abuses of existing laws are absolutely necessary and no decision to sterilize a person should be made without the concurrence of representatives of that person's family, the legal and the medical professions, and public representation at large. Laws authorizing enforced sterilization for genetic reasons should be strongly rejected, largely because the rights of couples to make their own decisions, even if this decision might result in the birth of a defective child, must be defended. Improvements in education in human biology, and a greater availability of genetic counseling and related services, should go a long way toward enabling people to make rational decisions about reproduction and toward reducing the numbers of children born with genetically determined illness. The marked change in popular attitudes toward abortion in many societies is a good example of how attitudes regarding reproductive practices can alter rapidly.

Other ethical problems may arise when genetic counseling is extended to family investigations. Some genetic diseases may be delayed in the onset of symptoms and their carriers may not know that they are affected. Identification of a clinically affected patient allows the performance of diagnostic tests of the relatives at risk. Following diagnosis of a disease in its early stages life-saving treatment may be initiated. There is little question that case-finding among relatives is strongly indicated when treatment and prevention of the disease is possible, for example, in hereditary polyposis of the colon, Wilson's disease, and porphyria. How far should the physician or medical geneticist go in order to trace all persons at risk? Should health departments get involved to ensure case-finding among scattered families? Who should be responsible for checking that everyone at risk has been examined?

More problems arise if a disease is clearly genetic in origin but no definite treatment is available (for example, Huntington's chorea). Should one attempt to detect those who are affected before they are clinically ill? Would most persons want to know many years before symptoms develop that they will die prematurely of an incurable disease? If a person were told that he had a high probability of developing such a disease in his middle years, he might decide not to have children. What can be used as guidelines? The relatives may be completely unaware of the risks. The very communication of the problem might create anxiety in a person even if he or she decided not to pursue the matter. Should we insist that relatives at risk be given the relevant information? While no generally

applicable rules can be made, many observers point out that some information is better than none, and that the relatives have a right to know. The withholding of information is considered a form of medical paternalism. Nevertheless, some physicians occasionally decide not to pursue investigations to detect a genetic disease in family members when nothing can be done to prevent or cure the disease. Often the patient and his immediate family can provide assistance or guidance concerning the potential interest of other relatives in genetic counseling. We need many more data on these matters.

Intrauterine Diagnosis

The development of intrauterine diagnostic techniques, such as amniocentesis, for the detection of chromosomal errors, X-linked diseases, and certain inborn errors of metabolism, is revolutionizing genetic counseling (*28*). New sonographic and optical methods are being explored and may widen the scope of intrauterine diagnosis for other conditions. However, most problems requiring genetic counseling cannot yet be approached by intrauterine diagnosis. Researchers in this field foresee a time in the future when amniocentesis may be used routinely in the monitoring of most, if not all, pregnancies. Before this comes about, however, a variety of technical and logistical problems will have to be solved. More diseases need to be diagnosed and the absolute safety of the mother and fetus will have to be ensured. While it is difficult to prophesy, wide use of this procedure appears more likely than some of the more futuristic biological schemes under discussion. Unless it is used for every pregnancy, intrauterine diagnosis will have little impact on the population frequency of most birth defects (*29*).

When a fetus is found by intrauterine techniques to be genetically defective, the parents usually choose to abort it. Abortion causes serious ethical problems to many people for religious or personal reasons, although, first in Japan and more recently in the United States, there has been a rapid change in public acceptance of this procedure. The abortion of a fetus affected with a devastating disease such as Tay-Sachs or mongolism is accepted by many individuals who would oppose abortion for reasons of family limitation or convenience. More difficult problems will arise, however, as milder genetic defects are diagnosed as an unexpected finding following amniocentesis for indications of more harmful diseases. Should an abortion be performed for Klinefelter's (XXY) or Turner's (XO) syndromes? What about cleft palate where a single operation would cure the affected child? Difficult decisions will have to be made about the normality or abnormality of a fetus, because any fetus not considered up to "standard" might be rejected. The problem would became particularly acute should intrauterine diagnosis and abortion become simplified and more widely available. If it becomes possible to diagnose, and thus to abort, defective fetuses at an earlier stage in development than is now possible, many people might choose abortions who would hesitate to undergo this procedure during the early portion of the second trimester of gestation as is now required.

Scenarios have been considered in which the state enforces abortions to save money that would otherwise be spent on the care of persons with severe birth defects. Such a step seems unlikely. It is more probable that most people would voluntarily seek this method of avoiding birth defects. Some observers have suggested that the widespread acceptance of intrauterine diagnosis by many couples might lead to public rejection of children with preventable birth defects who could have been aborted. This development is also improbable: attitudes of the public and of medical personnel toward patients with cancer of the lung, which could have been prevented by their not smoking, is no different from attitudes toward patients with cancer of the colon, which we do not know how to prevent.

Many physicians refuse amniocentesis to pregnant mothers who say that they will not undergo abortion in the event of the fetus being found defective. They say that for these mothers, the early diagnosis of untreatable disease in the fetus would be harmful psychologically and would serve no purpose. In opposition to this viewpoint, one can point out that most amniocenteses give normal results, and that the total happiness generated in families receiving such results outweighs the anguish of the rare couple who know that they will have an affected child but choose not to abort. It is therefore difficult to establish absolute values regarding who should and who should not be given tests that are available.

The possible dysgenic consequences of selective abortion have been considered in detail elsewhere (*29*). While these practices will cause some increase in the numbers of deleterious genes, few serious long-term problems are likely to arise.

The most serious question concerning the ethics of widespread abortion to prevent the birth of genetically defective children is based on the following reasoning: Why go to all the trouble and expense of doing intrauterine tests that might harm the fetus if inspection of the infant and diagnostic tests at birth would be much easier? An infant with serious birth defects could be "terminated" at that time (*30*). Proponents of this viewpoint suggest that a newborn baby should not be considered legally "human" until certain standards of normality have been assured, pointing out that passive infanticide, that is, the withholding of treatment, has always been practiced with severe birth defects. There are awesome implications in these arguments. Most societies differentiate between life in the womb and life after birth. Each month of pregnancy allows for the development of emotional bonds, particularly between the mother and her infant. Perhaps because of recognizing these bonds, most societies in the 20th century have rejected infanticide and place great value on human life after birth. To practice active infanticide for medical purposes to me appears regressive and loathsome, and in effect would officially sanction already existing trends toward the blunting of human sensitivity. The next step, logically, might be the extension of such practices to so-called "mercy killings" at all ages of life, starting with the aged and incurably ill. The experiences of Nazi Germany only 30 years ago show that such practices, which were followed by genocide of almost half of the world's Jewish population, can become a reality.

It is sometimes said that selective abortion after intrauterine diagnosis is an interim measure, and that in the future it will be possible to treat birth defects and genetic diseases either pre- or postnatally. This view is probably unrealistic. Efficacious treatment for a complex defect such as Down's syndrome and similar structural defects is difficult to imagine. Many types of existing and future postnatal therapies cause a certain amount of suffering in the child. Prenatal therapy applied to the fetus may be dangerous to the mother also. Therefore, even when ef-

fective treatments for more birth defects have been developed, many parents will probably prefer a safe abortion with the assurance that their next child will not be affected with the disorder for which selective abortion was performed. This means that abortion for genetic defects discovered by intrauterine diagnosis is here to stay for a long time.

The control of common recessive diseases, such as cystic fibrosis, is most likely to be achieved by detecting heterozygous carriers before or after marriage or mating and by developing methods that will enable physicians to differentiate between normal, heterozygous, and affected fetuses by intrauterine techniques. Carriers would be informed of the 25 percent probability of their offspring being affected if they mated with a carrier of the same disease, and diagnosis could be made in utero, with the mother having the choice of aborting an affected fetus.

Such an approach, if applied by a large fraction of the population, would reduce the numbers of children born with such recessive genetic diseases, and therefore might receive high priority in the allocation of funds for medical research. As a consequence, more basic investigations of this and similar diseases might be deemphasized, or abandoned, in favor of developments of methods leading to the intrauterine diagnostic approach. It is therefore conceivable that treatment of recessive diseases based on a fundamental causative understanding might not be developed because of lack of research efforts. While the discovery of good screening methods and intrauterine tests requires a certain amount of basic understanding, it is clear that the goal of intrauterine diagnosis is more limited and requires fewer total resources than more comprehensive research.

Sex Choice

Determination of the sex of a fetus is already feasible with amniocentesis, and this makes possible sex choice by selective abortion. Since the procedures are somewhat novel, and since a second trimester abortion is required, this technique is rarely used except to detect and abort male fetuses affected with genetic diseases which are linked to the X chromosome, such as hemophilia and the Duchenne type of muscular dystrophy. The procedure is usually refused to couples who desire a child of a certain sex after they have had several children of one sex only. If prenatal amniocentesis becomes a routine procedure, however, sex choice will probably be practiced more often.

While abortion as a means of sex choice may be objectionable, other more acceptable procedures by which to choose the sex of a child may soon be discovered. For example, it might become possible to separate X from Y sperms, in which case sex choice by using the husband's X or Y sperms for insemination would be a simple way of having children of the desired sex. A sociologist has pointed out that if sex choice were widely practiced, more males would be selected than females and, because of this, there would be significant long-term effects on society, such as an increase in homosexuality (*31*). The social effects of a preference for male children would be delayed for almost a generation, however, and it is of interest in this regard that the state of Alaska already has an excess of males, but has not encountered serious societal dislocations.

Significant changes in sex ratio could probably be avoided if the composition of the population were carefully monitored, so that any deviation from an acceptable ratio could be brought to the attention of the public. Widely disseminated discussions regarding possible untoward consequences might then change preferences in sex selection of children. The recent rapid change in styles of family size indicates that swift alterations in reproductive practices do occur. Thus, there is no indication that research on sex choice should be placed under rigid control. In fact, such research should be encouraged, since the discovery of a simple method for choosing the sex of children would allow ideal family planning.

Population Screening for Genetic Reasons

Screening for diseases, such as PKU, which are potentially treatable or preventable by medical or surgical methods, raises fewer problems than screening for conditions for which patients require either conventional genetic counseling about recurrence risks or intrauterine diagnosis following genetic advice. There are several recessive diseases, such as sickle cell anemia, thalassemia major, Tay-Sachs disease, and cystic fibrosis, that are either very difficult to treat or cannot be treated effectively. Each of these conditions is relatively frequent in a certain ethnic group; the conditions range in frequency from 1 in 100 for sickle cell anemia in certain populations in Africa to 1 in 4000 for Tay-Sachs disease in Ashkenazi Jews. Such frequency figures indicate that a significant fraction (3 to 25 percent) of the respective populations are heterozygous carriers for the relevant genes. Tests for detecting carriers of these diseases already exist (except for cystic fibrosis). When carriers receive counseling, they are informed of the 25 percent chance of their children being affected if they marry a carrier of the same gene. In Tay-Sachs disease, intrauterine diagnosis and selective abortion of affected fetuses is already possible. To be most effective, testing procedures should be initiated prospectively, that is, before a child with the disease is ever born. Retrospective counseling following the birth of an affected child is not an effective means of disease prevention since only 12.5 to 25 percent of cases can be prevented in this way (*29*). Some geneticists believe that even in the absence of intrauterine diagnosis, population screening followed by genetic counseling of all carriers would cause a reduction in disease frequency because of reproductive restraint among married carriers or appropriate mating choice among those not yet married.

In practice, the widespread screening for sickling in the United States probably has had several untoward consequences (*32*). Many screening programs were set up without counseling components, and many carriers of the harmless sickle cell trait, because they were not informed otherwise, came to believe that they had a mild form of, or a tendency to, sickle cell anemia, Social stigmatization, occupational discrimination, uprating of insurance premiums, and psychologic invalidism of sickle cell trait carriers were among the results of these programs. In addition, there was a lessened choice of marriage partners for the many people who mistakenly believed that a sickle cell trait carrier was a less desirable mate. In some instances, when a child with a positive sickling test was found to have two nonsickling parents, the illegitimacy thus detected became known to the legal father.

These well-meaning screening programs therefore produced serious problems because the social consequences to a person being identified as a carrier were not taken into consideration (*33*). Before anyone is asked to give consent for screening, they should be fully informed of all the possible social, as

well as medical, consequences of being diagnosed as a carrier. Certainly, before programs for screening the total populations at risk are developed, there should be an extensive assessment of existing practices. Many, but not all, of the problems in sickle cell screening apply to the screening of other diseases of this type.

Much of the misunderstanding about sickle cell anemia and other recessive diseases would certainly be eliminated if the entire population at risk received special educational programs during their early years. Genetic counseling of trait carriers alone would not be satisfactory because the total population at risk needs to be informed.

A better long-term solution to the problem of sickle cell anemia and other hemoglobinopathies, in my view, would be the development of techniques for diagnosing them in utero as are already available for Tay-Sach's disease. The carrier status of a potential mate would then be less important since intrauterine tests could be offered to all couples where both partners were carriers, and affected fetuses could be aborted if desired by the parents. Although this approach has raised cries of "genocide" among some black leaders, programs of this kind for Tay-Sachs disease are in operation in some Jewish communities (*34*). The approach used in these programs is an attempt to make all members of the Jewish community aware of the disease and of its frequency in the Jewish population, and to encourage all members to be tested. An end result similar to that obtained by screening the total population at risk could be obtained if obstetricians tested all pregnant Jewish women (*35*) and arranged for the testing of husbands only if their wives showed positive tests. More medically oriented schemes of this type have the advantage of arriving at the same results without alarming the whole community. On the other hand, in the United States the community approach appears more practicable at this time than enlisting the cooperation of obstetricians and general practitioners who attend the pregnancies of Jewish women.

A program that omits community participation runs against the current trends that aim at maximum dialogue between experts and the public. Nevertheless, complex issues of this kind are understood with difficulty by many people and therefore will cause unnecessary anxiety. Physicians are not required to inform their patients about all possible medical risks of a given procedure, for if they did so, every simple intervention might cause much anxiety. In a recent court ruling, it was stated that untoward risks of a medical or surgical procedure that carry a risk of 1 percent or less need not be discussed with patients. An analogous rule for genetic diseases might be worked out. Thus, genetic diseases that affect fewer than a small fraction of the population might best be dealt with medically without extensive community involvement.

As soon as the absolute safety of intrauterine diagnosis is established, it would be prudent to initiate the screening of all pregnant women older than about 38 years for fetuses affected with Down's syndrome (mongolism). All physicians, regardless of their attitudes toward abortion, should know about the procedures and should fully inform appropriate patients about the possibility of their giving birth to affected children and about the alternatives available. Fortunately, with more effective and more widespread family planning, there will be fewer pregnancies among women of relatively advanced maternal age, and consequently fewer cases of Down's syndrome.

Problems in Early Detection of Genetic Disease of Late Onset

In the future it might be possible to detect early in life, even at birth, a variety of diseases that may cause medical problems later in life. In this category are the hyperlipoproteinemias which predispose affected persons to myocardial infarction in middle age (*36*). Although we have no proof yet that drugs and dietary manipulations defer the onset of coronary disease if instituted early, such an outcome is likely. We should, therefore, consider some of the problems that might have to be faced in the future. For example, what would be the reaction of parents who were told that their hyperlipidemic child had a 50 percent chance of having a heart attack at age 50 years? Would this be enough of a risk to make them change the family diet, or administer a drug all through childhood? Would they be willing to educate the child to a life style that would reduce the probability of his having a heart attack? Would it be child neglect if the parents refused to use a medical or dietary regimen that would help the child 50 years later? Would society be able to ensure in some manner that children would be provided with the environment their genotype required for optimum health?

Particularly difficult problems would be encountered if it became possible to identify future psychiatric disease. We already know that a person with an XXY chromosomal constitution (Klinefelter's syndrome) has an increased risk of suffering mental retardation and of minor sociopathy, but we know of no way to reduce these risks. What should the parents of an XXY child be told? If amniocentesis were to be applied universally, the identification of XXY would probably lead to abortion of many such fetuses. The data regarding the XYY chromosome pattern are still too confused (*37*) to be certain about the risks of criminal or antisocial behavior. It is certain, however, that many parents would choose abortion of an XYY fetus if the risk of its showing such behavior were significantly increased over that of the general population.

The detection of individuals predisposed to schizophrenia could create serious problems if we did not also find a way to prevent the manifestations of the disease. Would it not be tragic for parents to know that their newborn child would develop a serious crippling mental disease at age 20 years? While research on the genetics of schizophrenia and on the effects of the environment on the manifestation of the disease is proceeding, many families participating in this research may obtain information about their children that they probably would rather not know. If a major gene for schizophrenia could be identified, it is likely that tests for this gene could be done in utero and many parents might decide to abort an affected fetus. Thus, it is clear from developments in many genetic diseases that intrauterine diagnosis followed by selective abortion will have wide applicability.

Artificial Insemination

Artificial insemination with donor sperm (AID) in cases of male infertility has been practiced for many years. The practice is handled by a few physicians who usually select donors to match the husband's general appearance and background. Genetic investigation of the donors by history or laboratory tests is not usually done, and the legal status of children born after AID has not been well defined. The use of donor sperm if both members of a couple carry the same recessive gene can prevent the birth of a defective

child. This practice, however, is not often selected in genetic counseling as an alternative method of reproduction.

In recent years, sperm banks have been formed in several cities of the United States to make it possible for men to leave a specimen at a bank before undergoing vasectomy, so that they can have children if for any reason they choose to do so. While the short-term storage of sperm appears to be safe, the effects of long-term storage have not been fully tested, and research in this area raises problems concerning human experimentation. There are many questions that have not been satisfactorily answered by existing sperm banks and none of the banks, as far as I know, have been licensed by any federal or state agency.

Sperm banks could be used to widen considerably the selection of potential donors for AID, particularly if all donors were subjected to genetic investigations. Such a development would bring us close to Huxley's *Brave New World*, except that the donors would be chosen by the physician in consultation with the couple, rather than by the state. The usual practice of the donor remaining anonymous to the couple receiving AID would probably be continued because it prevents undue psychological attachment by the mother to the donor. Sperm banks could also be used for the storage of sperm by young men who might want to have children later in life, but who want to reduce the risk of mutations that occur at a higher frequency in the sperm of older persons. Persons receiving exposure to radiation or mutagenic chemicals could avoid potential problems by depositing their sperm in a bank before exposure. The use of sperm from outstanding human individuals has been recommended by Muller (*38*) as a method of upgrading the genetic constitution of man. He recommended that the sperm be stored until the "candidate" had died so that there could be general agreement about his social worth. Such a scheme is unlikely to be adopted by most women. Furthermore, we know too little about the genetics of desirable human qualities to be able to forecast the outcome of such a practice.

Fertilization in vitro

There has been much discussion about the problems that would arise if it became possible to produce human "test-tube babies" (*39*) In this procedure, human ova would be removed from a woman and would be fertilized in vitro. After some cell divisions the resulting blastocyst would then be reimplanted in the uterus (*40*) where development would proceed as in normal pregnancies. Such "test-tube babies" can be produced in lower species and only a variety of technical, rather than conceptual, obstacles prevent the application of the procedures to man. In its simplest application, a woman with a blocked fallopian tube could thus become pregnant with her own ova fertilized by her husband's sperm. The ova and sperm could, however, be from any human source, and any woman could serve as the "baby carrier."

Fears have been expressed that a government might use these techniques in schemes to breed its citizens. However, in the absence of knowledge of the genetics and the gene-environment interaction of most normal human traits, directed human breeding is not possible; the results would be no more predictable than they are now when a couple has a child in the conventional way. A moratorium on research in this area, as suggested by the American Medical Association (*41*), would serve no useful purpose because prohibition on research in one country can easily be circumvented by such research being conducted elsewhere. Only a moratorium declared by an international commission would be likely to have results. Pointing out the possible dangers of misuse in a wide variety of forums may be the most effective means of preventing abuse.

The achievement of human fertilization in vitro will raise many problems concerning the safety of the procedure. For example, how could a couple give consent to a procedure that might lead to their child being born with a birth defect? This problem is analogous to many earlier situations where women have used birth control pills or antifertility drugs that might have harmed the fetus. Experimentation with long-stored sperm raises similar difficulties. The prohibition of experimentation of this kind with human beings would effectively stop a wide variety of studies. For example, all work on intrauterine diagnosis would have to stop because we cannot yet be absolutely certain that a fetus subjected to amniocentesis is not harmed in some subtle way. If the use of fertilization in vitro for human beings were preceded by thorough studies of the process in subhuman primates, some of the risks involved might be reduced. Fortunately, the early period of embryonic development appears particularly resistant to birth defects in experimental animals, so that some observers feel that experimentation with nonhuman primates could be dispensed with. Furthermore, any pregnancies in women brought about by fertilization in vitro could be very carefully monitored by chromosomal and other inspection techniques. Even with these precautions, however, some defects might not be discovered and a defective baby might be born. In this context it should be recalled that at least 2 percent of all infants born following conventional pregnancy have severe birth defects.

Provided that the decision to use fertilization in vitro is made voluntarily by the couple wanting a child and, ideally, provided that physicians other than the investigators make the couple fully aware of all the potential dangers, there should be no reason to prevent such a couple from participating in this kind of human research. Sufficient experience might be gained in this manner to ensure its safety. Because a couple who would otherwise be sterile could, by fertilization in vitro, be given a chance of having a normal child of their own, it is difficult to agree with those who suggest that normal procreation is human and fertilization in vitro is inhuman (*39*). I consider novel reproductive technologies as a more human activity than making babies in the usual way. Thus, reproduction by intercourse in man differs little from sexual reproduction in most animal species. Nevertheless, it is clear that unlike the prevention and treatment of relatively rare genetic diseases which may be considered as medical problems, the various social and ethical issues raised by fertilization in vitro deserve wide discussion.

Embryo Research

If we are to acquire new insights into the biology of man and his birth defects, studies of developmental biology must include research on human embryos. A large number of embryos are aborted in the United States, Japan, and the Scandinavian countries. Some of these embryos, or at least parts of them, are used for studies aimed at understanding mechanisms of development. Since most of the embryos are dead within minutes of being aborted, and since autopsy is a medical tradition, these studies raise few ethical problems. Difficulties arise when embryos removed

by abortion procedures are kept alive for research purposes. The use of living embryos facilitates studies of human development and of the effects of physical, chemical, and infectious agents on the embryo. While many individuals might not object to a fetus being kept alive for several hours, they might seriously object to a fetus being kept alive for the purpose of an experiment that might take days or even weeks to complete. Informed consent should undoubtedly be obtained before an embryo is kept alive for research purposes. Presumably, the mother who is to be aborted would be the most appropriate person to give such consent.

There are no compelling medical reasons to attempt ectogenesis, that is, fetal development entirely outside the body. However, a large amount of information that might eventually be of great value in finding methods for the prevention and treatment of birth defects could be gleaned from prolonged studies of fetal development in vitro, particularly if early embryos were used. While many biologists and medical investigators do not consider such studies to be unethical, there is sufficient public criticism of this work that any study of this sort needs the most meticulous scrutiny. However, the outright condemnation of such investigations must be deplored.

Cloning

Cloning of man would involve the creation of a human being who was genetically identical to the donor of a somatic cell nucleus implanted in an enucleated egg. Cloning has been accomplished in amphibians and has been discussed as a possibility for mammals (*42, 43*). Huxley anticipated the process by the Bokhanovski procedure in his *Brave New World*. If cloning of man ever became possible, there is no reason to believe that it would be widely used, even for medical purposes. Cloning as a means of dealing with genetic disease by duplicating either the mother's or the father's genotype is unlikely to be utilized.

The creation of groups of cloned military scientists or brute soldiers in the service of a state bent to conquer the world is a remote possibility. If such an event were to occur, one might presume that other countries would respond by cloning similar groups of individuals. However, simpler ways of subjugating people would probably be more attractive to politicians than cloning, because clones would take as long to develop as any normal human being. Extensive discussions of cloning can be found elsewhere (*42, 43*). Since so many ethical problems of immediate urgency are with us now, problems associated with cloning can be dealt with in due course—if they ever arise.

Gene Therapy: Genetic Engineering

Recent developments in molecular biology allow the synthesis of genes, and the possibility of introducing genes into cells by viral transduction has been raised. As a result, much recent discussion has been devoted to gene therapy (*44*). More generally, even the possibility of creating human beings to genetic specifications has been raised. Unfortunately, too much has been promised in this field. First of all, only defects in Mendelian traits whose biochemistry is understood (or possibly polygenic traits to which a major gene contributes) could be approached with gene therapy. We know next to nothing about the control mechanisms of mammalian cells. While a gene whose messenger RNA can be isolated can now be manufactured relatively easily, its safe introduction into the nucleus of a specialized cell followed by normal function remains exceedingly problematical. Moreover, each genetic disease presents different problems of gene therapy. While gene therapy of somatic cells appears far away, gene therapy of eggs or sperm, or of gonads, with ultimate genetic cure may never be achieved (*45*). A group of scientists interested in gene therapy have disclaimed an interest in that aspect of gene therapy which would preserve detrimental genes or maintain them in the population [see (*45*)].

Clinical investigations of gene therapy by means of viral transduction will raise serious ethical problems because of the possibility of untoward consequences such as cancer. Initially, gene therapy could be tried only for the most severe and lethal diseases, and only after very careful animal experimentation. However, most genetic diseases which are conceptually amenable to gene therapy are individually rare. The more common genetic diseases and birth defects are multifactorial and would not respond to gene therapy unless a major manipulatable gene could be identified. Most normal traits are polygenic, so that the manufacture of a man according to genetic specifications must remain in the realm of science fiction. The genetic manipulation of viruses for the prevention of viral diseases, possibly including cancer, is more likely to be achieved than is the management of genetic diseases by gene therapy. Similarly, genetic engineering of plants to provide more food for hungry man is another exciting possibility. In general, it has become clear that the techniques of intrauterine diagnosis and abortion of defective fetuses will be of much greater importance in the control of birth defects than will gene therapy.

Summary

Recent developments in biology and medicine are raising new problems in the prevention and treatment of birth defects, and in research on these diseases. The problems include immediate issues such as genetic counseling, abortion for birth defects, the withholding of complex treatments from individuals in some situations, screening for genetic and other diseases, artificial insemination, and fertilization in vitro. Other problems, such as the dysgenic effects of modern medicine and the possibilities of cloning and gene therapy, are more remote. Each of these issues should be considered on its own merits and by its immediate and remote consequences rather than by a priori absolute criteria. Ways must be found to deal with these issues in a manner acceptable to most human beings. Open discussions and freedom from coercion are the best guarantees for ultimate success. The ethical human brain is the highest accomplishment of biologic evolution. By harmonizing our scientific, cultural, and ethical capabilities, the potentially achievable results can place us at the threshold of a new era of better health and less human suffering.

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Decoding the Language of the Bee

Karl von Frisch

Some 60 years ago, many biologists thought that bees and other insects were totally color-blind animals. I was unable to believe it. For the bright colors of flowers can be understood only as an adaptation to color-sensitive visitors. This was the beginning of experiments on the color sense of the bee (*1*). On a table outdoors I placed a colored paper between papers of different shades of gray and on it I laid a small glass dish filled with sugar syrup. Bees from a nearby hive could be trained to recognize this color and demonstrated their ability to distinguish it from shades of gray. To prevent too great a gathering of bees, I instituted breaks between feedings. After these breaks, only sporadic scout bees came to the empty bowl and flew back home; the feeding table remained deserted. If a scout bee, however, found the bowl filled and returned home successfully, within a few minutes the entire forager group was back. Had she reported her findings to the hive? This question subsequently became the starting point for further investigations.

In order that the behavior of foragers could be seen after their return to the hive, a small colony was placed in an observation hive with glass windows, and a feeding bowl was placed next to it. The individual foragers were marked with colored dots, that is, numbered according to a certain system. Now an astonishing picture could be seen in the observation hive: Even before the returning bees turned over the contents of their honey sack to other bees, they ran over the comb in close circles, alternately to the right and the left. This round dance caused the numbered bees moving behind them to undertake a new excursion to the feeding place.

But foragers from one hive do not always fly to the same feeding source. Foraging groups form: One may collect from dandelions, another from clover, and a third from forget-me-nots. Even in flowering plants the food supply often becomes scarce, and a "feeding break" ensues. Were the bees in the experiment able to alert those very same foragers who were at the bowl with them? Did they know each other individually?

To settle the question, I installed two feeding places at which two groups from the same observation hive collected separately. During a feeding break, both groups stayed on the honeycomb and mingled with each other. Then one of the bowls was refilled. The bees coming from the filled bowl alerted by their dances not only their own group but also bees of the second group, which responded by flying to their customary feeding place where they investigated the empty bowl.

However, the natural stopping places of bees are not glass bowls but flowers. Therefore, the experiment was modified; one of two groups of bees collected food from linden blossoms, the other one from robinias. Now the picture changed. After the feeding break, the

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The author is professor emeritus of zoology at the University of Munich. This article is an English translation of the lecture he delivered in Stockholm, Sweden, on 12 December 1973 when he received the Nobel Prize for Physiology or Medicine, a prize he shared with Nikolaas Tinbergen and Konrad Z. Lorenz. The article is published here with the permission of the Nobel Foundation and will also be included in the complete volume of *Les Prix Nobel en 1973* as well as in the series Nobel Lectures (in English) published by the Elsevier Publishing Company, Amsterdam and New York. The lecture by Professor Tinbergen appeared in the 5 July issue, page 20, and that by Professor Lorenz appeared in the 19 July issue, page 229.